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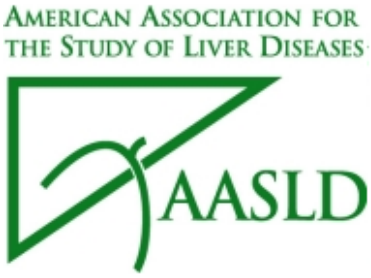


Collaborating Partner

Recommendations for Testing, Managing, and Treating Hepatitis C

Revised Date: December 19, 2014
Complete revision made to Initial*,* Retreatment*,* Monitoring*, and Unique Populations (*HIV/HCV Coinfection*,* Cirrhosis*,* Post-Liver Transplantation*, and* Renal Impairment*) sections on December 19, 2014.*

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version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this.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), have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. The IAS–USA provides the structure and assistance to sustain the process that represents the work of leading authorities in hepatitis C prevention, diagnosis, and treatment in adults.

The AASLD/IDSA/IAS–USA hepatitis C Guidance 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 graded with regard to the level of the evidence and strength of the recommendation. The AASLD/IDSA/IAS–USA hepatitis C Guidance 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 panel of 5 co-chairs and have selected panel members from the 2 societies and the collaborating partner based on their expertise in hepatitis C research and care**.** Likewise, the Guidance development process is generally consistent with that used by the IAS-USA (https://www.iasusa.org/about/program-development-policy).

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 September 25, 2014.

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 graded 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**.

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 and 1 representing the Collaborating Partner. 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 the work of the panel. Full transparency of potential financial conflicts is an important goal for the guidance that best ensures the credibility of the processed 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) and the collaborative partner (IAS–USA). 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. 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 but is not considered a criterion for exclusion. 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. The International Antiviral Society-USA (IAS-USA) is the Collaborating Partner responsible for managing the Panel and the Guidance development process. 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
Grading 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 hcvguidelines@iasusa.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, grades, and evidence summary but should not be contacted for individual patient

	management questions.

Changes on this page made on November 20, 2014.

Methods Table 2. Grading 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, 2011); (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.

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
BOC	boceprevir
CBC	complete blood cell (eg, complete blood cell count)
CrCl	creatinine clearance
CTP	Child Turcotte Pugh (see below)
DAA	direct-acting antiviral
ESRD	end-stage renal disease
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
OATP	organic anion-transporting polypeptide
P-gp	p-glycoprotein
RAV	resistance-associated variant
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
US FDA	US Food and Drug Administration

Definition of Terms			
Child Turcotte Pugh	**Class A**	**Class B**	**Class C**

(CTP) classification of the severity of cirrhosis	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			

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.

HCV testing is recommended at least once for persons born between 1945 and 1965.

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*

Long-term hemodialysis (ever)

Getting a tattoo in an unregulated setting

Healthcare, emergency medical, and public safety workers after needle sticks, 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 medical conditions*

HIV infection

Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels

Rating: Class I, Level B

Of the estimated 2.7 million to 3.9 million persons (1999 to 2008 National Health and Nutrition Examination Survey data [Armstrong, 2006]) chronically infected with HCV in the United States, 45% to 85% are unaware that they are infected. (Smith, 2012) Identification of those with active infection is the first step toward improving health outcomes among persons with HCV infection and preventing transmission. (Smith, 2012); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998)

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 non-injection 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. Health-care 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, needle-stick 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 having received a tattoo in an unregulated setting. 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) Recent data also support testing in all cadaveric and living solid-organ donors because of the risk of HCV infection posed to the recipient. (Seem, 2013); (Lai, 2013)

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 1-time HCV test to all

persons born between 1945 and 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 5-times higher prevalence (3.25%) than other persons, reflecting a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000 versus 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 1-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 1-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.

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.

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive 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 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Rating: Class I, Level C

Among persons suspected 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 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 6 months (including those who are possibly reinfected after previous spontaneous or treatment-related viral clearance) because these persons may be anti-HCV negative. 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.

Prior to the initiation of HCV therapy, quantitative HCV RNA testing is necessary to document the baseline level of viremia (ie, viral load), because the degree of initial viral decline is a crucial marker of the effectiveness of treatment. Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen. Persons who have positive results for an anti-HCV test and negative results for HCV RNA by PCR should be informed that they do not have laboratory evidence of current (active) HCV infection. Additional HCV testing is typically unnecessary. However, some 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 2 different tests. (Vermeersch, 2008); (Centers for Disease Control and Prevention [CDC]), 2013) The HCV RNA test can be repeated when there is a high index of suspicion of infection or in patients with prior or ongoing risk factors for 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, or non-invasive markers, is recommended in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).*

   Rating: Class I, Level B

4. *Vaccination against hepatitis A and hepatitis B is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis.*

   Rating: Class IIa, Level C

5. *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 even the development of HCC. (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004)

Excess alcohol intake may also cause steatohepatitis. 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 have a deleterious effect on the liver; however, these data are controversial. (Westin, 2002) 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.

HBV and HIV coinfection have been associated with poorer prognosis of HCV in cohort studies. (Thein, 2008a); (Zarski, 1998) Due 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 HBsAg using standard assays for screening (Moyer, 2013); (Centers for Disease Control and Prevention, 2008) (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm) and counseled 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 generally 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, semi-quantitative information regarding the amount and pattern of collagen or scar tissue in the liver, which can assist with treatment and monitoring plans. The Metavir fibrosis score (0-4) 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) Non-invasive methods frequently used to estimate liver disease severity include a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine transaminase, albumin, bilirubin, international normalized ratio levels, and complete cell blood counts with platelets), serum fibrosis

marker panels, liver imaging (eg, ultrasound, computed tomography scan), and liver elastography. Simple blood tests (eg, serum aspartate aminotransferase/platelet ratio index) (Wai, 2003) (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri) 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 but can only reliably distinguish cirrhosis from non-cirrhosis. (Castera, 2012) Since 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 also should avoid ulcerogenic drugs and receive ongoing imaging surveillance for liver cancer and varices. (Sangiovanni, 2006); (Fontana, 2010)

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 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.

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

Rating: Class IIa, level C

The definition of evaluation is: *Patient has attended a medical care visit with a practitioner able to complete a full assessment, the pros and cons of antiviral therapy have been discussed, and the patient has been transitioned into treatment, if appropriate.*

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 is required for persons with HCV infection who have advanced fibrosis/cirrhosis (stage III or above on METAVIR scale), including possible referral for consideration of liver transplantation. In the United States, only an estimated 13% to 18% of persons chronically infected with HCV receive treatment. (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) Some possible strategies to address these barriers are listed in **Testing and Linkage to Care Table 3**. One strategy that addresses several barriers is co-localization of HCV screening, evaluation, and treatment with other medical or social services. Co-localization 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)

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://www.echohcvexperts.com]) 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.

Additional strategies of enhancing linkage to care could be adapted from other fields, such as tuberculosis and HIV, but remain to be evaluated for HCV infection. For example, use of directly observed therapy has enhanced adherence to TB treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care. (Govindasamy, 2012) An assessment of efficacy and comparative effectiveness of these 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.

Testing and Linkage to Care Box: Summary of Recommendations for Testing and Linkage to Care

Testing and Linkage To Care Box. Summary of Recommendations for Testing and Linkage to Care

HCV testing is recommended at least once for persons born between 1945 and 1965.

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*

    Long-term hemodialysis (ever)

    Getting a tattoo in an unregulated setting

    Healthcare, emergency medical, and public safety workers after needle sticks, 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 medical conditions*

HIV infection

Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels

Rating: Class I, Level B

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

An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive 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 6 months; testing for HCV RNA can also be considered in persons who are immunocompromised.

Rating: Class I, Level C

Among persons suspected 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 PCR, persons should be informed that they do not have evidence of current (active) HCV infection.

Rating: Class I, Level A

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 is recommended using liver biopsy, imaging, or non-invasive markers in all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).*

   Rating: Class I, Level B

4. *Vaccination against hepatitis A and hepatitis B is recommended for all persons with HCV infection who are susceptible to these types of viral hepatitis.*

   Rating: Class IIa, Level C

5. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*

Rating: Class I, level C

Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

Rating: Class IIa, level C

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

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott	EIA (Manual)
Advia Centaur HCV	Siemens	CIA (Automated)
ARCHITECT Anti-HCV	Abbott	CMIA (Automated)
AxSYM Anti-HCV	Abbott	MEIA (Automated)
OraQuick HCV Rapid Antibody Test	OraSure	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.

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.

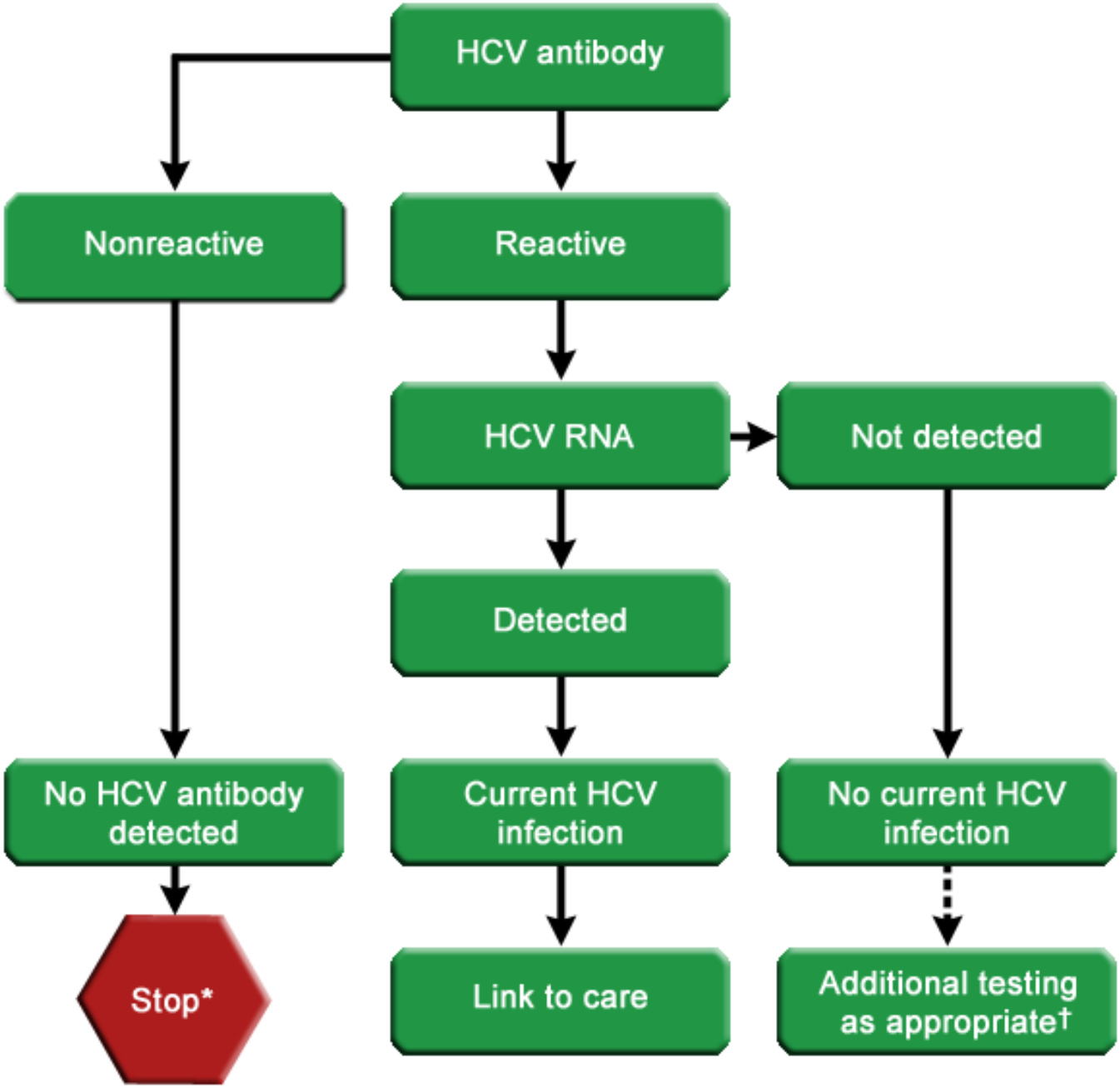
Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

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)

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)

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. Evidence clearly supports treatment in all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions (See sections on HIV/HCV coinfection, cirrhosis, liver transplantation, and renal impairment). Urgent initiation of treatment is recommended for some patients, such as those with advanced fibrosis or compensated cirrhosis (see Table 1).

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 an SVR.

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 serum, liver tissue, or mononuclear cells, and achieve substantial liver histology improvement. (Marcellin, 1997); (Coppola, 2013); (Garcia-Bengoechea, 1999) Assessment of viral response, including documentation of SVR, requires use of US Food and Drug Administration (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 achieving 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) 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) HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful antiviral 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 achieving SVR have substantially improved quality of life, which includes physical, emotional, and social health. (Neary, 1999); (Younossi, 2013) Because of the myriad 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 their chronic HCV infection before the development of severe liver disease and other complications.

Recommendations for when and in whom to initiate treatment

Treatment is recommended for patients with chronic HCV infection.

Rating: Class I, Level A

Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C (Table 1).

Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority (Table 1).

Ratings: See tables

The most immediate and high-impact benefits of SVR will be realized by populations that are at the highest risk for liver-related complications due to progressive liver disease (Metavir F3 or F4) and transplant recipients or those with clinically severe extrahepatic manifestations **(**Table 1**)**.

Other populations at high risk for liver disease progression (Metavir F2) or with substantial extrahepatic manifestations **(**Table 1**)** are also expected to garner appreciable benefits, although the time course for realizing these benefits may be more protracted.

SVR will also remove the risk of further transmission. Treatment of individuals at high risk to transmit HCV to others **(**Table 2**)** may yield long-term future benefits from decreased transmission and a potential decrease in HCV disease prevalence.

When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications

Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)

Rating: Class I, Level A

Organ transplant

Rating: Class I, Level B

Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)

Rating: Class I, Level B

Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

Rating: Class IIa, Level B

High Priority for Treatment Owing to High Risk for Complications

Fibrosis (Metavir F2)

Rating: Class I, level B

HIV-1 coinfection

Rating: Class I, Level B

Hepatitis B virus (HBV) coinfection

Rating: Class IIa, Level C

Other coexistent liver disease (eg, [NASH])

Rating: Class IIa, Level C

Debilitating fatigue

Rating: Class IIa, Level B

Type 2 Diabetes mellitus (insulin resistant)

Rating: Class IIa, Level B

Porphyria cutanea tarda

Rating: Class IIb, Level C

Ratings refer to the strength and level of evidence with regard to benefits of treatment in these settings.

When and in Whom to Initiate HCV Therapy Table 2. Persons At Elevated Risk of HCV Transmission* and in Whom HCV Treatment May Yield Transmission Reduction Benefits

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Men who have sex with men (MSM) with high-risk sexual practices

Active injection drug users

Incarcerated persons

Persons on long-term hemodialysis

HCV-infected women of child-bearing potential wishing to get pregnant

Rating: Class IIa, Level C

*Patients at substantial risk of transmitting HCV should be counseled on ways to decrease transmission and minimize the risk of reinfection.

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 hepatocellular carcinoma 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 hepatocellular carcinoma, 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, hepatocellular carcinoma, or advance 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, hepatocellular carcinoma, 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], .17, 95% confidence interval [CI], .06–.46), development of liver-related morbidity and mortality (HR, .15, 95% CI, .06–.38) and hepatocellular carcinoma (HR, .19, 95% CI, .04–.80). (Dienstag, 2011) Based on these considerations, prompt HCV treatment is recommended for persons with advanced liver disease unless contraindicated (eg, hypersensitivity) or substantial nonhepatic life-limiting comorbidities are present. Importantly, persons with advanced liver disease also require long-term follow-up and hepatocellular carcinoma (HCC) surveillance regardless of treatment outcome (see **Monitoring Section**).

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, in general, be treated by physicians with experience in treating HCV in conjunction with a liver transplantation center if possible.

Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the allograft occurs universally in patients in whom viral replication is ongoing 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, untreated, up to 30% 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 post- transplantation has led to shorter period of graft survival for recipients with HCV infection than for recipients who undergo liver transplantation for other indications. (Forman, 2002)

Effective antiviral therapy pre-transplantation resulting in a SVR (virologic cure) prevents HCV recurrence post-transplantation. (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 are wait-listed for liver transplantation that included patients with MELD scores up to 14 and CPT scores up to 8 found that treatment with sofosbuvir and weight-based ribavirin (RBV) for up to 48 weeks was well tolerated and was associated with an overall post-transplant SVR of 69%. (Curry, 2013b) Post-transplant SVR was near ubiquitous among patients who had undetectable HCV RNA for 28 days or longer prior to transplantation.

Treatment of established HCV infection post-transplantation also yields substantial improvements in patient and graft survival. (Berenguer, 2008); (Picciotto, 2007) The availability of effective IFN-free HCV treatment regimens has addressed the major hurdles to treating HCV recurrence post-transplantation: poor tolerability and efficacy. In a multicenter, open-label study evaluating the ability of sofosbuvir plus RBV to induce virologic suppression in 40 post–liver-transplant patients with compensated recurrence of HCV infection, daily sofosbuvir and RBV for 24 weeks achieved an SVR at 12 weeks (SVR12) in 70%. (Charlton, 2014b) 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 with sofosbuvir and any of the concomitant immunosuppressive agents reported. In contrast, treatment with sofosbuvir plus RBV with or without PEG in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 of 57% and a mortality rate of 25%. (Forns, 2013c) On an intent-to-treat basis, treatment was associated with clinical improvement in 64% and stable disease in 11% of patients.

Persons at Greater Risk of 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. Patients with these conditions should be prioritized for hepatitis C therapy.

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) 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 1 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, argue for treatment prioritization in this population, regardless of the current fibrosis stage. (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 hepatocellular carcinoma.

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, it is prudent to periodically retest HBV DNA and HCV RNA levels during and after therapy, particularly if only one of the viruses is being treated at a time. Treatment of HCV in such cases utilizes the same genotype-specific regimens as are recommended for HCV monoinfection **(see** Treatment Section**)**. 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 to exacerbate them.

Persons with Severe Extrahepatic Manifestations of Chronic HCV Infection

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 should be prioritized 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 direct-acting antiviral (DAA) regimens is an attractive alternative for these patients. Organ-threatening disease (eg, severe neuropathy, renal failure, digital ischemia), in addition to the antiviral HCV therapy, should also 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 the nephrotic syndrome, but usually does not fully ameliorate azotemia. (Johnson, 1994) No clinical trial data are yet available using IFN-free regimens, but the high rates of SVR (virologic cure) using antiviral therapy support their use in management of hepatitis C-related renal disease and cryoglobulinemia.

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 over 40 years of age. (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 impaired response to IFN-based therapy. (Petta, 2008) Patients with type 2 diabetes and insulin resistance also are at increased risk for hepatocellular carcinoma. (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 of ESRD, 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 in patients with pre-diabetes who have hepatitis C may prevent progression to diabetes and reduce renal and cardiovascular complications in hepatitis C patients with established diabetes.

Persons with Other Extrahepatic Manifestations of HCV Infection

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. (Bonkovsky, 2007) In the Virahep-C study, 401 HCV patients were evaluated for fatigue prior to treatment and after therapy using validated scales assessing 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 who achieved an SVR12 from the NEUTRINO and FUSION trials treated with a sofosbuvir-containing regimen demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level. (Younossi, 2014) After achieving an SVR12, participants had marked improvement in fatigue over their pretreatment scores using 3 separate validated questionnaires.

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 achieving an SVR improves 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 the 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)

Persons With Elevated Risk of Transmitting HCV

Persons who have successfully achieved an SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment 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 between couples and among families to eradicating HCV infection 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.

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 the target populations.

Persons who inject drugs. Injection drug use is the most common risk factor for HCV infection in the United States and Europe with an HCV seroprevalence from 10% to 70%; (Amon, 2008); (Nelson, 2011) injection drug use also accounts for the majority of new infections (approximately 70%) and is the key driving force in 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 using 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 including opiate substitution therapy and needle and syringe exchange programs. (Martin, 2013a)

Studies of IFN-containing treatments in persons who inject drugs have shown comparable adherence and efficacy rates to patients who do not use injection drugs. A recent meta-analysis of treatment in active or recent injection drug users with PEG with or without RBV showed SVR rates of 37% and 67% for genotype 1 or 4 and 2 or 3, respectively. (Aspinall, 2013) As shorter, better-tolerated, 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 incident infection in the injection drug user population in general (6.1-27.2/100 person years); though reinfection increases with active or ongoing injection drug use (6.44/100 person years) and available data are limited in follow-up duration. (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 injection drug use should not be seen as an absolute contraindication to HCV 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) with high-risk sexual practices. Over the past

decade a dramatic increase in incident HCV infections has been demonstrated in several US cities among HIV-infected MSM who did not report injection drug use as a risk factor. (van de Laar, 2010) Recognition and treatment of HCV (including acute infection) in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV-infected MSM with 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 HCV seroprevalence ranges from 30% to 60% (Post, 2013) and an acute infection rate of about 1%. (Larney, 2013) Screening for HCV 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 treatment owing to release from prison during therapy has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities. (Post, 2013); (Chew, 2009) Shorter (12-week 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 toxicity concerns. 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 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 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 persons on hemodialysis without HCV infection. (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 combined with the substantial clinical impact of HCV infection in those on hemodialysis suggest that this group should also be prioritized for HCV therapy as effective antiviral regimens that can be used in advanced renal failure become available.

For all these populations, the decision to treat should be based on a favorable risk-benefit ratio taking into account the anticipated reduction in transmission(s) versus the likelihood of reinfection.

Populations Unlikely to Benefit from HCV Treatment

Patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. 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) due 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

An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.

Rating: Class I, Level A

An accurate assessment of fibrosis is vital in assessing the urgency for treatment. The degree of hepatic fibrosis is one of the most robust prognostic factors used to predict disease progression and clinical outcomes. (Everhart, 2010) Those with substantial fibrosis (defined as Metavir F2 or higher) should be given priority for therapy in an effort to decrease the risk of clinical consequences such as cirrhosis, liver failure, and hepatocellular cancer. However, those with severe fibrosis (Metavir stage F3 and F4) are most in need of immediate therapy. In addition to urgency for antiviral therapy, individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function. (Garcia-Tsao, 2007); (Bruix, 2011)

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. A cutoff value of 8.7 kPa correlates with Metavir F2 or higher fibrosis stage; greater than 9.5 kPa with F3; and 14.5 or higher kPa with F4 or cirrhosis. The measurement range does overlap between stages. (Ziol, 2005)

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. (Boursier, 2012) A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making. For example, 1 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 aspartate aminotransferase-to-platelet ratio index (APRI) or fibrosis-4 index (FIB-4) can help identify those most likely to have F3 or F4 fibrosis stage. (Sebastiani, 2009); (Castera, 2010); (Chou, 2013b) An APRI above 2.0 or FIB-4 above 3.25 has a high specificity for advanced fibrosis or cirrhosis, although neither test

is sensitive enough to rule out substantial fibrosis if values are below these thresholds. (Chou, 2013b) 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).

Recommendation 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. Among individuals with less-advanced stages of fibrosis, fibrosis progression over time will help determine the urgency of subsequent antiviral therapy. Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (**Table 3**). (Feld, 2006) Fibrosis may not progress linearly. Some individuals (often those who are aged 50 years or older) 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 is associated with more rapid fibrosis progression. (Ghany, 2003) However, even patients with normal alanine aminotransferase (ALT) levels may develop substantial liver fibrosis over time. (Pradat, 2002); (Nutt, 2000)

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 as well as elevated body mass index and insulin resistance are associated with fibrosis progression, as is iron overload. (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.

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

The level of virus in the serum (HCV RNA) is not highly correlated with the stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with genotype 3 HCV infection. (Kanwal, 2014) (Bochud, 2009) Aside from coinfections 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 update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of every 6 months evaluation.

When and in Whom to Initiate HCV Therapy Table 3. Factors Associated with Accelerated Fibrosis Progression

Host	Viral
Non-Modifiable Fibrosis stage Inflammation grade Older age at time of infection Male sex Organ transplant **Modifiable** Alcohol consumption Nonalcoholic fatty liver disease Obesity Insulin resistance	Genotype 3 Coinfection with hepatisis B virus (HBV) or HIV

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

When and in Whom to Initiate HCV Therapy Box. 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 an SVR.

Rating: Class I, Level A

Recommendations for when and in whom to initiate treatment

Treatment is recommended for patients with chronic HCV infection.

Rating: Class I, Level A

Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C (Table 1).

Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority (Table 1).

Ratings: See tables

Recommendations for pretreatment assessment

An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver

biopsy, is recommended.

Rating: Class I, Level A

Recommendation for repeat liver disease assessment

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

Rating: Class I, Level C

Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) **Rating:** Class I, Level A
Organ transplant **Rating:** Class I, Level B
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis) **Rating:** Class I, Level B
Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis **Rating:** Class IIa, Level B

High Priority for Treatment Owing to High Risk for Complications
Fibrosis (Metavir F2) **Rating:** Class I, level B **HIV-1 coinfection** **Rating:** Class I, Level B **HBV coinfection** **Rating:** Class IIa, Level C **Other coexistent liver disease (eg, NASH)** **Rating:** Class IIa, Level C **Debilitating fatigue** **Rating:** Class IIa, Level B **Type 2 Diabetes mellitus (insulin resistant)** **Rating:** Class IIa, Level B **Porphyria cutanea tarda** **Rating:** Class IIb, Level C

Ratings refer to the strength and level of evidence with regard to benefits of treatment in these settings.

Table 2. Persons At Elevated Risk of HCV Transmission* and in Whom HCV Treatment May Yield Transmission Reduction Benefits

Men who have sex with men (MSM) with high-risk sexual practices

Active injection drug users

Incarcerated persons

Persons on long-term hemodialysis

HCV-infected women of child-bearing potential wishing to get pregnant

Rating: Class IIa, Level C

*Patients at substantial risk of transmitting HCV should be counseled on ways to decrease transmission and minimize the risk of reinfection.

Table 3. Factors Associated with Accelerated Fibrosis Progression

Host	Viral
Non-Modifiable	Genotype 3
Fibrosis stage	Coinfection with HBV or HIV
Inflammation grade	
Older age at time of infection	
Male sex	
Organ transplant	
Modifiable	
Alcohol consumption	
Nonalcoholic fatty liver disease	
Obesity	
Insulin resistance	

INITIAL TREATMENT OF HCV INFECTION

/*-->*/

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

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***.***

The level of evidence available to inform the best treatment decision for each patient varies, as does the strength of the recommendation, and is rated accordingly (see **Methods Table 2**). In addition, when treatment differs for a particular group, such as those infected with specific HCV genotype or subtype, specific recommendations are given. A regimen is classified as "Recommended" when it is favored for most patients and "Alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "Not Recommended." 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**),** post–liver transplant **HCV infection, and those with severe** renal impairment **or end-stage renal disease are addressed in other sections of the Guidance.**

When several regimens are offered at the same recommendation level they are listed in alphabetic order. In this case consideration of 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 RBV is included in the regimen. (See Monitoring Section)

I. Genotype 1

Three highly potent DAA oral combination regimens are recommended for HCV genotype 1–infected patients, although there are differences in the recommended regimens based on the HCV subtype. Patients with HCV genotype 1a tend to have higher relapse rates than patients with HCV genotype 1b with certain regimens. Genotype 1 HCV infection that cannot be subtyped should be treated as genotype 1a infection.

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with other concomitant medications used by patients, 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. In particular, the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) has a potential interaction with acid-suppressing medications, for example proton pump inhibitors, which may result in decreased absorption of ledipasvir

and lower exposures. Because of over-the-counter access to acid-suppressing medications, a comprehensive assessment of all prescribed and over-the-counter medications is recommended prior to initiating treatment. If possible, acid-suppressing medications should be held prior to and during the HCV treatment period to optimize ledipasvir exposure. For patients in whom interruption of acid suppression is not possible, dosing of acid suppressants is recommended per the prescribing information.

Similarly, the daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir) has a substantial interaction with the long-acting inhaled beta-adrenoceptor agonist salmeterol, and concurrent administration is not recommended owing to an increased risk of cardiovascular adverse events including QT segment prolongation.

A. Genotype 1a

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1a infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks* is recommended for treatment-naive patients with HCV genotype 1a infection.
***See text for further detail on** length of treatment

Rating: Class I, Level A

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class IIa, Level B

For HCV genotype 1a–infected, treatment-naive patients, there are 3 regimens of comparable efficacy, as outlined above.

Ledipasvir/sofosbuvir was approved by the FDA for the treatment of HCV genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1(865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for RBV. (Afdhal, 2014a) Sustained virologic response at 12 weeks (SVR12) was 97% to 99% across all arms, with no difference in SVR based on length of treatment, use of RBV, or HCV genotype 1 subtype. Sixteen percent of subjects enrolled were classified as having cirrhosis. There was no difference in SVR12 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 RBV). (Kowdley, 2014) SVR12 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 of 431) regardless of RBV use compared with the 12-week arm (3 of 216). Post hoc analyses of the 2 RBV-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 of 123), and was the same for patients with similar baseline HCV RNA levels who received 12 weeks (2%; 2 of 131). This analysis was not controlled and thus substantially limits the generalizability of this approach to clinical practice. Shortening treatment to less than 12 weeks should be done with caution and performed at the discretion of the practitioner.

Paritaprevir/ritonavir/ombitasvir plus dasabuvir and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) was approved by the FDA for the treatment of HCV genotype 1a infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a HCV infection; those with cirrhosis were excluded), PEARL-IV (305 treatment-naive patients with genotype 1a; those with cirrhosis were excluded), and TURQOUISE-II (261 treatment-naive and -experienced patients with genotype 1a; those with cirrhosis were included). The SAPPHIRE-I trial reported a high SVR12 rate (95.3%) with 12 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV. (Feld, 2014) Overall, virologic failure was higher for patients with HCV genotype 1a (7 of 8) than patients with HCV genotype 1b (1 virologic failure). PEARL-IV was specifically designed to determine the role of paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without weight-based RBV for treatment-naive, HCV genotype 1a–infected patients without cirrhosis. (Ferenci, 2014) SVR12 was lower in the RBV-free arm than in the RBV-containing arm (90% vs 97%, respectively) owing to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based RBV for patients with HCV genotype 1a. TURQUOISE-II enrolled treatment-naive 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 paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV. Overall, SVR12 rates were 89% in the 12-week arm and 95% in the 24-week arm. (Ombitasvir/Paritaprevir/Ritonavir prescribing information); (Poordad, 2014) This difference in SVR12 rate between arms was primarily driven by patients with null response to PEG-IFN and RBV; there was less difference in SVR rates in the patients with cirrhosis who were naive to therapy (92% and 95%, respectively). (Ombitasvir/Paritaprevir/Ritonavir prescribing information); (Poordad, 2014)

COSMOS was a phase II clinical trial of sofosbuvir plus simeprevir that included treatment-naive and -experienced patients, including those with cirrhosis. (Lawitz, 2014a) The study enrolled 2 cohorts: cohort 1 included 80 patients with a prior null response to PEG-IFN and RBV with Metavir F0 to F2 fibrosis, and cohort 2 included 87 patients who were either treatment naive or had a prior null response to PEG-IFN and RBV with Metavir stage F3 or F4 fibrosis. Each cohort had 4 arms to address length of treatment (12 weeks vs 24 weeks) and the role of weight-based RBV. Across both cohorts, the SVR12 rate ranged from 79.3% to 100%, with no clear benefit of extended treatment or use of RBV; however, the small size per arm limited the analysis. In a pooled analysis of all RBV-free arms, 95% (20/21) with Metavir stage F0 to F3 fibrosis who received 12 weeks of sofosbuvir and simeprevir achieved SVR12 compared with 86% (6/7)

of those with Metavir stage F4 fibrosis. (Lawitz, 2014b) Among patients with cirrhosis who received 24 weeks of therapy, the SVR rate was 100% (10/10).

Based on this analysis, the FDA recommends 24 weeks for all patients with cirrhosis, regardless of treatment experience. An ongoing phase III trial (NCT02114151) will provide more definitive information on the response rates of patients with cirrhosis receiving 12 weeks of sofosbuvir and simeprevir without RBV. Until that time, the use of 24 weeks of sofosbuvir and simeprevir for patients with cirrhosis is recommended. Overall, only 6 patients in the COSMOS trial experienced virologic failure (relapse), all had HCV genotype 1a infection, and 4 had virus with the Q80K polymorphism at baseline. When simeprevir is combined with PEG-IFN and RBV, patients with HCV genotype 1a infection and a baseline Q80K polymorphism have higher virologic failure rates than patients with genotype 1b infection or genotype 1a infection without this baseline mutation. This led to the recommendation for baseline Q80K testing for all HCV genotype 1a–infected patients prior to the use of simeprevir with PEG-IFN and RBV. In contrast, the presence of the Q80K polymorphism does not preclude treatment with simeprevir and sofosbuvir, because the SVR rate was high in patients with HCV genotype 1a and the Q80K polymorphism (88%; 51/58). (Lawitz, 2014b) Given the low but finite failure rates, the role of RBV with simperevir and sofosbuvir in patients with HCV genotype 1a is unclear. Thus, RBV use may be considered until results from the larger phase III trials can more definitively address these questions (NCT02114151, NCT02114177).

The safety profiles of all the recommended regimens above are excellent. 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 RBV-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

B. Genotype 1b

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1b infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks* is recommended for treatment-naive patients with HCV genotype 1b infection.
***See text for further detail on length of treatment**

Rating: Class I, Level A

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 recommended for treatment-naive patients with HCV genotype 1b infection. **Rating:** Class I, Level A
The addition of weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg]) is recommended in patients with cirrhosis.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks (no cirrhosis) or

24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class IIa, Level B

For HCV genotype 1b–infected, treatment-naive patients, there are 3 regimens of comparable efficacy, as outlined above.

There is no measurable difference demonstrated to date in treatment response to ledipasvir/sofosbuvir for HCV genotype 1 subtypes, thus the supporting evidence remains the same as for HCV genotype 1a–infected patients (see Genotype 1).

Paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without cirrhosis and RBV (cirrhosis) was approved by the FDA for the treatment of HCV genotype 1b infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (151 treatment-naive patients with genotype 1b HCV; those with cirrhosis were excluded), PEARL-III (419 treatment-naive patients, all with genotype 1b; those with cirrhosis were excluded), and TURQOUISE-II (119 treatment-naive and -experienced patients with genotype 1b; those with cirrhosis were included). SAPPHIRE-I reported a high SVR12 rate (98%) with 12 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV 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 RBV with paritaprevir/ritonavir/ombitasvir plus dasabuvir in treatment-naive patients with HCV genotype 1b without cirrhosis. (Ferenci, 2014) SVR12 rate was 99% in both arms, confirming the lack of added benefit of weight-based RBV for patients without cirrhosis with HCV genotype 1b. TURQUOISE-II enrolled treatment-naive and -experienced patients with CTP class A cirrhosis to receive either 12 weeks or 24 weeks of treatment with paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV. Overall, SVR12 rates were 98.5% in the 12-week arm and 100% in the 24-week arm. (Poordad, 2014) Owing to the high SVR rates, a phase III study is currently underway to determine if RBV is required as part of this regimen for HCV genotype 1b–infected patients with cirrhosis (TURQUOISE-III, NCT02219503). Until these data are available, treatment-naive patients with HCV genotype 1b infection and cirrhosis should receive RBV with paritaprevir/ritonavir/ombitasvir plus dasabuvir.

As noted, COSMOS was a phase II clinical trial of sofosbuvir plus simeprevir with or without weight-based RBV for 12 weeks or 24 weeks. (Lawitz, 2014a) The study enrolled 2 cohorts: cohort 1 included 80 patients with a prior null response to PEG-IFN and RBV with Metavir stage F0 to F2 fibrosis and cohort 2 included 87 patients who were treatment naive or who had a prior null response to PEG-IFN and RBV with Metavir stage F3 or F4 fibrosis. No virologic failure occurred in patients with HCV genotype 1b infection, suggesting high efficacy of this regimen for this genotype. Preliminary data from large prospective observational cohort studies demonstrate high SVR rates (>90%) in patients with HCV genotype 1b infection treated with sofosbuvir plus simeprevir in clinical practice. These data provide additional support for use of this DAA combination for the treatment of HCV genotype 1b. (Jensen, 2014); (Dieterich, 2014a) The FDA approval of this combination recommends 24 weeks of the combination without RBV in all patients with cirrhosis. Phase III study data of this regimen should be available in mid-2015 and are expected to provide further insight into the treatment of patients with HCV genotype 1b, including the need for RBV and optimal treatment duration for patients with cirrhosis (NCT02114151, NCT02114177).

The safety profiles to date of all recommended regimens above are excellent. 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 RBV-containing arms. Discontinuation rates were higher for patients with cirrhosis (approximately 2% for some trials) but still very low.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1.*

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 24 weeks.

Rating: Class IIb, Level A

PEG-IFN and RBV with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks.

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

*See sections on HIV/HCV coinfection, decompensated cirrhosis, liver transplantation, and renal impairment.

Although regimens of sofosbuvir and RBV or PEG-IFN and RBV plus sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks (some using response-guided therapy) are also FDA approved, they are inferior to the current recommended regimens. Most of the IFN-containing regimens are associated with higher rates of serious adverse events (eg, anemia and rash), longer treatment duration, high pill burden, numerous drug-drug interactions, more frequent dosing, higher intensity of monitoring for continuation and stopping of therapy, and the requirement to be taken with food or with high-fat meals. Although the phase III NEUTRINO trial reported the highest SVR rate (89%) for an IFN-containing regimen (sofosbuvir [400 mg daily]) in combination with PEG-IFN 2a (180 ?g by subcutaneous injection weekly) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) in HCV genotype 1 infection and limited exposure to IFN to just 12 weeks, the safety and tolerability profile limits its usefulness in the setting of FDA-approved, highly efficacious oral DAA combinations. (Lawitz, 2013a)

PEG-IFN and RBV for 48 weeks for treatment-naive patients with HCV genotype 1 has been superseded by treatments incorporating DAAs and should not be used.

II. Genotype 2

Recommended regimen for treatment-naive patients with HCV genotype 2 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

Extending treatment to 16 weeks is recommended in patients with cirrhosis.

Rating: Class IIb, Level C

Sofosbuvir (400 mg daily) was combined with weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for treatment-naive patients with HCV genotype 2 infection in 3 clinical trials, each of which enrolled patients with genotype 2 or 3 HCV: FISSION, POSITRON, and VALENCE. (Lawitz, 2013a); (Jacobson, 2013c); (Zeuzem, 2013c) The FISSION study randomized patients to receive daily PEG-IFN and RBV (800 mg) for 24 weeks or sofosbuvir plus daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks. (Lawitz, 2013a) The SVR rate was higher (94%) in patients who received sofosbuvir plus RBV than in those who received PEG-IFN and RBV (78%; 52/67). Across all 3 trials, 201 of the 214 (94%) patients with HCV genotype 2 achieved SVR with sofosbuvir plus RBV. Among patients who did not achieve SVR, sofosbuvir resistance–associated variants (RAVs) were not detected. (US FDA, 2013a) Based on real-world data from Trio Health, lower response rates were seen in treatment-naive patients with cirrhosis than in those without cirrhosis. (Dieterich, 2014a) Although data to support extension of therapy are not yet available for treatment-naive patients with HCV genotype 2 infection, longer treatment duration improves SVR in treatment-experienced patients with cirrhosis. (Jacobson, 2013c) Owing to the small numbers of patients with HCV genotype 2 infection and cirrhosis enrolled in the registration trials, several phase IIIB studies are ongoing to specifically determine the appropriate length of treatment for this subgroup of patients (NCT01962441, NCT 02128542). Until these data are available, extending treatment from 12 weeks to 16 weeks in HCV genotype 2–infected patients with cirrhosis is recommended**.**

Alternative regimens for treatment-naive patients with HCV genotype 2 infection.

None.

Although there are no alternative regimens listed, several available DAAs have activity in vitro and in vivo against HCV genotype 2. Simeprevir has moderate potency against HCV genotype 2 but has not formally been tested in combination with sofosbuvir in HCV genotype 2 infection. (Moreno, 2012) Daclatasvir (60 mg/day) with sofosbuvir (400 mg/day) for 24 weeks was associated with high rates of SVR in treatment-naive patients with HCV genotype 2 infection. Although the 50% effective concentration (EC_{50}) for daclatasvir increases several logs in the presence of the prevalent M31 polymorphism, the drug maintains

adequate activity against HCV genotype 2. (Wang, 2014) Although approved by regulatory authorities in some regions, daclatasvir is not approved by the FDA for use in the United States at this time. For patients who require treatment but cannot tolerate RBV, a discussion with a practitioner with expertise in the treatment of HCV infection is recommended prior to the use of approved RBV-free DAA combinations for HCV genotype 2 infection.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 2.

PEG-IFN and RBV for 24 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or ledipasvir-containing regimens

Rating: Class III, Level A

PEG-IFN 2a (180 µg weekly) or PEG-IFN 2b (1.5 µg/kg weekly) plus RBV (800 mg daily) for 24 weeks was compared with sofosbuvir (400 mg daily) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) in the FISSION trial. (Lawitz, 2013a) The SVR12 rate achieved with PEG-IFN and RBV was lower than that achieved with sofosbuvir and RBV overall (78% and 95%, respectively) and in the subgroups of patients with or without cirrhosis. Safety and tolerability of PEG-IFN and RBV was inferior to that observed with sofosbuvir and RBV, with greater frequency of reported adverse events and laboratory abnormalities and a higher rate of treatment discontinuation owing to adverse events. Further, therapy with PEG-IFN and RBV is 12 weeks longer than that with sofosbuvir plus RBV.

Because of its poor activity in vitro and in vivo, boceprevir should not be used as therapy for patients with HCV genotype 2 infection. Although telaprevir plus PEG-IFN and RBV has antiviral activity against HCV genotype 2, (Foster, 2011) the additional adverse effects and longer duration of therapy required do not support use of this regimen. Similarly, although ledipasvir has adequate activity against HCV genotype 2, this is lost in the presence of the highly prevalent M31 polymorphism and thus is not recommended for treatment of HCV genotype 2 infection. (Nakamoto, 2014)

III. Genotype 3

Recommended regimen for treatment-naive patients with HCV genotype 3 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV

genotype 3 infection.

Rating: Class I, Level B

The VALENCE study, which enrolled patients with genotype 2 or 3 HCV infection, assessed the efficacy and safety of sofosbuvir (400 mg daily) plus weight-based RBV for 24 weeks. This trial included 250 treatment-naive (42%) and -experienced (58%) subjects with HCV genotype 3 infection. The overall SVR12 rate was 84% and was higher among treatment-naive than -experienced patients (93% vs 77%, respectively). (Zeuzem, 2014) These results suggest that higher response rates can be achieved with a 24-week duration of sofosbuvir plus RBV than those reported for HCV genotype 3–infected participants receiving 12- or 16-week regimens in the FISSION (Lawitz, 2013a) (12 weeks, SVR12 rate: 63%), POSITRON, (Jacobson, 2013c) (12 weeks, SVR 12 rate: 61%) and FUSION (12 weeks, SVR12 rate: 30%; 16 weeks, SVR12 rate: 62%) trials. The primary reason for the higher SVR rate with extended therapy among treatment-naive patients was a reduction in the relapse rate from 40% to 5%. In a subanalysis, response rates were similarly high among those with (n=45) and without (n=100) cirrhosis (92% and 93%, respectively).

Alternative regimens for treatment-naive patients with HCV genotype 3 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an acceptable regimen for IFN-eligible, treatment-naive patients with HCV genotype 3 infection.

Rating: Class IIa, Level A

The combination of sofosbuvir plus PEG-IFN and RBV was evaluated in patients with HCV genotype 3 infection. In 2 phase II clinical trials, PROTON and ELECTRON, 38 of 39 (97%) treatment-naive patients with HCV genotype 3 infection achieved SVR with sofosbuvir plus PEG-IFN (4-12 weeks of therapy) and RBV. (Gane, 2013b) For many patients with HCV genotype 3 infection, the adverse effects and increased monitoring requirements of PEG-IFN make this less acceptable than the recommended regimen of sofosbuvir plus weight-based RBV. However, the shortened treatment period may be of interest to some.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 3 infection.

PEG-IFN and RBV for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with genotype 3 HCV infection.

Rating: Class III, Level A

Although the combination of PEG-IFN and RBV is an FDA-approved regimen for HCV genotype 3 infection, its less acceptable adverse effect profile, need for more intensive monitoring, and overall lower efficacy make it less desirable than the recommended regimen.

Because of their limited in vitro and in vivo activity against HCV genotype 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for patients with HCV genotype 3 infection.

Very limited phase II data are available from a single-center study (ELECTRON-II), which examined ledipasvir/sofosbuvir with (n=26) or without (n=25) RBV for 12 weeks in treatment-naive patients with HCV genotype 3 infection, 15% of whom had cirrhosis. All 26 (100%) patients in the RBV-containing arm achieved SVR12 compared with 16 of 25 (64%) of those in the RBV-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 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, 2013b)

ALLY 3 is a phase III study of the investigational once-daily nonstructual protein 5A (NS5A) inhibitor daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks; the study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, and in treatment-naive patients with cirrhosis (Metavir F4), 58% achieved SVR12. (Nelson, 2014) Although approved by regulatory authorities in some regions, daclatasvir is not available for use in the United States at this time.

IV. Genotype 4

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 4 infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

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

(25 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class I, Level B

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIa, Level B

PEARL-I was an open-label phase IIb study that included a cohort of 86 treatment-naive patients with HCV genotype 4 infection with or without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir with or without weight-based RBV. SVR12 rates were 100% (42/42) in the group receiving RBV and 90.9% (40/44) in the group not receiving RBV. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events. (Pol, 2014)

Several studies support the use of sofosbuvir and RBV in treatment-naive patients with HCV genotype 4 infection. In a small study of Egyptian patients in the United States treated with sofosbuvir plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]), SVR12 was achieved in 79% (11/14) and 100% (14/14) of treatment-naive patients treated for 12 weeks and 24 weeks, respectively. (Ruane, 2014) In a phase II study in Egypt, patients with HCV genotype 4 infection received daily sofosbuvir plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks or 24 weeks; among treatment-naive patients, SVR12 rates were 84% (21/25) and 92% (22/24), respectively. (Esmat, 2014) PHOTON-2, an open-label study of HIV/HCV-coinfected patients, included 31 treatment-naive patients with HCV genotype 4 infection who received daily sofosbuvir plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 24 weeks. In this study, 84% of patients (26/31) achieved SVR12. (Molina, 2014)

The SYNERGY trial is an open-label study evaluating 12 weeks of ledipasvir/sofosbuvir in 21 HCV genotype 4–infected patients, of whom 60% were treatment-naive and 43% had advanced fibrosis (Metavir F3 or F4). One patient took the first dose and then withdrew consent. In an interim analysis in which 20 patients had completed posttreatment week 12 follow-up, SVR12 rate was 95% by intention-to-treat analysis and 100% by per-protocol analysis. (Kapoor, 2014)

Alternative regimens for treatment-naive patients with HCV genotype 4 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.

Rating: Class II, Level B

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

In the phase III NEUTRINO trial, (Lawitz, 2013a) 28 treatment-naive patients with HCV genotype 4 infection were treated with sofosbuvir (400 mg daily) plus PEG-IFN 2a (180 µg weekly) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks. Of the 28 patients with HCV genotype 4 infection, 27 (96%) achieved SVR12. The single patient who did not achieve SVR had cirrhosis and had a relapse after therapy. The adverse event profile was similar to that associated with PEG-IFN and RBV therapy.

There are limited clinical data to date to support the use of the combination of 12 weeks of daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75kg] to 1200 mg [?75mg]) in HCV genotype 4–infected patients, although studies are planned. Given the demonstrated activity of simeprevir in vitro and in vivo against HCV genotype 4, this combination may be considered as an alternative regimen. The open-label phase III RESTORE trial assessed the efficacy of simeprevir in combination with PEG-IFN and RBV in 107 patients with HCV genotype 4 infection, including 35 treatment-naive patients. In these treatment-naive patients, daily simeprevir (150 mg) for 12 weeks in combination with PEG-IFN and RBV for 24 weeks to 48 weeks (by response-guided therapy) produced an SVR in 83% (29 of 35). (Moreno, 2013a) These results are comparable to SVR rates observed with similar regimens in patients with HCV genotype 1 infection, suggesting that efficacy of sofosbuvir plus simeprevir for HCV genotype 4 infection may be roughly in line with the SVR rates of patients with HCV genotype 1 infection shown in the COSMOS trial. This combination has been approved in Europe for patients with HCV genotype 4 infection but is not FDA-approved for use in the United States.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 4 infection.

PEG-IFN and RBV with or without simeprevir for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

PEG-IFN and RBV for 48 weeks was the previously recommended regimen for patients with HCV genotype 4 infection. (Ghany, 2009); (AASLD/IDSA/IAS-USA, 2014) Adding sofosbuvir (400 mg daily) to PEG-IFN and RBV increases response rates and markedly shortens therapy with no apparent additional adverse effects. The addition of simeprevir to PEG-IFN and RBV increases response rates but has inferior SVR rates to the other available regimens and requires a longer duration of PEG-IFN and RBV, which increases the risk of adverse events and thus is no longer recommended. (Moreno, 2013b)

Because of their limited activity against genotype 4 HCV in vitro and in vivo, boceprevir and telaprevir should not be used as therapy for patients with HCV genotype 4 infection.

V. Genotype 5 and 6

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

Recommended regimen for treatment-naive patients with HCV genotype 5 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is recommended for treatment-naive patients with HCV genotype 5 infection.

Rating: Class IIa, Level B

In the phase III NEUTRINO trial, (Lawitz, 2013a) treatment-naive 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 RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks. All 6 patients with HCV genotype 6 and the 1 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 and RBV therapy.

Alternative regimen for treatment-naive patients with HCV genotype 5 infection.

Weekly PEG-IFN plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 48 weeks is an alternative regimen for IFN-eligible, treatment-naive patients with HCV genotype 5 infection.

Rating: Class IIb, Level A

PEG-IFN and RBV for 48 weeks was the previously recommended regimen for patients infected with HCV

genotype 5, but the availability of recommended regimens that substantially reduce exposure to IFN and RBV make this regimen less appealing.

Recommended regimen for treatment-naive patients with HCV genotype 6 infection.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 6 infection.

Rating: Class IIa, Level B

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (exception 6e). (Wong, 2013); (Kohler, 2014) A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with HCV genotype 6 infection. Twenty-five patients (92% treatment naive) who were primarily Asian (88%) had infection from 7 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.

Alternative regimen for treatment-naive patients with HCV genotype 6 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative regimen for IFN-eligible, treatment-naive patients with HCV genotype 6 infection.

Rating: Class IIa, Level B

In the phase III NEUTRINO trial, (Lawitz, 2013a) treatment-naive 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 RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks. All 6 patients with HCV genotype 6 and the 1 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 and RBV therapy.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 5 or 6 infection.

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

Because of their limited activity against genotypes 5 and 6 HCV in vitro and in vivo, boceprevir and telaprevir should not be used as therapy for patients with HCV genotype 5 or 6 infection.

Initial Treatment Table: Drug Interactions With Direct-Acting Antivirals and Selected Concomitant Medications

Concomitant Medications	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbu
Acid-reducing agents*	X	X		
Alfuzosin/tamsulosin		X		
Anticonvulsants	X	X	X	X
Antiretrovirals*	Coming Soon	Coming Soon	Coming Soon	tipranavi
Azole antifungals*		X	X	
Buprenorphine/naloxone		X		
Calcineurin inhibitors*		X	X	
Calcium channel blockers*		X	X	
Cisapride		X	X	
Digoxin	X		X	
Ergot derivatives		X		
Ethinyl estradiol–containing products		X		
Furosemide		X		
Gemfibrozil		X		
Glucocorticoids		X (inhaled, intranasal	X	
Herbals				
St. John’s wort		X	X	X
Milk thistle	X		X	
Macrolide antimicrobials*			X	
Other antiarrythmics*		X	X	
Phosphodiesterase type 5 inhibitors*		X	X	
Pimozide		X		
Rifamycin antimicrobials*	X	X	X	X
Salmeterol		X		
Sedatives*		X	X	
Simeprevir	X			
Statins*	X	X	X	

***Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.**

Complete revision made on this section on December 19, 2014.

Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection or Who Experienced Relapse after Prior PEG/RBV Therapy, by HCV Genotype

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Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection or Who Experienced Relapse after Prior PEG/RBV Therapy, by HCV Genotype

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1a infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks* is recommended for treatment-naive patients with HCV genotype 1a infection.
***See text for further detail on** length of treatment

Rating: Class I, Level A

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1a infection.

Rating: Class IIa, Level B

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 1b infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks* is recommended for treatment-naive patients with HCV genotype 1b infection.
***See text for further detail on length of treatment**

Rating: Class I, Level A

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 recommended for treatment-naive patients with HCV genotype 1b infection. **Rating:** Class I, Level A
The addition of weight-based RBV (1000 mg [<75kg] to 1200 mg [≥75 kg]) is recommended in patients with cirrhosis.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) is recommended for treatment-naive patients with HCV genotype 1b infection.

Rating: Class IIa, Level B

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 1.*

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks.

Rating: Class IIb, Level A

PEG-IFN and RBV with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 weeks to 48 weeks.

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

*See sections on HIV/HCV coinfection, decompensated cirrhosis, liver transplantation, and renal impairment.

Recommended regimen for treatment-naive patients with HCV genotype 2 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

Extending treatment to 16 weeks is recommended in patients with cirrhosis.

Rating: Class IIb, Level C

Alternative regimens for treatment-naive patients with HCV genotype 2 infection.

None.

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 2.

PEG-IFN and RBV for 24 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or ledipasvir-containing regimens

Rating: Class III, Level A

Recommended regimen for treatment-naive patients with HCV genotype 3 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 3 infection.

Rating: Class I, Level B

Alternative regimens for treatment-naive patients with HCV genotype 3 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an acceptable regimen for IFN-eligible, treatment-naive patients with HCV genotype 3 infection.

Rating: Class IIa, Level A

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 3 infection.

PEG-IFN and RBV for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with genotype 3 HCV infection.

Rating: Class III, Level A

Three options with similar efficacy in general are recommended for treatment-naive patients with HCV genotype 4 infection (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class I, Level B

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg

[≥75 kg]) for 24 weeks is recommended for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIa, Level B

Alternative regimens for treatment-naive patients with HCV genotype 4 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.

Rating: Class II, Level B

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is an acceptable regimen for treatment-naive patients with HCV genotype 4 infection.

Rating: Class IIb, Level B

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 4 infection.

PEG-IFN and RBV with or without simeprevir for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

Recommended regimen for treatment-naive patients with HCV genotype 5 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is recommended for treatment-naive patients with HCV genotype 5 infection.

Rating: Class IIa, Level B

Alternative regimen for treatment-naive patients with HCV genotype 5 infection.

Weekly PEG-IFN plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 48 weeks is an alternative regimen for IFN-eligible, treatment-naive patients with HCV genotype 5 infection.

Rating: Class IIb, Level A

Recommended regimen for treatment-naive patients with HCV genotype 6 infection.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for treatment-naive patients with HCV genotype 6 infection.

Rating: Class IIa, Level B

Alternative regimen for treatment-naive patients with HCV genotype 6 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative regimen for IFN-eligible, treatment-naive patients with HCV genotype 6 infection.

Rating: Class IIa, Level B

The following regimens are NOT recommended for treatment-naive patients with HCV genotype 5 or 6 infection.

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

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 supporting the best treatment for each patient and the corresponding confidence in the recommendation varies as does the strength of the recommendation, and is rated in the same manner as the section on initial treatment of treatment-naive patients (Methods Table 2). In addition, when treatment differs for a particular group (eg, those infected with various genotypes) specific recommendations are given. A regimen is classified as "Recommended" when it is favored for most patients or "Alternative" when it might be optimal in a particular subset of patients in that category. When a treatment is clearly inferior or should not be used, it is classified as "Not Recommended." 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**),** post–liver transplant **HCV infection, and those with severe** renal impairment **or end-stage renal disease are addressed in other sections of the Guidance.**

When several regimens are offered at the same recommendation level, choice of regimen should be based on patient-specific data, including potential drug interactions. As always, patients receiving direct-acting antiviral (DAA) therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if RBV is included in the regimen. (See Monitoring Section)

I. Genotype 1

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

The introduction of DAAs into HCV treatment regimens increased the risk of drug interactions with other concomitant medications used by patients, 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. In particular, the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) has a potential interaction with acid-suppressing medications, for example proton pump inhibitors, which may result in decreased absorption of ledipasvir and lower exposures. Because of over-the-counter access to acid-suppressing medications, a comprehensive assessment of all prescribed and over-the-counter medications is recommended prior to

initiating treatment. If possible, acid-suppressing medications should be held prior to and during the HCV treatment period to optimize ledipasvir exposure. For patients in whom interruption of acid suppression is not possible, dosing of acid suppressants is recommended per the prescribing information.

Three options with similar efficacy in general are recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Three options with similar efficacy in general are recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

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 recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Recommended regimens for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients with HCV genotype 1a infection and for 12 weeks for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients with HCV genotype 1 infection, regardless of subtype, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Ledipasvir/sofosbuvir has been evaluated in patients with and without cirrhosis in whom prior treatment with PEG-IFN and RBV, with or without HCV protease inhibitors (telaprevir or boceprevir), failed. In the ION-2 study, patients who had not responded to prior PEG-IFN and RBV were treated with ledipasvir/sofosbuvir. This regimen was given for 12 weeks or 24 weeks, with or without RBV. 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 and RBV, 33 of 35 (94%) achieved a sustained virologic response (SVR) after treatment with ledipasvir/sofosbuvir alone, and 38 of 38 (100%) patients achieved SVR after treatment with ledipasvir/sofosbuvir and RBV. (Afdhal, 2014b) This regimen was well tolerated in all groups, with no serious adverse events reported in the 12-week regimen with or without RBV. 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 RBV.

In SIRIUS, a double-blind placebo-controlled French study, patients with cirrhosis who did not respond to PEG-IFN and RBV plus telaprevir or boceprevir, were randomized to receive placebo for 12 weeks followed by ledipasvir/sofosbuvir plus RBV 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 RBV 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-naive 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 RBV for 12 weeks; no difference in SVR was detected between the latter 2 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 RBV. (Bourliere, 2014a); (Bourliere, 2014b)

The daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 mg]) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV) has been investigated for treatment of patients with HCV genotype 1 in whom previous PEG-IFN and RBV therapy failed. (Zeuzem, 2014) In this phase III trial, patients who did not have cirrhosis who were treated for a total of 12 weeks had a high overall rate of response with 286 of 297 (96.3%) patients achieving SVR at 12 weeks (SVR12). Response rates did not differ substantially when stratified by genotype subtype (genotype 1a, 96.0% [166/173]; genotype 1b, 96.7% [119/123]) or kinetics of prior response to PEG-IFN and RBV (relapse, 95.3% [82/86]; partial response, 100% [139/146]; 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 and RBV failed, were treated with paritaprevir/ritonavir/ombitasvir plus dasabuvir with or without weight-based RBV for 12

weeks. (Andreone, 2014) SVR rates were high in both arms: 100% (91/91) in the RBV-free arm and 96.6% (85/88) in the RBV-containing arm, supporting the recommendation that this regimen may be used without RBV for patients with HCV genotype 1b.

In the TURQUOISE-II study, patients with CTP class A cirrhosis were treated with paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV for 12 weeks or 24 weeks. (Poordad, 2014) Of the 380 patients enrolled in this study, prior PEG-IFN and RBV therapy had failed in 220. 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 and RBV 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 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%).

COSMOS is a phase IIa randomized trial in which participants received sofosbuvir (400 mg once daily) plus simeprevir (150 mg once daily) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks or 24 weeks. (Lawitz, 2013a); (Jacobson, 2013b) Of the 80 patients with a null response to PEG-IFN and RBV treatment who had fibrosis (Metavir stage ?F2) included in this trial, 79% to 96% achieved SVR (79%-96% in the RBV-containing arms and 93% in both RBV-free arms). Although benefit from RBV is not apparent from these results, this study was not powered to show noninferiority of RBV-free regimens. Preliminary data from large prospective observational cohort studies confirm high SVR rates (>80%) in patients treated with sofosbuvir plus simeprevir in clinical practice. (Jensen, 2014); (Dieterich, 2014a) These studies also demonstrate higher rates of virologic failure in patients with HCV genotype 1a infection than patients with HCV genotype 1b infection, but additional data have not been provided regarding the contribution of treatment duration (12 weeks vs 24 weeks), use of RBV, and presence of the Q80K polymorphism to observed rates of HCV treatment failure in genotype 1a infection. In patients with cirrhosis, high SVR rates (96%) occurred in patients treated for a longer duration, supporting the recommendation that these patients be treated for 24 weeks. (Janssen Therapeutics, 2013); (Lawitz, 2014b)

Recommended regimen for patients without advanced fibrosis, in whom a previous sofosbuvir-containing regimen has failed.

Based on the limited data available for effective therapy, patients without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider treatment within clinical trial settings.

Rating: Class IIb, Level C

Recommended regimen for patients who have advanced fibrosis, in whom a previous sofosbuvir-containing regimen has failed.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients who have cirrhosis, in whom a previous sofosbuvir-containing regimen has failed.

Rating : Class IIa, Level C

Emerging data suggest that approximately 10% to 15% of patients with HCV genotype 1 infection treated for 12 weeks with the combination of simeprevir plus sofosbuvir will experience treatment failure, typically owing to viral relapse after discontinuing therapy. Treatment failure appears to be more common in persons infected with HCV genotype 1a and those with cirrhosis. Data from the COSMOS study indicate that treatment failure following simeprevir plus sofosbuvir is associated with resistance to simeprevir with cross-resistance to other HCV nonstructural protein 3/4A (NS3/4A) protease inhibitors such as paritaprevir, telaprevir, and boceprevir. On the other hand, sofosbuvir resistance–associated variants were not observed in the COSMOS trial and are likely to be rare in clinical practice.

To date, clinical experience and trial data on the retreatment of such patients is 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 has been reported.

Retreatment with ledipasvir/sofosbuvir in subjects with HCV genotype 1, with or without cirrhosis, in whom a sofosbuvir-containing regimen failed has been evaluated in 2 small pilot studies utilizing ledipasvir/sofosbuvir for 12 weeks.

With prior failures of 24 weeks of sofosbuvir plus RBV, high SVR rates were noted when patients were retreated with ledipasvir/sofosbuvir for 12 weeks. (Osinusi, 2014a) Ledipasvir/sofosbuvir plus RBV has also been evaluated in subjects in whom prior treatment with sofosbuvir plus PEG-IFN and RBV or sofosbuvir and RBV failed. In this pilot study, viral response at the end of treatment is promising, however, SVR12 data are pending. (Wyles, 2014a)

In the absence of data, for patients in whom prior treatment with simeprevir plus sofosbuvir failed, strong consideration should be given to enrolling them in clinical trials. For patients with minimal liver disease, consideration should be given to deferral of retreatment pending the availability of data. In patients who require retreatment more urgently, based on emerging data and the expected pattern of HCV drug resistance, patients in whom simeprevir plus sofosbuvir does not result in a cure may be treated with ledipasvir/sofosbuvir with or without RBV for 24 weeks.

Recommended regimen for patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for retreatment of patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class I, Level A

Two options with similar efficacy in general are recommended for patients with cirrhosis

who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and an HCV protease inhibitor regimen has failed.

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended for retreatment of patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class I, Level A

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class IIa, Level B

The safety and efficacy of ledipasvir/sofosbuvir were evaluated in subjects in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus PEG-IFN and RBV 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 presence of cirrhosis or NS5A resistance–associated variants at baseline were the major reasons for the higher relapse rate in the 12-week arm. Thus, patients with cirrhosis in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen 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 RBV for 12 weeks.

The following regimens are NOT recommended for patients with HCV genotype 1 infection, in whom prior treatment that included an HCV protease inhibitor has failed.

Any regimen containing PEG-IFN, including

Simeprevir, PEG-IFN, and RBV

Sofosbuvir, PEG-IFN, and RBV

Telaprevir or boceprevir, PEG-IFN, and RBV

PEG-IFN and RBV alone

Rating: Class IIb Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Any interferon-free regimen containing an HCV protease inhibitor

Simeprevir

Paritaprevir

Rating: Class IIb, Level A

Simeprevir was combined with PEG-IFN and RBV in patients in whom previous PEG-IFN and RBV dual therapy failed, in the phase IIb ASPIRE trial. (Zeuzem, 2013a); (Janssen Therapeutics, 2013); (www.fda.gov; package insert) SVR24 after 48 total weeks of therapy in the simeprevir 150 mg per day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17). Based on relatively poor response, need for prolonged therapy, and poor tolerability, this treatment is no longer recommended.

Sofosbuvir combined with PEG-IFN and RBV has high efficacy in treatment-naive patients but has not been studied prospectively in the treatment-experienced population. Based on limited prospective data and poor tolerability of PEG-IFN–based regimens, this treatment is no longer recommended.

Triple therapy with boceprevir plus PEG-IFN and RBV for 48 weeks may result in SVR for up to 52% of patients with a partial response to previous PEG-IFN and RBV treatment (RESPOND 2; [Bacon, 2011]), and up to 38% of patients with a prior null response (PROVIDE; [Di Bisceglie, 2013]). Similarly, telaprevir plus PEG-IFN and RBV resulted in an SVR24 rate of 54% to 59% among patients with a partial response to previous treatment and an SVR24 rate of 29% to 33% among those with a prior null response (REALIZE; [Zeuzem, 2011]). Because of the relatively poor efficacy, need for prolonged therapy (48 weeks), and poor tolerability, these regimens are no longer recommended.

Monotherapy with PEG-IFN, RBV, or any of the available DAAs is ineffective; further, DAA monotherapy leads to rapid selection of resistant variants.

II. Genotype 2

Recommended regimen for patients with HCV genotype 2 infection, in whom prior PEG-IFN and RBV treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks to 16 weeks is recommended for patients with HCV

genotype 2 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

High SVR12 rates were demonstrated in patients with HCV genotype 2 in whom prior treatment with PEG-IFN and RBV failed who were retreated with 12 weeks of sofosbuvir plus RBV. Limited data are available for treatment-experienced patients with HCV genotype 2 infection and cirrhosis; however, in the FUSION study, numerically higher SVR12 rates were seen with extension of therapy from 12 weeks (60%) to 16 weeks (78%). (Jacobson, 2013b) In contrast, the VALENCE trial found high SVR12 rates among HCV genotype 2–infected persons with cirrhosis after only 12 weeks of sofosbuvir plus RBV (88%). (Zeuzem, 2013b) Thus, definitive recommendations on the appropriate duration of sofosbuvir and RBV for treatment-experienced, HCV genotype 2–infected persons with cirrhosis cannot be made at this time. The decision to extend therapy to 16 weeks should be made on a case-by-case basis.

Alternative regimen for patients in whom previous PEG-IFN and RBV treatment failed who have HCV genotype 2 infection and are eligible to receive IFN.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative for patients in whom previous PEG-IFN and RBV treatment failed who have HCV genotype 2 infection and are eligible to receive IFN.

Rating: Class IIa Level B

In recognition of the potential limitations of sofosbuvir plus RBV in harder-to-treat, HCV genotype 2–infected patients with a prior treatment failure, particularly those with cirrhosis, combination therapy with PEG-IFN has been studied. The LONESTAR-2 trial (an open-label, single-site, single-arm, phase II trial) evaluated PEG-IFN (180 ?g weekly), sofosbuvir (400 mg daily), and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg] daily in 2 divided doses for 12 weeks) in treatment-experienced patients with HCV genotype 2 or 3. (Lawitz, 2014a) Cirrhosis was present at baseline in 61% of patients. SVR12 was achieved in 22 of 23 (96%) persons with HCV genotype 2 infection. For patients with and without cirrhosis, SVR occurred in 13 of 14 (93%) and 9 of 9 (100%), respectively. Despite the limitations of this small study and accounting for the potential challenges inherent with IFN therapy, sofosbuvir plus PEG-IFN and RBV is an alternative 12-week regimen for HCV genotype 2–infected patients with cirrhosis.

The following regimens are NOT recommended for patients with HCV genotype 2 infection in whom prior HCV therapy with PEG-IFN and RBV has failed.

PEG-IFN and RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg)

Rating: Class III, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of HCV genotype 2 infection. However, there is in vitro and in vivo evidence that simeprevir has activity against HCV genotype 2. Although PEG-IFN plus RBV has been the mainstay of treatment for HCV genotype 2, it requires a longer duration of therapy, is less efficacious, and has more adverse effects than the regimen recommended above.

III. Genotype 3

Recommended regimen for patients with HCV genotype 3 infection in whom prior PEG-IFN and RBV treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment of HCV genotype 3 infection in patients in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level B

The phase III FUSION trial compared 12 weeks (n=103) with 16 weeks (n=98) of daily sofosbuvir (400 mg) and weight-based RBV in patients with HCV genotype 2 or 3 in whom previous PEG-IFN and RBV therapy failed. Of all patients, 63% had HCV genotype 3 and 34% had cirrhosis. Because persons who had experienced prior relapses to IFN-based therapy accounted for 75% of patients, the number of patients with a prior nonresponse in the study was limited. The SVR rate for patients with HCV genotype 3 in the 12-week arm was 30% (19% among patients with cirrhosis and 37% among patients without cirrhosis). Extending therapy to 16 weeks increased the SVR rate to 62%.

Based on results from the FUSION study, the phase III multicenter, randomized, placebo-controlled VALENCE trial was amended to evaluate the effects of extending sofosbuvir plus RBV therapy to 24 weeks in all patients with HCV genotype 3. As with the FUSION study, most (65%) treatment-experienced patients had a relapse. The SVR12 rate after 24 weeks of therapy for treatment-experienced patients with HCV genotype 3 was 79% (60% among patients with cirrhosis and 87% in those without cirrhosis). The increased efficacy with 24 weeks of sofosbuvir plus RBV therapy across all fibrosis stages combined with a

favorable safety and tolerability profile supports the recommendation to use 24 weeks of sofosbuvir plus RBV for all HCV genotype 3–infected patients, despite the minimal number of patients studied to date. The response rate for HCV genotype 3–infected patients with cirrhosis treated for 24 weeks in the VALENCE trial (60%) was similar to that observed after 16 weeks of treatment in the FUSION trial (61%).

Alternate regimen for patients with HCV genotype 3 who are eligible to receive IFN, in whom prior PEG-IFN and RBV treatment has failed.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative for patients with HCV genotype 3 infection who are eligible to receive IFN, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa Level B

Choice of specific regimen may be influenced by previous or anticipated tolerance to PEG-IFN or by the presence of advanced fibrosis or cirrhosis. For most patients, the ease of administration and tolerability of sofosbuvir plus RBV will outweigh any potential benefit associated with the addition of PEG-IFN. However, for HCV genotype 3–infected patients who have cirrhosis, responses to sofosbuvir and RBV alone for 24 weeks were suboptimal.

In the LONESTAR-2 study, adding 12 weeks of PEG-IFN to the sofosbuvir and RBV regimen resulted in numerically higher response rates among persons with HCV genotype 3 than those obtained with sofosbuvir and RBV alone for 24 weeks. Of HCV genotype 3–infected patients with and without cirrhosis, 10 of 12 (83%) achieved SVR. Given the limited number of patients in this demographic in both the VALENCE and LONESTAR-2 studies, these differences in response rates should be interpreted with caution.

The following regimens are NOT recommended for patients with HCV genotype 3 infection in whom prior PEG-IFN and RBV treatment has failed.

PEG-IFN and RBV for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with HCV genotype 3 infection.

Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of HCV genotype 3 infection. Although PEG-IFN plus RBV has been the mainstay of treatment of HCV genotype 3 infection, it is less efficacious and has more adverse effects than the recommended regimens.

IV. Genotype 4

Data are limited to help guide decision making for patients infected with HCV genotype 4. Nonetheless, for patients in whom treatment is required, the following recommendations can be made.

Four options with similar efficacy in general are recommended for patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is an acceptable regimen for patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is recommended for retreatment of IFN-eligible patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

PEARL-I was an open-label phase IIb study that included a cohort of 49 treatment-experienced patients without cirrhosis with HCV genotype 4 infection who received 12 weeks of paritaprevir/ritonavir/ombitasvir with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]). In intention-to-treat analysis, SVR12 was achieved in 100% (41/41) of patients. This regimen was well tolerated with no serious adverse events reported. (Pol, 2014)

Sofosbuvir-based regimens have also shown efficacy in patients infected with HCV genotype 4. Sofosbuvir administered with PEG-IFN and RBV for 12 weeks was investigated in the phase III NEUTRINO trial. (Lawitz, 2013a) Of the 28 treatment-naive patients with HCV genotype 4 infection, 27 (96%) achieved SVR12. In a pilot study of treatment-experienced patients of Egyptian ancestry with HCV genotype 4 infection, patients were randomized to receive sofosbuvir and RBV for 12 weeks or 24 weeks. SVR12 rate was numerically higher in the 24-week arm (89% [24/27] in the 24-week arm vs 70% [19/27] in the 12-week arm), supporting the recommendation for longer treatment duration with a sofosbuvir and RBV regimen. (Esmat, 2014) In the SYNERGY trial, 20 patients with HCV genotype 4 were treated with ledipasvir/sofosbuvir for 12 weeks. Of these patients, 40% were treatment experienced and 40% had advanced fibrosis. Preliminary data support efficacy, with 95% achieving SVR12 in an intention-to-treat analysis. (Kapoor, 2014)

The following regimens are NOT recommended for patients with HCV genotype 4 infection in whom prior PEG-IFN and RBV treatment has failed.

PEG-IFN and RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

PEG-IFN and RBV for 48 weeks was previously recommended for patients with HCV genotype 4 infection. (AASLD/IDSA/IAS-USA, 2014) Adding sofosbuvir (400 mg daily) to PEG-IFN and RBV increases response rates and markedly shortens therapy with no apparent additional adverse effects. The addition of simeprevir to PEG-IFN and RBV increases response rates but has inferior SVR rates to the other available regimens and requires a longer duration of PEG-IFN and RBV, which increases the risk of adverse events and thus is no longer recommended. (Moreno, 2013b)

Because of their limited activity against HCV genotype 4 in vitro and in vivo, boceprevir and telaprevir should not be used as therapy for patients with HCV genotype 4 infection.

V. Genotype 5 and 6

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

Recommended regimen for patients with HCV genotype 5 infection in whom prior treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is recommended for patients with HCV genotype 5 infection in whom prior treatment has failed.

Rating: Class IIa, Level B

In the phase III NEUTRINO trial, (Lawitz, 2013a) treatment-naive 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 RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) for 12 weeks. All 6 patients with HCV genotype 6 and the 1 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 and RBV therapy.

Alternative regimen for patients with HCV genotype 5 infection in whom prior treatment has failed.

Weekly PEG-IFN plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 48 weeks is an alternative regimen for IFN-eligible patients with HCV genotype 5 infection in whom prior treatment has failed.

Rating: Class IIb, Level A

PEG-IFN and RBV for 48 weeks was the previously recommended regimen for patients infected with HCV genotype 5, but the availability of recommended regimens that substantially reduce exposure to IFN and RBV make this regimen less appealing.

Recommended regimen for patients with HCV genotype 6 infection in whom prior treatment has failed.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 6 infection in whom prior treatment has failed.

Rating: Class IIa, Level B

Ledipasvir has in vitro activity against most HCV genotype 6 subtypes (exception 6e). (Wong, 2013); (Kohler, 2014) A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with HCV genotype 6 infection. Twenty-five patients (92% treatment naive) who were primarily Asian (88%) had infection from 7 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.

Alternative regimen for patients with HCV genotype 6 infection in whom prior treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative regimen for patients with HCV genotype 6 infection in whom prior treatment has failed who are IFN-eligible.

Rating: Class IIa, Level B

In the phase III NEUTRINO trial, this regimen has been shown to have efficacy in a small number of patients with HCV genotype 6 infection (6 of 6 patients with SVR12). (Lawitz, 2013a)

The following regimens are NOT recommended for patients with HCV genotype 5 or 6 infection in whom prior treatment has failed.

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

Because of their limited activity against genotypes 5 and 6 HCV in vitro and in vivo, boceprevir and telaprevir should not be used as therapy for patients with HCV genotype 5 or 6 infection.

Complete revision made to this section on December 19, 2014.

Retreatment Box. Summary of Recommendations for Patients in Whom Previous Treatment Has Failed

Retreatment Box. Recommendations for Patients in Whom Previous Treatment Has Failed

Three options with similar efficacy in general are recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Three options with similar efficacy in general are recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

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

weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

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 recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1b infection who do not have cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Recommended regimens for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1a or 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients with HCV genotype 1a infection and for 12 weeks for patients with HCV genotype 1b infection who have compensated cirrhosis, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients with HCV genotype 1 infection, regardless of subtype, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Recommended regimen for patients without advanced fibrosis, in whom a previous sofosbuvir-containing regimen has failed.

Based on the limited data available for effective therapy, patients without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider treatment within clinical trial settings.

Rating: Class IIb, Level C

Recommended regimen for patients who have advanced fibrosis, in whom a previous sofosbuvir-containing regimen has failed.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients who have cirrhosis, in whom a previous sofosbuvir-containing regimen has failed.

Rating : Class IIa, Level C

Recommended regimen for patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for retreatment of patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class I, Level A

Two options with similar efficacy in general are recommended for patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and an HCV protease inhibitor regimen has failed.

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended for retreatment of patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class I, Level A

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of patients with cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class IIa, Level B

The following regimens are NOT recommended for patients with HCV genotype 1 infection, in whom prior treatment that included an HCV protease inhibitor has failed.

Any regimen containing PEG-IFN, including

Simeprevir, PEG-IFN, and RBV

Sofosbuvir, PEG-IFN, and RBV

Telaprevir or boceprevir, PEG-IFN, and RBV

PEG-IFN and RBV alone

Rating: Class IIb Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Any interferon-free regimen containing an HCV protease inhibitor

Simeprevir

Paritaprevir

Rating: Class IIb, Level A

Recommended regimen for patients with HCV genotype 2 infection, in whom prior PEG-IFN and RBV treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks to 16 weeks is recommended for patients with HCV genotype 2 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level A

Alternative regimen for patients in whom previous PEG-IFN and RBV treatment failed who have HCV genotype 2 infection and are eligible to receive IFN.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative for patients in whom previous PEG-IFN and RBV treatment failed who have HCV genotype 2 infection and are eligible to receive IFN.

Rating: Class IIa Level B

The following regimens are NOT recommended for patients with HCV genotype 2 infection in whom prior HCV therapy with PEG-IFN and RBV has failed.

PEG-IFN and RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg)

Rating: Class III, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Recommended regimen for patients with HCV genotype 3 infection in whom prior PEG-IFN and RBV treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for treatment of HCV genotype 3 infection in patients in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class I, Level B

Alternate regimen for patients with HCV genotype 3 who are eligible to receive IFN, in whom prior PEG-IFN and RBV treatment has failed.

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative for patients with HCV genotype 3 infection who are eligible to receive IFN, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa Level B

The following regimens are NOT recommended for patients with HCV genotype 3 infection in whom prior PEG-IFN and RBV treatment has failed.

PEG-IFN and RBV for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens should not be used for patients with HCV genotype 3 infection.

Rating: Class III, Level A

Four options with similar efficacy in general are recommended for patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed (listed in alphabetic order; see text).

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is an acceptable regimen for patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is recommended for retreatment of IFN-eligible patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for retreatment of patients with HCV genotype 4 infection, in whom prior PEG-IFN and RBV treatment has failed.

Rating: Class IIa, Level B

The following regimens are NOT recommended for patients with HCV genotype 4 infection in whom prior PEG-IFN and RBV treatment has failed.

PEG-IFN and RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Recommended regimen for patients with HCV genotype 5 infection in whom prior treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is recommended for patients with HCV genotype 5 infection in whom prior treatment has failed.

Rating: Class IIa, Level B

Alternative regimen for patients with HCV genotype 5 infection in whom prior treatment has failed.

Weekly PEG-IFN plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 48 weeks is an alternative regimen for IFN-eligible patients with HCV genotype 5 infection in whom prior treatment has failed.

Rating: Class IIb, Level A

Recommended regimen for patients with HCV genotype 6 infection in whom prior treatment has failed.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for patients with HCV genotype 6 infection in whom prior treatment has failed.

Rating: Class IIa, Level B

Alternative regimen for patients with HCV genotype 6 infection in whom prior treatment has failed.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG-IFN for 12 weeks is an alternative regimen for patients with HCV genotype 6 infection in whom prior treatment has failed who are IFN-eligible.

Rating: Class IIa, Level B

The following regimens are NOT recommended for patients with HCV genotype 5 or 6 infection in whom prior treatment has failed.

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

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 3 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.

Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy.

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)**
- **Thyroid-stimulating hormone (TSH) if IFN is used**
- **Calculated glomerular filtration rate (GFR)**

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

- **HCV genotype and subtype**
- **Quantitative HCV viral load, except in the circumstance that a quantitative viral load will influence duration of therapy**

Rating for all statements above: Class I, Level C

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 RBV) is recommended as clinically indicated.

Prompt discontinuation of therapy is recommended for any a) 10-fold increase in alanine aminotransferase (ALT) activity at week 4; or b) any increase in ALT of less than 10-fold at week 4 that is accompanied by any weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or international normalized ratio. 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.

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

Recommendations for discontinuation of treatment because of lack of efficacy.

If quantitative HCV viral load 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 RBV.

Women of childbearing age should be cautioned not to become pregnant while receiving RBV-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 RBV.

Rating: Class I, Level C

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

Rating: Class I, Level C

The following regimens are NOT recommended with regard to pregnancy-related issues.

Treatment with RBV is NOT recommended for pregnant women or for women who are unwilling to adhere to use of adequate contraception, including those who are receiving RBV themselves or are sexual partners of male patients who are receiving RBV.

Rating: Class III, Level C

Female patients who have received RBV and sexual partners of male patients who have received RBV should NOT become pregnant for at least 6 months after stopping RBV.

Rating: Class III, 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 **Whom and When to Treat**].

Prior to starting treatment, patients should be evaluated for potential drug-drug interactions with selected antiviral medications (eg, **http://www.hep-druginteractions.org/**). Patients should also be educated on the proper administration of medications (eg, dose of medications, frequency of taking medicines, with or without food, missed doses, expected duration, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment.

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.

The availability of IFN-free treatment regimens has simplified hepatitis C therapy by allowing shorter-duration, all-oral therapy for most patients. However, PEG-IFN and RBV–based regimens are beneficial for selected patients, and these require specific monitoring for the toxic effects (eg, anemia or neutropenia) associated with PEG-IFN or RBV use. (RBV prescribing information, 2014a); (PEG-IFN prescribing information, 2014b) In patients with a history of cardiovascular disease, RBV dose reduction to 600 mg per day is recommended for those with hemoglobin (Hgb) level below 10 g/dL and discontinuation is recommended for those with Hgb below 8.5 g/dL. In addition, although the newer all-oral regimens are generally well tolerated, adverse effects do occur. Expansion of therapy into a large population of patients may reveal toxic effects that are not apparent in registration trials. Furthermore, drug-drug interactions are possible.

RBV 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 2 reliable forms of effective contraception during treatment and for a period of 6 months thereafter. It is recommended that the health care practitioner document the discussion of potential teratogenic effects of RBV 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 RBV-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.

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 ration (INR) is recommended.

Rating: Class I, Level C

Surveillance for hepatocellular carcinoma with ultrasound testing every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).

Rating: Class I, Level C

Endoscopic surveillance 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

The following monitoring is NOT recommended during therapy.

Routine monitoring for HCV drug resistance–associated variants during therapy is NOT recommended.

Rating: Class III, 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.

A small number of 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 1 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 variants (RAVs) results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. The presence

of baseline RAVs does not preclude achieving an SVR with a combination direct-acting antiviral regimen. Furthermore, RAVs are often not detectable with routine (population sequencing) detection methods, nor with more sensitive tests of HCV variants, 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 nucleotide polymerase inhibitors (eg, sofosbuvir), may overcome the presence of resistance to 1 or more antivirals. Certain telaprevir and boceprevir RAVs may impact simeprevir activity in vitro. However, with the exception of testing for Q80K polymorphism at baseline in patients with HCV genotype 1a infection before treatment with simeprevir plus PEG-IFN and RBV, testing for RAVs before repeat antiviral treatment is not routinely recommended. If in doubt, 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 testing 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

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving an SVR among adherent, immunologically competent, treatment-naive patients with compensated liver disease generally exceeds 90%. Of patients who achieved an SVR with PEG-IFN and RBV 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.

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.

Changes made on this section on December 19, 2014.

Monitoring Box. Summary of the Recommendations for Monitoring Patients Who Are Starting HCV Treatment, Are On Treatment, Or Have Completed Therapy

Monitoring Box. 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.

Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy.

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)**
- **Thyroid-stimulating hormone (TSH) if IFN is used**
- **Calculated glomerular filtration rate (GFR)**

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

- **HCV genotype and subtype**
- **Quantitative HCV viral load, except in the circumstance that a quantitative viral load will influence duration of therapy**

Rating for all statements above: Class I, Level C

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 RBV) is recommended as clinically indicated.

Prompt discontinuation of therapy is recommended for any a) 10-fold increase in alanine aminotransferase (ALT) activity at week 4; or b) any increase in ALT of less than 10-fold at week 4 that is accompanied by any weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or international normalized ratio. 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.

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

Recommendations for discontinuation of treatment because of lack of efficacy.

If quantitative HCV viral load 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 RBV.

Women of childbearing age should be cautioned not to become pregnant while receiving RBV-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 RBV.

Rating: Class I, Level C

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

Rating: Class I, Level C

The following regimens are NOT recommended with regard to pregnancy-related issues.

Treatment with RBV is NOT recommended for pregnant women or for women who are unwilling to adhere to use of adequate contraception, including those who are receiving RBV themselves or are sexual partners of male patients who are receiving RBV.

Rating: Class III, Level C

Female patients who have received RBV and sexual partners of male patients who have received RBV should NOT become pregnant for at least 6 months after stopping RBV.

Rating: Class III, 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 ration (INR) is recommended.

Rating: Class I, Level C

Surveillance for hepatocellular carcinoma with ultrasound testing every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).

Rating: Class I, Level C

Endoscopic surveillance 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

The following monitoring is NOT recommended during therapy.

Routine monitoring for HCV drug resistance–associated variants during therapy is NOT recommended.

Rating: Class III, Level C

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 testing 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

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

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, 2008b); (de Ledinghen, 2008); (Fierer, 2013); (Kirk, 2013)

Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with PEG-IFN and RBV have lower rates of hepatic decompensation, hepatocellular carcinoma, 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, 2006b); (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. A chart of known interactions with most US Food and Drug Administration (FDA)-approved agents is found here.

Recommendations related to HCV medication interactions with HIV antiretroviral medications.

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

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg):

> **Because ledipasvir increases tenofovir levels, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect is expected when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high.**

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) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir):

> **Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which it does not have substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, and atazanavir.**
>
> **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

Simeprevir:

> **Simeprevir should only be used with antiretroviral drugs with which it does not have clinically significant interactions: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.**

Rating: Class IIa, Level B

The following are NOT recommended or should not be used.

Antiretroviral treatment interruption to allow HCV therapy is NOT recommended.

Rating: Class III, Level A

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) should NOT be used with cobicistat and elvitegravir, pending further data.

Rating: Class III, Level C

Sofosbuvir or ledipasvir/sofosbuvir should NOT be used with tipranavir.

Rating: Class III, Level B

Fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir) should NOT be used with efavirenz, rilpivirine, darunavir, or ritonavir-boosted lopinavir.

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

Simeprevir should NOT be used with efavirenz, etravirine, nevirapine, cobicistat, or any HIV protease inhibitors.

Rating: Class III, Level B

RBV should NOT be used with didanosine, stavudine, or zidovudine.

Rating: Class III, Level B

Pharmacokinetics and Drug Interactions

Extensive recommendations for antiretroviral therapy use, including in persons anticipating HCV treatment, are found at jama.jamanetwork.com and aidsinfo.nih.gov.

Antiretroviral regimen 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; DHHS Guidelines; 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.

Sofosbuvir

Sofosbuvir is not metabolized by the hepatic P450 enzyme complex and is a substrate (but not an inhibitor) of drug transporters, p-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). It is not a substrate of organic anion-transporting polypeptide (OATP). Drug interaction studies with antiretroviral drugs (ie, efavirenz, tenofovir, emtricitabine, rilpivirine, ritonavir-boosted darunavir, and raltegravir) in noninfected persons identified no clinically significant interactions (Kirby, 2013). Sofosbuvir is not recommended for use with tipranavir because of the potential of this antiretroviral drug to induce P-gp (see prescribing information).

Ledipasvir

Ledipasvir is minimally metabolized and is a substrate and inhibitor of drug transporters P-gp and BCRP. At high doses (exceeding clinical concentrations), it is an inhibitor of OATPs. Drug interaction studies of ledipasvir and sofosbuvir with antiretroviral drugs in noninfected persons did not identify clinically significant interactions with raltegravir, rilpivirine, abacavir, lamivudine, or emtricitabine. (German, 2014) Interactions with dolutegravir, maraviroc, and enfuvirtide are not expected based on their pharmacologic profiles. Ledipasvir area under the curve (AUC) serum levels are 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, as their clinical significance is unknown and ledipasvir is available only as a part of a fixed-dose combination with sofosbuvir.

Ledipasvir plus Sofosbuvir

Fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) increases tenofovir levels when coadministered with rilpivirine. The effect of ledipasvir/sofosbuvir on tenofovir levels was greater in magnitude when coadministered with efavirenz. Although not yet studied in HIV/HCV-coinfected individuals, there is concern of an even greater increase in tenofovir levels when ledipasvir/sofosbuvir is administered with tenofovir and HIV protease inhibitors. (Gilead Sciences, 2014);(prescribing information) In the ERADICATE study, ledipasvir/sofosbuvir was administered to 37 HIV/HCV-coinfected patients taking combination antiretroviral therapy, including 16 taking regimens containing tenofovir, emtricitabine, and efavirenz, and all with baseline creatinine clearance (CrCl) rate of 60 mL/min or higher. (Osinusi, 2014a) Changes in creatinine level or glomerular filtration rate (GFR) in these 37 patients were similar to patients not taking antiretroviral therapy. From the phase III ION-4 study, further safety data may be available regarding interactions between ledipasvir/sofosbuvir and raltegravir, rilpivirine, or efavirenz, each in combination with fixed-dose tenofovir and emtricitabine (hereafter tenofovir/emtricitabine).

Renal parameters should therefore be checked at baseline and regularly while on therapy when

ledipasvir/sofosbuvir is administered with tenofovir-containing regimens. Baseline parameters should include measuring creatinine level, electrolytes (including phosphorus), and urinary protein and glucose levels, 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 CrCl between 30 mL/min and 60 mL/min or who have preexisting evidence of Fanconi syndrome) and particularly those taking tenofovir or ritonavir-boosted HIV protease inhibitors, as there are currently few efficacy or safety data for these combinations. (Gilead Sciences, 2014) 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 or ritonavir-boosted HIV protease inhibitors. Tenofovir should also be properly dosed and adjusted for CrCl rate at baseline and while on therapy. (Lucas, 2014)

Fixed-dose Paritaprevir, Ritonavir, and Ombitasvir plus Dasabuvir

Paritaprevir is an inhibitor of the OATP1B1 bilirubin transporter and may increase indirect bilirubin, especially in those taking atazanavir. (Eron, 2014) Paritaprevir is metabolized by cytochrome P450 3A4 (CYP3A4) and has therefore been studied with a variety of antiretroviral drugs that are also metabolized by this enzyme; it requires ritonavir boosting to achieve long-lasting serum levels. 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.

Paritaprevir has been studied as part of the entire regimen with the boosted HIV protease inhibitors atazanavir, darunavir, and lopinavir in noninfected individuals. There were minimal changes to maximum concentration (C_{max}) and AUC for these antiretroviral drugs, although trough concentrations were increased for atazanavir and lopinavir, and decreased for darunavir. Although paritaprevir C_{max} and AUC values were minimally to moderately increased, no dose adjustment has been recommended. (Khatri, 2014a) Because 100 mg of ritonavir is coformulated with paritaprevir and ombitasvir, the total dose of ritonavir must be carefully considered when using ritonavir-containing antiretroviral regimens. Coadministration with ritonavir-boosted lopinavir would result in 300 mg daily of ritonavir, a dose associated with substantial gastrointestinal adverse effects, this combination is not recommended. The daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [?75 mg]) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV) was not added to unboosted HIV protease inhibitors. Twenty-eight HIV/HCV-coinfected subjects already taking ritonavir-boosted atazanavir (with the ritonavir coming from the HCV regimen during the time of coadministration) were treated with a paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV regimen as part of the TURQUOISE-1 study. (Wyles, 2014a)

In noninfected volunteers, when paritaprevir/ritonavir/dasabuvir was combined with efavirenz, emtricitabine, and tenofovir, clinically significant gastrointestinal and neurologic adverse events occurred, coincident with elevations of alanine aminotransferase levels. When the entire regimen was combined with rilpivirine, exposures to rilpivirine were substantially increased. Therefore, rilpivirine and efavirenz should not be used with paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV. In contrast, noninfected volunteer studies did not reveal notable pharmacologic interactions with fixed-dose tenofovir and emtricitabine (hereafter tenofovir/emtricitabine) (when tested separately from other fixed-dose combinations) or raltegravir. (Khatri, 2014b)

Simeprevir

Simeprevir is metabolized primarily by CYP3A4 and is therefore susceptible to drug interactions with inhibitors and inducers of the enzyme. Simeprevir is also an inhibitor of the OATP and P-gp transporters, leading to additional drug interaction concerns. Drug interaction studies with antiretroviral drugs in noninfected 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)

RBV

RBV has the potential for dangerous drug interactions with didanosine resulting in mitochondrial toxicity with hepatomegaly and steatosis, pancreatitis, and lactic acidosis; thus, the concomitant administration of these 2 drugs is contraindicated. (Fleischer, 2004) The combined use of RBV and zidovudine has been reported to increase the rates of anemia and the need for RBV dose reduction; thus, zidovudine is not recommended for use with RBV. (Alvarez, 2006)

Recommended regimens for HIV/HCV-coinfected individuals.

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 sections).

Rating: Class I, Level B

Although fewer HIV/HCV-coinfected patients have been treated than HCV-monoinfected patients in trials of DAAs, efficacy rates thus far have been remarkably similar between the groups. (Sulkowski, 2013a); (Sulkowski, 2013d); (Sulkowski, 2014); (Dieterich, 2014b); (Rodriguez-Torres, 2013); (Townsend, 2014); (Wyles, 2014a); (Dieterich, 2014c) 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 HIV/HCV coinfection studies is included here.

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, treatment-naive patients without cirrhosis from an urban population in a single-center, open-label clinical trial. 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-naive 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, estimated GFR, CrCl, urinary beta-2 microglobulin,

proteinuria, and glycosuria). No clinically significant changes in these parameters or renal toxicity were observed. There were no clinically significant changes in CD4+ T cell counts or HIV RNA levels in the study subjects. Thus, these early data suggest that 12 weeks of ledipasvir/sofosbuvir may be a safe and effective regimen for HIV/HCV-coinfected patients with HCV genotype 1 without cirrhosis taking select antiretroviral therapy. (Townsend, 2014) There are no data regarding an 8-week duration of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients; therefore, the shortened course that is considered for persons without HIV and cirrhosis who have HCV RNA levels less than 6 million IU/mL cannot yet be endorsed.

Paritaprevir/ritonavir/ombitasvir plus dasabuvir was FDA-approved for use in HCV genotypes 1a and 1b because of its efficacy and safety in treatment-naive patients and PEG-IFN and RBV 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-I study. In this study, treatment-naive (n=42) and -experienced (n=21) patients were randomized to receive either 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV. 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 healthy volunteer pharmacokinetic data: 35 patients entered taking tenofovir/emtricitabine with raltegravir and 28 patients entered taking tenofovir/emtricitabine with ritonavir-boosted atazanavir (with the ritonavir coming from the HCV regimen during the time of coadministration). Of the 31 patients to receive 12 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and RBV, 29 (93.5%) achieved SVR12, 1 relapsed, and 1 withdrew consent from study participation. Similarly, of the 32 subjects in the 24-week arm, 29 (90.6%) achieved 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. (Wyles, 2014a)

The combination of simeprevir plus sofosbuvir with or without RBV has been studied in the phase II COSMOS trial in patients with HCV monoinfection. (Jacobson, 2013b) This study is the main basis for the recommendation supporting the use of this all-oral combination for HCV genotype 1a or 1b monoinfection. Sofosbuvir plus simeprevir has been used anecdotally in patients with HIV/HCV coinfection, with a recent report of achieving SVR in 11 (92%) of 12 patients. (Del Bello, 2014) 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**).** (Jacobson, 2013b)

The combined analysis of the phase III PHOTON 1 and PHOTON 2 studies was recently presented. These trials treated HIV/HCV-coinfected patients with HCV genotype 1 (treatment-naive), 2, 3, or 4 (treatment-naive and -experienced) with 400 mg of sofosbuvir and weight-based RBV. Treatment-naive patients with HCV genotype 1 (n=226) or 4 (n=31) received 24 weeks of treatment. Treatment-naive patients with HCV genotype 2 (n=45) received 12 weeks of treatment. Treatment-naive patients with HCV genotype 3 received 12 weeks (n=42) or 24 weeks (n=57) of treatment. All treatment-experienced patients with HCV genotype 2, 3, or 4 (n=30, n=66, and n=31, respectively) were treated for 24 weeks. Patients with compensated cirrhosis (15%) were included. Antiretroviral regimens allowed included combinations of tenofovir and emtricitabine with efavirenz, raltegrevir, ritonavir-boosted atazanavir, ritonavir-boosted darunavir, or rilpivirine. High SVR12 rates were observed for all HCV genotypes (81% for genotype 1, 89%

for genotype 2, 84% each for genotypes 3 and 4). SVR12 rates were lower for patients with cirrhosis with HCV genotype 1a and treatment-experienced patients with HCV genotype 3 who were treated for 24 weeks (65% vs 85%, respectively, and 95% vs 79%, respectively) but not for others. Sofosbuvir and RBV were well tolerated. Of note, 6 patients had transient breakthrough of HIV viral load, although none required change of antiretroviral drugs. Sofosbuvir and RBV can be an effective therapy for HIV/HCV-coinfected patients, particularly for those with HCV genotypes 2, 3, or 4. (Rockstroh, 2014)

Because of response rates observed in the PHOTON 1 and PHOTON 2 trials that are similar to those seen in studies of HCV-monoinfected patients, sofosbuvir plus RBV for 12 weeks to 16 weeks is recommended for treatment-naive, HIV/HCV-coinfected patients with HCV genotype 2, and sofosbuvir plus RBV for 24 weeks is recommended for HCV genotypes 3 and 4. Current recommendations for the retreatment of HIV-infected patients coinfected with HCV genotype 2 or 3 are the same as those for HCV-monoinfected patients. For HCV genotype 1 infection, sofosbuvir plus RBV for 24 weeks is not recommended because of the availability of more effective regimens, assuming antiretroviral regimen compatibility can be achieved.

Data are lacking regarding the use of sofosbuvir among HIV/HCV-coinfected patients with HCV genotype 5 or 6. Given the evidence of the safety and efficacy of sofosbuvir-based regimens for HIV/HCV-coinfected individuals infected with other HCV genotypes and the efficacy data from HCV-monoinfected individuals with these genotypes, the recommended regimens for treatment-naive and -experienced patients with HIV/HCV coinfection and these genotypes are the same as those for HCV-monoinfected patients.

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 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.

Some HIV/HCV-coinfected patients must remain on antiretroviral regimens with drug interactions that absolutely preclude otherwise recommended DAAs that are currently available. For these situations, expert consultation is recommended.

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.

The following regimens are NOT recommended for treatment-naive or -experienced HIV/HCV-coinfected patients.

PEG-IFN and RBV with or without simeprevir, telaprevir, or boceprevir for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Owing to its prolonged treatment course, adverse effects, and poor response rates, PEG-IFN with RBV is no longer recommended for the treatment of patients with any HCV genotype who are coinfected with HIV. Telaprevir, boceprevir, or simeprevir combined with PEG-IFN and RBV have similar reported efficacy and safety in patients with HIV/HCV coinfection and HCV genotype 1 to that for patients with HCV monoinfection and genotype 1, but require 24 weeks to 48 weeks of HCV treatment. (Sulkowski, 2013a);(Sulkowski, 2013d); (Dieterich, 2014b) Telaprevir, boceprevir, and simeprevir are each substrates and to varying degrees inhibitors of CYP3A4 and thus have substantial drug interactions with antiretroviral drugs. (van Heeswijk, 2011a); (van Heeswijk, 2011b); (Kakuda, 2012); (Johnson, 2013); (Kasserra, 2011); (Hulskotte, 2013); (Garraffo, 2013); (de Kanter, 2012); (Hammond, 2013); (Vourvahis, 2013) Owing to the adverse effect profile, a prolonged required course of PEG-IFN and RBV, lower efficacy than other recommended regimens, and substantial drug interactions, these regimens are no longer recommended for HIV/HCV-coinfected patients.

Because of their limited activity in vitro and in vivo against HCV genotypes 2 and 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for HIV/HCV-coinfected patients with HCV genotype 2 or 3 infection. Boceprevir and telaprevir also have limited activity against HCV genotype 4 and should not be used as therapy for HIV/HCV-coinfected patients with HCV genotype 4 infection. There are currently insufficient data to support a recommendation for the use of simeprevir for HCV genotype 4 infection in HIV/HCV-coinfected patients.

Complete revision made to this section on December 19, 2014.

Unique Patient Populations: HIV/HCV Coinfection Box. Summary of Recommendations for HIV/HCV-Coinfected Patients Who are Being Treated for HCV, by Genotype

Unique Patient Populations: HIV/HCV Coinfection Box. Recommendations for HIV/HCV-Coinfected Patients Who are Being Treated for HCV, by Genotype

Recommendations related to HCV medication interactions with HIV antiretroviral medications.

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

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg):

> **Because ledipasvir increases tenofovir levels, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect is expected when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high.**

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) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir):

> **Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which it does not have substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, and atazanavir.**
>
> **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

Simeprevir:

> **Simeprevir should only be used with antiretroviral drugs with which it does not have clinically significant interactions: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.**

Rating: Class IIa, Level B

The following are NOT recommended or should not be used.

Antiretroviral treatment interruption to allow HCV therapy is NOT recommended.

Rating: Class III, Level A

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) should NOT be used with cobicistat and elvitegravir, pending further data.

Rating: Class III, Level C

Sofosbuvir or ledipasvir/sofosbuvir should NOT be used with tipranavir.

Rating: Class III, Level B

Fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir) should NOT be used with efavirenz, rilpivirine, darunavir, or ritonavir-boosted lopinavir.

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

Simeprevir should NOT be used with efavirenz, etravirine, nevirapine, cobicistat, or any HIV protease inhibitors.

Rating: Class III, Level B

RBV should NOT be used with didanosine, stavudine, or zidovudine.

Rating: Class III, Level B

Recommended regimens for HIV/HCV-coinfected individuals.

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 sections).

Rating: Class I, Level B

The following regimens are NOT recommended for treatment-naive or -experienced HIV/HCV-coinfected patients.

PEG-IFN and RBV with or without simeprevir, telaprevir, or boceprevir for 24 weeks to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

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.

Decompensated Cirrhosis: Genotype 1 and 4

Patients with HCV genotype 1 or 4 with 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 regimen for patients with 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. This regimen should be used only by highly experienced HCV practitioners.

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks is recommended for patients with decompensated cirrhosis.

Rating: Class IIb, Level C

For patients with decompensated cirrhosis and anemia or RBV intolerance, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended.

Rating: Class IIb, Level C

For patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 24 weeks is an alternative regimen.

Rating: Class IIb, Level C

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-naive or -experienced, with Child Turcotte Pugh (CTP) class B cirrhosis (score 7 to 9) or CTP class C cirrhosis (score 10 to 12), were randomly assigned to receive daily fixed-dose combination ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) and RBV (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 a creatinine clearance rate greater than 40 mL/min. (Flamm, 2014)

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. Posttherapy 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 posttherapy compared with baseline in both treatment groups. Baseline CTP and Model for End-Stage Liver Disease (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 RBV (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 RBV at 600 mg per day did not receive higher doses. As of December 2014, there are no data from studies of ledipasvir/sofosbuvir without RBV in patients with decompensated cirrhosis. However, 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, 2014b) In addition, preliminary 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 RBV (initial dose of 600 mg, increased as tolerated) led to a 98% rate of SVR at 4 weeks (SVR4). (Wyles, 2014b)

Another multicenter double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared with daily ledipasvir/sofosbuvir and RBV 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 and RBV treatment had failed (for most, treatment with PEG-IFN, RBV, and a protease inhibitor had also failed). (Bourliere, 2014a) The mean MELD score was 7 (range, 6-16), 26% 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 RBV for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Decompensated Cirrhosis: Genotype 2 and 3

Patients with HCV genotype 2 or 3 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 regimen for patients with HCV genotype 2 or 3 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. This regimen should be used only by highly experienced HCV practitioners.***

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) (with consideration of the patient's creatinine clearance rate and hemoglobin level) for up to 48 weeks is recommended for patients with HCV genotype 2 or 3 who have decompensated cirrhosis. This regimen should be used only by highly experienced HCV practitioners.

Rating: Class IIb, Level B

In one study, 61 patients with HCV infection and hepatocellular carcinoma meeting Milan criteria for liver transplantation were treated with sofosbuvir plus RBV for up to 48 weeks. (Curry, 2014) At the time of treatment initiation, the median MELD score was 8 (range, 6-14), 17 patients had CTP scores of 7 or 8 (CTP class B cirrhosis), 45 (73%) patients had HCV genotype 1, 8 (13%) had HCV genotype 2, and 7 (11%) had HCV genotype 3. Forty-six patients underwent liver transplantation. At 12 weeks posttransplant, 30 of the 43 patients (70%) had undetectable HCV RNA levels, consistent with prevention of recurrent HCV infection. Ten patients experienced recurrent HCV infection, 9 of whom had undetectable HCV RNA levels for a duration less than 30 days pretransplant.

The most common adverse effects were fatigue (38%), anemia (21%), and headache (23%); adverse effects led to treatment discontinuation for 2 patients (3%), and 12 patients (20%) required a dose reduction of RBV. The only independent predictor of posttransplant SVR12 was the number of days of undetectable HCV RNA level pretransplant. In addition, 10 of the 11 (91%) subjects with HCV genotype 2 or 3 achieved SVR12, and only 19 of the 29 (65%) patients with HCV genotype 1 achieved SVR12. These data suggest that sofosbuvir and RBV can be given to liver transplant candidates with hepatocellular carcinoma and mildy decompensated cirrhosis but that more than 30 days of undetectable HCV RNA level are required to achieve SVR12 posttransplant.

In a sofosbuvir compassionate-use program for patients with severe recurrent HCV infection following liver transplantation who were predicted to have a less than 6-month survival rate, (Forns, 2013b) 78 subjects were treated: 44 patients were treated with sofosbuvir plus RBV, and 32 patients also received PEG-IFN. At treatment initiation, the median MELD score was 16 (range, 6-43), and fibrosing cholestatic hepatitis was documented in 20 patients. After week 12 of treatment, 91% of patients treated with sofosbuvir plus RBV and 75% of those treated with the addition of PEG-IFN achieved HCV RNA levels below the lower limit of quantification. Of 27 patients evaluated at 12 weeks posttreatment, 15 patients (56%) achieved SVR. Overall, 75% had improved or stable clinical liver disease, including improvement in hyperbilirubinemia and coagulopathy and decrease in MELD score. In this very sick population, 8 patients died and most deaths were caused by liver disease progression.

Finally, preliminary data from the ELECTRON-2 study of daily ledipasvir/sofosbuvir with or without weight-based RBV (n=26 and n=25, respectively) in previously untreated patients with HCV genotype 3 without

cirrhosis have been presented. (Gane, 2014) In this study, the SVR12 rate was 100% in the group that received ledipasvir/sofosbuvir with RBV compared with only 64% in the group that received ledipasvir/sofosbuvir alone. Although there are currently no data regarding the use of ledipasvir/sofosbuvir with RBV in patients with decompensated cirrhosis and HCV genotype 3, this regimen may be of value if proven safe and effective.

The following regimens are NOT recommended for patients with decompensated cirrhosis ***(moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).***

Any IFN-based therapy

Rating: Class III, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens

Pariteprevir-, ombitasvir-, or dasabuvir-based regimens

Rating: Class III, Level A

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. Neither telaprevir nor boceprevir should be used for this population because they must be coadministered with PEG-IFN and RBV. Very minimal data exist for the use of simeprevir in patients with decompensated cirrhosis. Until additional data become available, simeprevir should not be used in patients with decompensated cirrhosis.

Complete revision made to this section on December 19, 2014. Additional minor changes were made on December 29, 2014.

Unique Patient Populations: Cirrhosis Box. Summary of Recommendations for Patients with DecompensatedCirrhosis

Unique Patient Populations: Cirrhosis Box. Summary of Recommendations for Patients with Decompensated Cirrhosis

Patients with HCV genotype 1 or 4 with 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 regimen for patients with 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. This regimen should be used only by highly experienced HCV practitioners.***

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks is recommended for patients with decompensated cirrhosis**.**

Rating: Class IIb, Level C

For patients with decompensated cirrhosis **and anemia or RBV intolerance, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended.**

Rating: Class IIb, Level C

For patients with decompensated cirrhosis **in whom prior sofosbuvir-based treatment has failed, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 24 weeks is an alternative regimen.**

Rating: Class IIb, Level C

Patients with HCV genotype 2 or 3 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 regimen for patients with HCV genotype 2 or 3 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. This regimen should be used only by highly experienced HCV practitioners.***

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) (with consideration of the patient's creatinine clearance rate and hemoglobin level) for up to 48 weeks is recommended for patients with HCV genotype 2 or 3 who have decompensated cirrhosis**. This regimen should be used only by highly experienced HCV practitioners.**

Rating: Class IIb, Level B

The following regimens are NOT recommended for patients with decompensated cirrhosis ***(moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).***

Any IFN-based therapy

Rating: Class III, Level A

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens

Paritepreviir-, ombitasvir-, or dasabuvir-based regimens

Rating: Class III, Level A

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.

Recommended regimen for treatment-naive and -experienced patients with HCV genotype 1, 3, or 4 infection in the allograft, including compensated cirrhosis.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1, 3, or 4 infection in the allograft, including compensated cirrhosis.

Rating: Class I, Level B

Alternative regimen for treatment-naive patients with HCV genotype 1, 3, or 4 infection in the allograft with compensated liver disease who are RBV intolerant or ineligible.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an alternative regimen for treatment-naive patients with HCV genotype 1, 3, or 4 infection in the allograft with compensated liver disease who are RBV intolerant or ineligible.

Rating: Class I, Level B

Alternative regimen for patients with HCV genotype 1 in the allograft, including compensated cirrhosis.

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks for an alternative regimen for patients with HCV genotype 1 in the allograft, including compensated cirrhosis.

Recommended regimen for treatment-naive and -experienced patients with HCV genotype 2 in the allograft, including compensated cirrhosis***.***

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients with HCV genotype 2 in the allograft, including compensated cirrhosis**.**

Rating: Class IIb, Level C

Alternative regimen for patients with HCV genotype 1 in the allograft, including early (Metavir fibrosis stage F0-F2) recurrence.

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 mg]) for 24 weeks is an alternative regimen for patients with HCV genotype 1 in the allograft, without cirrhosis (Metavir fibrosis stage F0-F2).

Rating: Class 1, Level B

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 compensated Child Turcotte Pugh [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 RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for either 12 weeks or 24 weeks. On an intention-to-treat basis, sustained virologic response (SVR) was achieved in 96% of patients with Metavir stage F0 to F3 fibrosis and in 96% of those with compensated cirrhosis, in both the 12- and 24-week arms; all patients received RBV. RBV dose was weight based for patients with Metavir fibrosis stage of F0 to F3 and CTP class A cirrhosis. For patients with CTP class B or C cirrhosis, RBV 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% SVR at 12 weeks [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.

As the importance of RBV cannot be ascertained from the SOLAR study, in which all patients received RBV, the safest presumption is that RBV 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 RBV, with SVR12 achieved in 70%. (Charlton, 2014) Although the basis for attenuated SVR rate observed in patients with more advanced HCV infection post-liver transplant, these results together with those of the sofosbuvir compassionate-use program (Forns, 2013a) suggest that the optimal period to initiate therapy may be the first 6 months to 12 months post-transplant to minimize the likelihood of having to treat patients with more advanced liver disease.

In a multicenter study of 34 liver transplant recipients with mild recurrence (Metavir fibrosis stage of 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) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir) and RBV (1000 mg [75 kg] to 1200 mg [≥75 kg]) was given for 24 weeks and achieved an SVR24 rate of 96%. (Mantry, 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.

Prospective studies of simeprevir with sofosbuvir in the posttransplant setting are ongoing. A retrospective multicenter analysis of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily) with or without RBV in 77 recipients reported an SVR4 rate of 92%. (Pungpapong, 2014) The coadministration of single-dose cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentrations and no change in simeprevir concentrations (see simeprevir prescribing information). However, in an interim analysis of an ongoing study (TMC435HPC3016), concomitant use of simeprevir (plus daclatasvir and RBV) 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. Although the current US Food and Drug Administration labeling does not recommend against coadministration of simeprevir and cyclosporine, given these new findings, simeprevir should not be coadministered with cyclosporine.

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 also 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 RBV (eg, patients with impaired renal function or anemia) or who are unable to forego proton pump inhibitor therapy (proton pump inhibitors attenuate ledipasvir absorption by >90%). A further option in patients who are RBV intolerant is 24 weeks of ledipasvir/sofosbuvir.

The following regimens are NOT recommended for treatment-naive patients with compensated allograft HCV infection.

Regimens containing PEG-IFN

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens should not be used for patients with compensated allograft HCV infection.

Rating: Class III, Level A

Telaprevir or boceprevir should not be used in the post–liver transplant population because of associated toxicities and drug interactions with calcineurin inhibitors**.**

Decompensated Cirrhosis

Recommended regimen for treatment-naive and -experienced liver transplant recipients with decompensated cirrhosis ***(***Child Turcotte Pugh class B or C***) due to HCV genotype 1, 3, or 4 infection in the allograft.***

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with a low initial dose of RBV (600 mg, increasing as tolerated) for 12 weeks is recommended for liver transplant recipients with decompensated cirrhosis **(Child Turcotte Pugh class B or C) due to HCV genotype 1, 3, or 4 infection in the allograft.**

Rating: Class I, Level B

Recommended regimen for treatment-naive and -experienced liver transplant recipients with decompensated cirrhosis ***(***Child Turcotte Pugh class B or C***) due to HCV genotype 2 infection in the allograft.***

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] mg) for 24 weeks is recommended for liver transplant recipients with decompensated cirrhosis **(Child Turcotte Pugh class B or C) due to HCV genotype 2 infection in the allograft.**

Rating: Class IIb, Level C

The following regimens are NOT recommended for patients with decompensated allograft HCV infection.

Regimens containing PEG-IFN

Regimens containing simeprevir

Fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg])

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

Complete revision made to this section on December 19, 2014.

Unique Patient Populations: Post-Liver Transplantation Box. Summary of Recommendations for Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

Unique Patient Population: Post-Liver Transplantation Box. The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation

Recommended regimen for treatment-naive and -experienced patients with HCV genotype 1, 3, or 4 infection in the allograft, including compensated cirrhosis***.***

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for patients with HCV genotype 1, 3, or 4 infection in the allograft, including compensated cirrhosis**.**

Rating: Class I, Level B

Alternative regimen for treatment-naive patients with HCV genotype 1, 3, or 4 infection in the allograft with compensated liver disease who are RBV intolerant or ineligible.

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is an alternative regimen for treatment-naive patients with HCV genotype 1, 3, or 4 infection in the allograft with compensated liver disease who are RBV intolerant or ineligible.

Rating: Class I, Level B

Alternative regimen for patients with HCV genotype 1 in the allograft, including compensated cirrhosis***.***

Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks for an alternative regimen for patients with HCV genotype 1 in the allograft, including compensated cirrhosis**.**

Recommended regimen for treatment-naive and -experienced patients with HCV genotype 2 in the allograft, including compensated cirrhosis***.***

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for patients with HCV genotype 2 in the allograft, including compensated cirrhosis**.**

Rating: Class IIb, Level C

Alternative regimen for patients with HCV genotype 1 in the allograft, including early (Metavir fibrosis stage F0-F2) recurrence.

Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 mg]) for 24 weeks is an alternative regimen for patients with HCV genotype 1 in the allograft, without cirrhosis (Metavir fibrosis stage F0-F2).

Rating: Class 1, Level B

The following regimens are NOT recommended for treatment-naive patients with compensated allograft HCV infection.

Regimens containing PEG-IFN

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens should not be used for patients with compensated allograft HCV infection.

Rating: Class III, Level A

Recommended regimen for treatment-naive and -experienced liver transplant recipients with decompensated cirrhosis ***(***Child Turcotte Pugh class B or C***) due to HCV genotype 1, 3, or 4 infection in the allograft.***

Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with a low initial dose of RBV (600 mg, increasing as tolerated) for 12 weeks is recommended for liver transplant recipients with decompensated cirrhosis **(Child Turcotte Pugh**

class B or C) due to HCV genotype 1, 3, or 4 infection in the allograft.

Rating: Class I, Level B

Recommended regimen for treatment-naive and -experienced liver transplant recipients with decompensated cirrhosis ***(***Child Turcotte Pugh class B or C***) due to HCV genotype 2 infection in the allograft.***

Daily sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] mg) for 24 weeks is recommended for liver transplant recipients with decompensated cirrhosis **(Child Turcotte Pugh class B or C) due to HCV genotype 2 infection in the allograft.**

Rating: Class IIb, Level C

The following regimens are NOT recommended for patients with decompensated allograft HCV infection.

Regimens containing PEG-IFN

Regimens containing simeprevir

Fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg])

Monotherapy with PEG-IFN, RBV, or a direct-acting antiviral

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

UNIQUE PATIENT POPULATIONS: PATIENTS WITH RENAL IMPAIRMENT

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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 (creatinine clearance <30 mL/min) or end-stage renal disease requiring hemodialysis or peritoneal dialysis is found in the BOX.

Recommended dosage adjustments for patients with renal impairment, including severe renal impairment (creatinine clearance [CrCl] >30 mL/min) or end-stage renal disease (ESRD).

For patients with mild to moderate renal impairment (CrCl >30 mL/min), no dosage adjustment is required when using sofosbuvir, simeprevir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) to treat or retreat HCV infection in patients with appropriate genotypes.

Rating: Class I, Level A

For patients with CrCl below 30 mL/min, treatment can be contemplated after consultation with an expert, because safety and efficacy data are not available for these patients.

Rating: Class IIb, Level C

Sofosbuvir enters the hepatocyte where it is metabolized to its active form, GS-461203. The downstream inactive nucleoside metabolite GS-331007 is almost exclusively eliminated from the body renally, mediated through a combination of glomerular filtration and active tubular secretion. Results of phase II and III clinical trials of sofosbuvir have excluded patients with serum creatinine levels greater than 2.5 mg/dL or creatinine clearance (CrCl) level less than 60 mL/min. The pharmacokinetics of a single 400 mg dose of sofosbuvir were assessed in persons not infected with HCV (study P7977-0915) with mild (estimated glomerular filtration rate [eGFR] >50 mL/min/1.73 m^2 and <80 mL/min/1.73 m^2), moderate (eGFR >30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2), or severe renal impairment (eGFR <30 mL/min/1.73 m^2) and persons with end-stage renal disease (ESRD) requiring hemodialysis.

Relative to persons with normal renal function (eGFR >80 mL/min/1.73 m^2), the sofosbuvir area under the

curve (AUC; 0-inf) was 61% higher, 107% higher, and 171% higher in subjects with mild, moderate, and severe renal impairment, respectively; GS-331007 AUC (0-inf) was 55% higher, 88% higher, and 451% higher, respectively. In subjects with ESRD (relative to subjects with normal renal function), sofosbuvir and GS-331007 AUC (0-inf) were 28% higher and 1280% higher, respectively, when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% higher and 2070% higher, respectively, when sofosbuvir was dosed 1 hour after hemodialysis. No dosage adjustment is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been established in patients with severe renal impairment or ESRD. Therefore, a dose recommendation cannot be provided for these populations at this time, although a dedicated study to evaluate optimal dosing of sofosbuvir in HCV-infected patients with severe renal impairment or ESRD on hemodialysis is currently underway.

No clinically relevant changes in ledipasvir pharmacokinetics were found between volunteers with normal renal function and those with severe renal impairment (eGFR <30 mL/min by Cockcroft-Gault) after a single dose of 90 mg of ledipasvir was administered.

Unique Patient Populations Table: Dose Adjustments Needed for Patients With Renal Impairment

Renal Impairment	eGFR / CrCl level (mL/min)	IFN	RBV	Sofosbuvir	Ledipasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
Mild	50-80	180 ug PEG-IFN (2a); PEG-IFN (2b) 1.5 ug/Kg	Standard	Standard	Standard	Standard	Standard	Standard	Standard
Moderate	30-50	180ug PEG-IFN (2a); PEG-IFN (2b) 1 ug/kg (25% reduction)	Alternating doses 200 mg and 400 mg every other day	Standard	Standard	Standard	Standard	Standard	Standard
Severe	<30	135 ug PEG-IFN (2a); PEG-IFN (2b) 1 ug/kg (50% reduction)	200 mg/d	Data not available	Data not available	Data not available	Data not available	Data not available	Standard
ESRD/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	Data not available	Data not available	Data not available	Data not available	Data not available	Data not available

Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HD, hemodialysis.

Complete revision made to this section on December 19, 2014.

Unique Patient Populations: Renal Impairment Box. Summary of Recommendations for Patients with Renal Impairment Including Severe Renal Impairment (CrCl <30 ML/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Renal Impairment Box. Summary of Recommendations for Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 ML/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Recommended dosage adjustments for patients with renal impairment, including severe renal impairment (creatinine clearance [CrCl] >30 mL/min) or end-stage renal disease (ESRD).

For patients with mild to moderate renal impairment (CrCl >30 mL/min), no dosage adjustment is required when using sofosbuvir, simeprevir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) to treat or retreat HCV infection in patients with appropriate genotypes.

Rating: Class I, Level A

For patients with CrCl below 30 mL/min, treatment can be contemplated after consultation with an expert, because safety and efficacy data are not available for these patients.

Rating: Class IIb, Level C

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 of chronic infection and the implications on the approach to acute hepatitis C treatment.

Acute HCV infection may result from exposure to the virus through a variety of routes. The highest risk is associated with repeated parenteral exposures from contaminated equipment in the setting of injection drug use (or user; IDU). Lower rates of HCV transmission occur in the setting of needle stick injuries in which health care workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low, but transmission rates are much higher among HIV-infected men who have sex with men (MSM) who have unprotected sex, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood, and possibly the presence of other ulcerative sexually transmitted infections. (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 infection and progression of liver disease. (Bruneau, 2014) Indeed, persons involved in high-risk behavior are known to 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 (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)

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 is recommended for 6 months.

Often, however, 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 $<10^4$ IU/mL) or fluctuating (>1 $\log_{10}$ 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 laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, 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 pre-exposure or post-exposure prophylaxis of HCV infection. Some studies have shown that post-exposure 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 log10 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 until the ALT level normalizes and HCV RNA becomes undetectable.

Rating: Class I, Level B

Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is recommended to detect spontaneous clearance of HCV 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 IDU.

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 **Testing and Linkage to Care**) For individuals with acute HCV infection who have a history of recent IDU, 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) at 2-week to 4-week intervals. (Blackard, 2008) Laboratory monitoring should continue until the ALT level normalizes and HCV RNA becomes undetectable, suggesting resolution of acute liver injury. Frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT level should follow recommendations for monitoring patients with chronic HCV infection. (See Monitoring Section)

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 Treat) Those with spontaneous clearance should not be treated with antiviral therapy, but they should be counseled about the possibility of reinfection. 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 **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 and When and in Whom to Treat)

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 is recommended to allow for spontaneous clearance before starting treatment.

Rating: Class IIa, Level C

Recommended regimens for patients with acute HCV infection

Owing to high efficacy and safety, the same regimens recommended for chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Treat sections) are also recommended for acute infection.

Rating: Class IIa, Level C

Alternative regimen for patients with acute HCV infection who are eligible to receive IFN

PEG with or without RBV for 16 weeks (for those with genotype 2 or 3 HCV who have a rapid virologic response [RVR]) to 24 weeks (for those with genotype 1 HCV).

Rating: Class II, Level A

For patients in whom HCV infection spontaneously clears, treatment is NOT recommended.

Rating: Class III, Level B

When the efficacy of the treatment of acute HCV infection (particularly for genotype 1) was superior to the treatment of chronic infection, there was a strong impetus to identify and treat acute HCV infection. (See 2009 AASLD guidelines, [Ghany, 2009]) The current availability of IFN-sparing HCV treatments that have high safety and efficacy for chronic HCV infection reduces (and possibly eliminates) the “efficacy advantage” of early treatment. Indeed, a randomized controlled study showed that delaying treatment was not inferior to early treatment, and many who received early IFN-based therapy were unable to complete

treatment because of adverse effects. (Deterding, 2013) Until data documenting the efficacy and safety of treatment of acute hepatitis C with IFN-sparing therapy are available, clinicians must recognize that IFN-based treatment requires a balance between being prompt (treatment within 12 weeks to 16 weeks) and allowing enough time for spontaneous resolution.

Some argue that the benefits of waiting until 6 months to document chronic hepatitis C and of using well-studied treatments for chronic hepatitis C outweigh the disadvantages of delaying treatment of acute infection for many patients. On the other hand, for some persons, there may be additional benefits of early treatment that include prevention of transmission to others (eg, IDUs or surgeons), prevention of severe complications (eg, someone with underlying compensated cirrhosis superinfected with acute HCV infection), and decreasing the chance of being lost to follow-up. In those instances, there are data documenting the efficacy of IFN-based HCV treatment when given within 12 weeks to 16 weeks of infection, as described in the 2009 AASLD guidelines. (Ghany, 2009) This prior AASLD recommendation was later supported by a meta-analysis that reported sustained virologic response (SVR) in 82.5% of acutely infected patients who started IFN-based treatment within 12 weeks of diagnosis compared with SVR rates of 66.9% in those starting treatment between 12 weeks and 24 weeks and 62.5% in those starting treatment after 24 weeks. (Corey, 2010) By analogy with studies of treatment of chronic infection, the duration of treatment of acute genotype 2 or 3 infection with PEG/RBV may be shortened to 16 weeks for patients in whom an RVR is achieved. (Dalgard, 2004); (Mangia, 2005); (von Wagner, 2005); (Yu, 2007); (Shiffman, 2007)

Acute Box. 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

Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended.

Rating: Class III, Level C

Recommendations for medical management and monitoring in acute HCV infection

Regular laboratory monitoring is recommended in the setting of acute HCV infection until the ALT level normalizes and HCV RNA becomes undetectable.

Rating: Class I, Level B

Monitoring HCV RNA (eg, every 4 weeks to 8 weeks) for 6 months to 12 months is recommended to detect spontaneous clearance of HCV 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 IDU.

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 and When and in Whom to Treat)

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 is recommended to allow for spontaneous clearance before starting treatment.

Rating: Class IIa, Level C

Recommended regimens for patients with acute HCV infection

Owing to high efficacy and safety, the same regimens recommended for chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Treat sections) are also recommended for acute infection.

Rating: Class IIa, Level C

Alternative regimen for patients with acute HCV infection who are eligible to receive IFN

PEG with or without RBV for 16 weeks (for those with genotype 2 or 3 HCV who have a rapid virologic response [RVR]) to 24 weeks (for those with genotype 1 HCV).

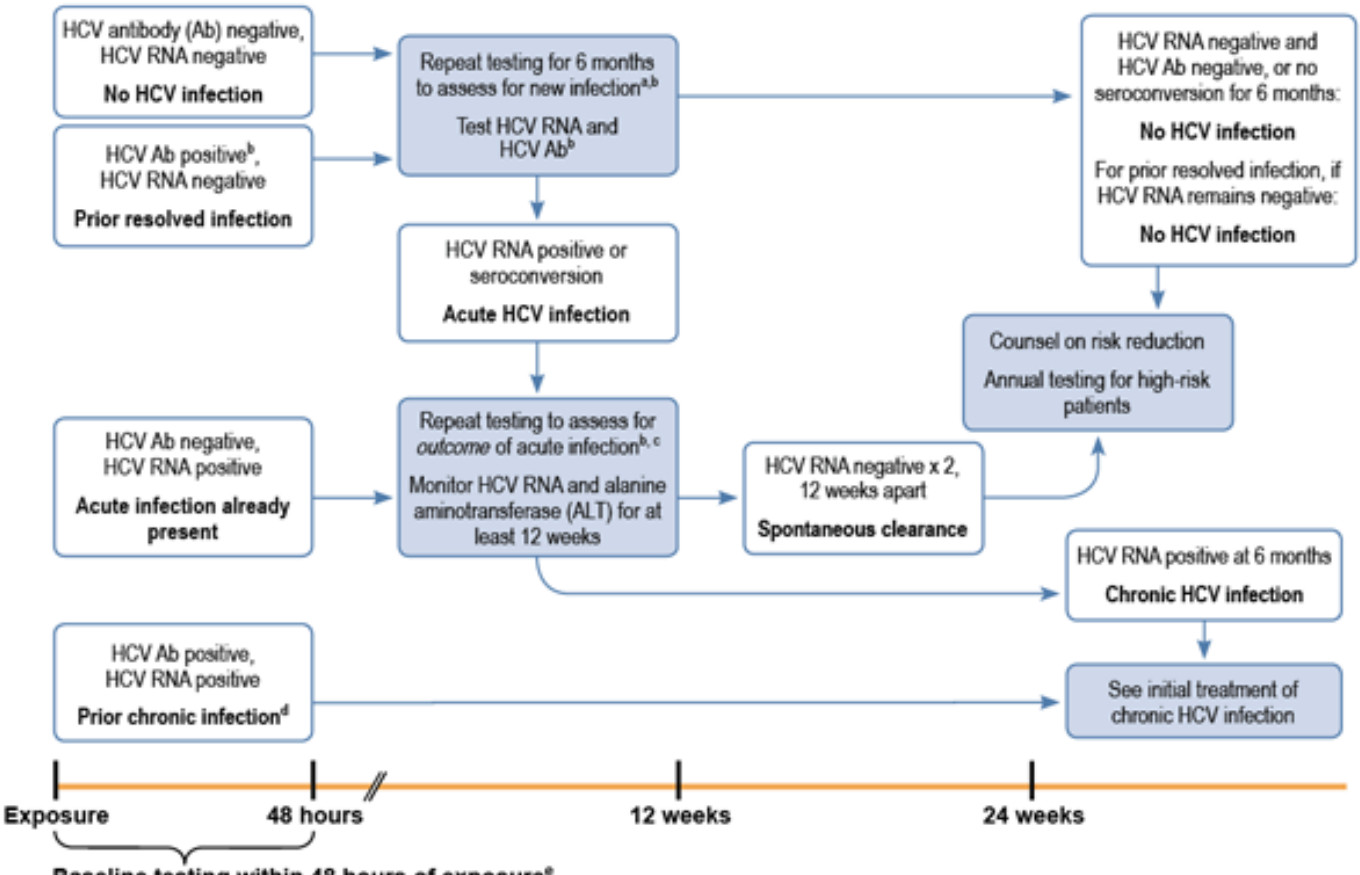
Rating: Class II, Level A

For patients in whom HCV infection spontaneously clears, treatment is NOT recommended.

Rating: Class III, Level B

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.

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