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Recommendations for Testing, Managing, and Treating Hepatitis C

Revised Date: October 8, 2014

Collaborating Partner

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version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this.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	The introduction of direct-acting agents against HCV in 2011 has rapidly changed the treatment of HCV and the timely diagnosis of infection remains essential. This ever increasing pace of change anticipates numerous additional therapies in the next few years, requiring timely guidance on how each new development changes 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 will be updated regularly, as new data, information, and tools and treatments become available. The initial recommendations addressed 4 areas of priority: screening, testing, and linkage to care; initial treatment regimens in persons for whom the decision to treat has been made; retreatment regimens and considerations for persons for whom the decision to treat has been made; and treatment in unique patient populations. Subsequent sections cover when and in whom to initiate treatment; monitoring; and management of acute HCV infection.
Panel members	The Panel members were chosen because of their expertise in the diagnosis, management, and treatment of HCV infection in terms of research and patient care. Members from the fields of hepatology and infectious diseases are included. Members were appointed by the respective Sponsor Societies after vetting by an appointed Sponsor Society committee. At least 1 representative from the hepatitis C community serves on the Panel. The Panel chairs were 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 (3 years), which may be renewed.
Conflict of interest management	The panel was established with the goal of having no personal (ie, direct payment to the individual) financial conflicts among its chairs and among fewer than half of its members. All potential panel members were asked to disclose any relationship with a pharmaceutical, biotechnology, medical device, or health-related company or venture that may result in financial benefit. Disclosures were obtained prior to the panel member appointments and prior to the initiation of the work of the panel (October 2013). Individuals were asked to report activities and personal financial relationships/investments that were current or planned and for the preceding year (prior to October 2013). Individuals were also asked to disclose commercial funding of research activities to their institutions or organizations. Disclosures were reviewed by the HCV Guidance Chairs , which made 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 were assessed. The following relationships were prohibited: ▪ Employment with an affected company ▪ An ownership interest in an affected company ▪ Participation in/payment for promotional or marketing activities including non-CME or speakers bureaus and lectures for affected companies The following relationships/activities were reportable but were not deemed to merit exclusion: ▪ Commercial support of Research. Due to the rapidly evolving nature of the subject matter, having individuals with expertise in the particular clinical topic was critical to developing the highest-quality and most-informed recommendations. To that end, research was not considered an unresolvable conflict if the funding of the research was paid to the institution, 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 or in consultancies sponsored by the research arm of a company (eg, study design or data safety monitoring board) was considered a potential personal conflict but was not considered a criterion for exclusion. The HCV Guidance Chairs achieved a majority of panel members with no personal financial interests. The Panel met face-to-face in October 2013 and meets by conference call regularly to develop and update the Guidance. Panel members were asked to inform the group of any changes to their disclosure status and were given the opportunity to recuse themselves (or be recused) from the discussion where a perceived conflict of interest that could not be resolved existed. 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 financial support. The International Antiviral Society-USA (IAS-USA) is the Collaborating Partner responsible for providing expertise and managing the Panel and the Guidance development process. Centers for Disease Control and Prevention (CDC) provided financial support for the 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 was 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 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. Unpublished or presented reports, data on file, and personal communications are generally not considered. Panel members were appointed based on their collective broad knowledge of available data and current research in the field. These experts were responsible for initially identifying and discussing relevant data, including recent reports from scientific conferences. An initial literature search was conducted on November 4, 2013, to ensure that the Panel addressed all relevant published data. A total of 3939 unique citations were retrieved. Medical subject headings and free text terms were 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. Review articles, studies using mice or rats, and in vitro studies were excluded from consideration. The Panel members regularly monitor the field for new evidence, and the literature search is updated as needed.
Grading of the evidence and RECOMMENDATIONS	The Guidance is presented in the form of RECOMMENDATIONS. Each RECOMMENDATION is graded in terms of the level of the evidence and strength of the recommendation, using a 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	The Guidance was initially divided into 3 subsections: 1) Testing and Linkage to Care; 2) Choice of Regimen in Treatment-Naive Patients For Whom the Decision to Treat Has Been Made, and 3) Retreatment for Patients in Whom the decision to treat has been made. It was later decided to make treatment for unique patient populations a separate section. Subgroups of the panel were assigned to collect, review, and prepare initial draft RECOMMENDATIONS. Draft RECOMMENDATIONS were reviewed at the first full Panel meeting in October 2013. Subgroups of the Panel then met regularly by conference call and presented their updated RECOMMENDATIONS and supporting evidence at each of 3 full-Panel conference calls. Final approval of all RECOMMENDATIONS was made by full-Panel, general consensus. Initial recommendations and their grades were individually

	subject to Panel survey; panelists were given the opportunity to agree, disagree, and provide comment. This procedure helped identify any disagreement or inconsistency between Panel members for each recommendation. Sponsor Societies have final review and approval of each recommendation prior to release of the Guidance on the website, www.hcvguidelines.org.
Update Process	The Guidance will be expanded to cover more management issues as needed, and will be updated on an ongoing basis. Panel members will regularly monitor the field for data that may warrant modification of the Guidance. 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. Updated RECOMMENDATIONS and ratings, once agreed on by the full Panel and approved by the Sponsor Societies, are posted on the Guidance website.
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 hcvguidelines@iasusa.org, or 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.

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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, 2008); (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

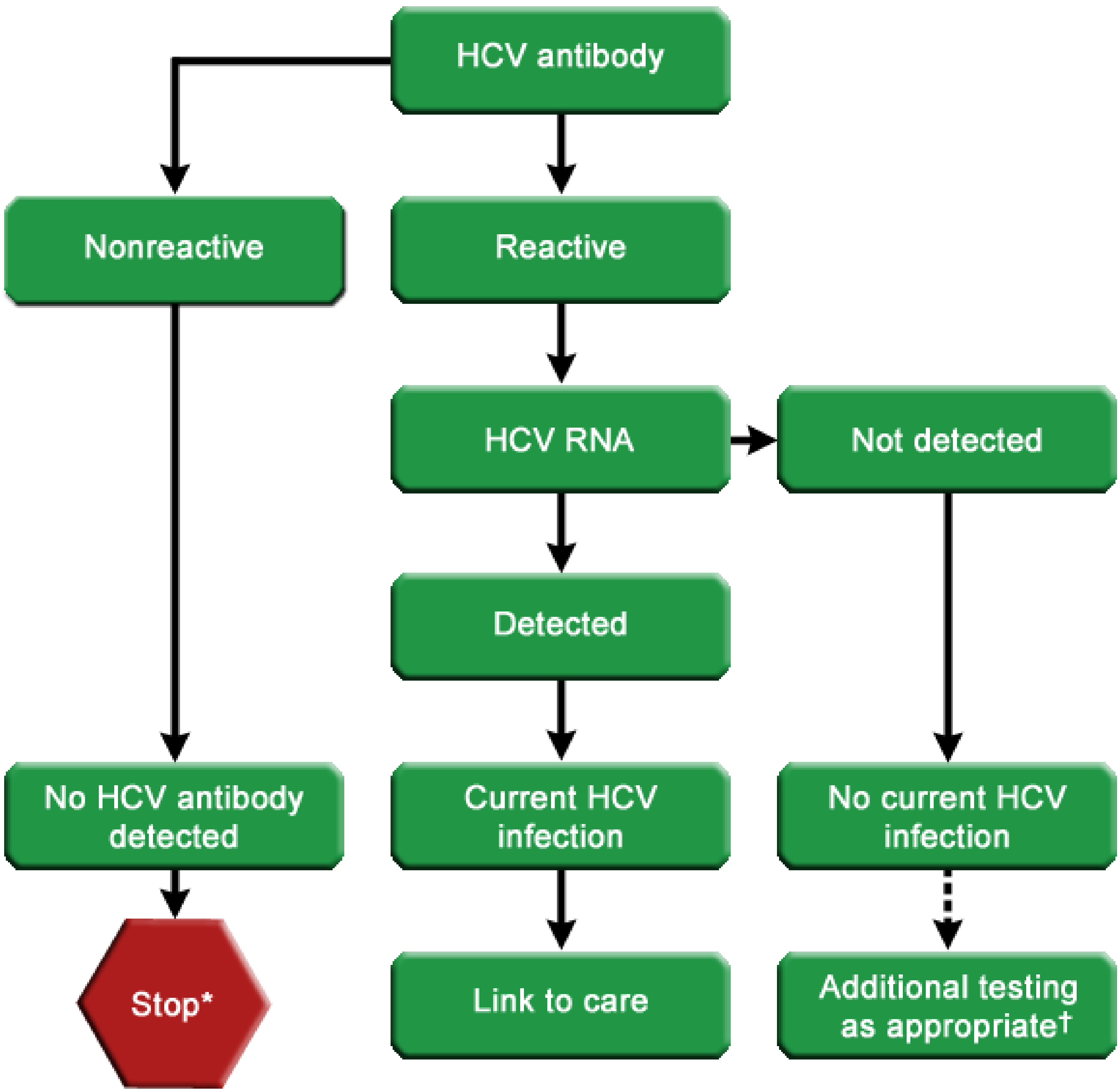
Persons with HCV infection should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood. Persons should be counseled to stop using illicit drugs and enter substance 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; virologic cure is expected to benefit chronically infected persons. Limitations of workforce and societal resources may limit the feasibility of treating all patients within a short period of time. Therefore, when such limitations exist, initiation of therapy should be prioritized first to those specific populations that will derive the most benefit or have the greatest impact on further HCV transmission. Others should be treated as resources allow.

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

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, 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 Whose Risk of HCV Transmission is High and in Whom HCV Treatment May Yield Transmission Reduction Benefits

High HCV Transmission Risk*

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

Active injection drug users

Incarcerated persons

Persons on long-term hemodialysis

Rating: Class IIa, Level C

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*Patients at high 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, 2013) 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 at High 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. The safety and efficacy of treating pregnant women to prevent transmission to the fetus have not yet been established.

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

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, 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 Whose Risk of HCV Transmission is High and in Whom HCV Treatment May Yield Transmission Reduction Benefits

High HCV Transmission Risk*

MSM with high-risk sexual practices

Active injection drug users

Incarcerated persons

Persons on long-term hemodialysis

Rating: Class IIa, Level C

*Patients at high 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 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 HBV or HIV

INITIAL TREATMENT OF HCV INFECTION IN PATIENTS STARTING TREATMENT

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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*.

This section provides guidance on the recommended initial treatments for persons with chronic HCV infection who are naive to HCV treatment or who have achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed (relapsers). Although PEG/RBV relapsers are being retreated, their treatment recommendations are presently the same as for persons being treated for the first time as described below. This section assumes that ***a decision to treat has been made*** and provides guidance regarding optimal treatment. In many instances, however, it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, DAA combinations in IFN-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future update to this guidance.

The level of evidence available to inform the best treatment decisions for each patient varies, as does the strength of the recommendation, and is graded accordingly (see **Methods Table 2**). In addition, when treatment differs for a particular group, such as those infected with specific HCV genotypes, specific recommendations are given. A regimen is classified as either "Recommended" when it is favored for most patients or "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, compensated and decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), post-liver transplant HCV, and those with severe renal impairment or ESRD are addressed in other sections of the document.

As always, patients receiving antiviral therapy require careful pretreatment assessment for comborbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen.

I. Genotype 1

Recommended regimen for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level A

Sofosbuvir is a prodrug of a nucleotide analogue inhibitor of the HCV NS5B RNA-dependent RNA polymerase. The phase 3 NEUTRINO trial evaluated sofosbuvir (400 mg daily) in combination with PEG (2a) (180 ?g by subcutaneous injection weekly) and weight-based RBV (1000 mg to 1200 mg daily) for 12 weeks in 291 treatment-naive patients with chronic HCV genotype 1 infection. (Lawitz, 2013b) The SVR12 for patients with genotype 1 infection was 89%. SVR12 did not differ substantially by baseline characteristic but was lower in patients with cirrhosis (80%) than in those without cirrhosis (92%). (Lawitz, 2013b)

Recommended regimen for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

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 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL
• A history of preexisting cardiac disease **patients with HCV genotype 1 infection, regardless of subtype.**

Rating: Class I, Level B

COSMOS is an ongoing phase 2 clinical trial of sofosbuvir (400 mg daily) plus simeprevir (150 mg daily), a specific inhibitor of the HCV NS3/4A serine protease, with or without RBV for 12 or 24 weeks. (Jacobson, 2013b) The study enrolled 2 cohorts: cohort 1 included patients with a prior null response to PEG/RBV with Metavir fibrosis stage of 0 or 2 (n=80); Cohort 2 included patients who were either treatment-naive or had a prior null response with Metavir fibrosis stage of 3 or 4 (n=87). In cohort 1, the 12-week treatment groups, SVR12 was 96% and 93% in patients treated with or without RBV, respectively. The 24-week treatment groups had SVR12 of 79.3% and 93% in patients treated with or without RBV, respectively. No viral breakthrough was observed in cohort 1 during treatment, and 3 patients experienced viral relapse after stopping therapy. All 3 patients with viral relapse were infected with HCV genotype 1a and had the Q80K polymorphism.

Preliminary SVR4 results are available for cohort 2. The 12-week treatment duration group had 100% SVR in treatment-naive patients treated with or without RBV, and 100% and 93.3% in prior null responder patients treated with or without RBV, respectively. No viral breakthrough was observed during treatment; 1 patient infected with HCV genotype 1a/Q80K experienced viral relapse after stopping therapy. No SVR data are yet available from cohort 2, which received 24 weeks of treatment.

Among patients who had viral relapse, simeprevir (protease) resistance-associated variants have been observed; sofosbuvir (polymerase) resistance-associated variants have not been detected. Safety data have been presented for all 167 patients treated. The combination was well tolerated, with only 2.4% of patients prematurely discontinuing therapy due to adverse events. Data on the use of simeprevir in patients with hepatic impairment are not available at this time.

For patients infected with genotype 1a HCV, baseline resistance testing for the Q80K polymorphism may be considered. However, in contrast to using simeprevir to treat a genotype 1a HCV patient with PEG/RBV when the mutation markedly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with simeprevir and sofosbuvir, because the SVR rate was high in patients with genotype 1a/Q80K infection (SVR12 rate for cohort 1 was 86% [24 of 28 patients]; SVR4 rate for cohort 2 was 90% [10 of 11 patients]). To date, virologic failure has not been observed in patients in either cohort infected with HCV genotype 1b and with HCV genotype 1a in the absence of the Q80K polymorphism. Thus Q80K testing can be considered but is not strongly recommended.

This regimen should be considered only in those patients who require immediate treatment, because it is anticipated that safer and more effective IFN-free regimens will be available by 2015.

Alternative regimens for treatment-naive patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 weeks is an acceptable regimen for IFN-eligible persons with either

1. *HCV genotype 1b or*
2. *HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment.*

Rating: Class IIa, Level A

Two randomized, placebo-controlled phase 3 trials evaluated the efficacy and safety of simeprevir (150 mg once daily) for 12 weeks plus PEG and weight-based RBV for a total of 24 weeks (RGT design found no advantage to extending PEG/RBV to 48 weeks). (Jacobson, 2013a); (Poordad, 2013)

In both studies, SVR24 rates were significantly higher among the simeprevir-containing arms (80% to 81%) than in the non-simeprevir-containing arms (50%). If the HCV RNA at week 4 of treatment is less than 25 IU/mL, therapy should be continued to week 24. If the HCV RNA is greater than 25 IU/mL at treatment week 4 or any treatment week thereafter, the regimen should be discontinued. In patients with HCV genotype 1a infection, the presence of a naturally occurring NS3-4A protease polymorphism (Q80K) prior to treatment was associated with a substantial reduction in SVR among patients treated with simeprevir. A statistically significant difference in SVR12 rates exists between simeprevir-treated persons who are infected with HCV genotype 1a but do not have the Q80K polymorphism and placebo-treated patients who likewise have no such polymorphism. This difference was noted in both the pooled treatment-naive studies and the relapser study (SVR rates of 84% versus 43%, respectively [treatment-naive study] and 78% versus 24%, respectively [relapse study]). The overall SVR in the subgroup of patients with baseline Q80K polymorphism was no better than that in the placebo group. In the United States, persons with genotype 1a HCV infection have a high prevalence of Q80K polymorphism. Because these persons may require alternative therapy, baseline testing for Q80K is recommended for all patients before treatment with the simeprevir plus PEG/RBV regimen is initiated.

For the simeprevir plus PEG/RBV treatment regimen, if the HCV RNA at week 4 of treatment is less than 25 IU/mL, therapy should be continued to week 24. If the HCV RNA is greater than 25 IU/mL at treatment week 4 or any treatment week thereafter, the regimen should be discontinued.

Alternative regimens for treatment-naive patients with HCV genotype 1 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is an acceptable regimen for 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL
• A history of preexisting cardiac disease **persons with HCV genotype 1 infection, regardless of subtype; however, preliminary data suggest that this regimen may be less effective than daily sofosbuvir (400 mg) plus simeprevir (150 mg), particularly among patients with cirrhosis.**

Rating: Class IIb, Level B

Sofosbuvir plus RBV was evaluated in 60 treatment-naive patients with HCV genotype 1 with unfavorable treatment characteristics (eg, African American race and advanced fibrosis). (Osinusi, 2013) In part 1 of the study, 10 participants with early to moderate liver fibrosis were treated with sofosbuvir (400 mg daily) plus weight-based RBV for 24 weeks. Nine participants (90%) achieved SVR24. In part 2, 50 participants with any stage of liver fibrosis were randomized 1:1 to receive 400 mg sofosbuvir with RBV either weight-based or low-dose (600 mg daily) for 24 weeks; SVR24 was 68% (17/25) in the weight-based group and 48% (12/25) in the low-dose group. The regimens used in part 2 of this study were well tolerated, with no discontinuations due to adverse events. Seven of the 13 participants (54%) with advanced liver fibrosis treated in this study relapsed, including all 4 with cirrhosis.

Several additional studies have evaluated the effectiveness of sofosbuvir in persons with HCV genotype 1. In the QUANTUM trial, 38 treatment-naive patients with HCV genotype 1 who did not have cirrhosis were assigned either 12 (n=19) or 24 (n=19) weeks of sofosbuvir (400 mg daily) and weight-based RBV. (Lalezari, 2013) Ten of 19 (53%) in the 12-week arm and 9 of 19 (47%) subjects in the 24-week arm achieved SVR12 (overall 50%). In the ELECTRON trial, 25 treatment-naive subjects with HCV genotype 1 who did not have cirrhosis received sofosbuvir plus RBV for 12 weeks. Twenty-one (84%) achieved SVR12. (Gane, 2013b) In the PHOTON-1 trial, 86 of 113 (76%) treatment-naive subjects with genotype 1 HCV/HIV coinfection achieved SVR12 with sofosbuvir plus RBV for 24 weeks. (Sulkowski, 2013c) Taken together, in a total of 211 subjects, the range of SVR for regimens incorporating sofosbuvir plus daily weight-based RBV (1000 mg to 1200 mg) for up to 24 weeks in treatment-naive persons with HCV genotype 1 was 50% to 84%, with an overall SVR of 72%. Sofosbuvir resistance-associated amino acid variants have not been detected among those patients treated with this combination who did not achieve SVR.

This regimen should be considered only in those patients who require immediate treatment. It is estimated that the FDA will approve safer and more effective IFN-free regimens by 2015.

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

PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Although regimens of PEG/RBV plus telaprevir or boceprevir for 24 to 48 weeks using RGT are also FDA approved, they are markedly inferior to the preferred and alternative regimens. These regimens are associated with their higher rates of serious adverse events (eg, anemia and rash), longer treatment duration, high pill burden, numerous drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and the requirement to be taken with food or with high-fat meals.

PEG/RBV for 48 weeks for treatment-naive subjects 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, regardless of eligibility for IFN therapy:

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

Sofosbuvir (400 mg daily) was combined with weight-based RBV (1000 mg to 1200 mg) to treat HCV genotype 2 treatment-naive patients across 3 clinical trials: FISSION, POSITRON, and VALENCE. (Lawitz, 2013b); (Jacobson, 2013c); (Zeuzem, 2013b) The FISSION study randomized patients to daily PEG/RBV (800 mg) for 24 weeks or sofosbuvir plus daily weight-based RBV (1000 mg to 1200 mg). (Lawitz, 2013b) The SVR was higher (94%) in patients who received sofosbuvir plus RBV compared with those who received PEG/RBV (78%) (52/67). Across all 3 trials, 201 of 214 (94%) patients with HCV genotype 2 achieved SVR with sofosbuvir plus RBV. Among patients who did not achieve SVR, sofosbuvir resistance-associated amino acid variants were not detected. (US FDA, 2013a)

Alternative Regimens for treatment-naive patients with genotype 2:

None

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

PEG/RBV for 24 weeks

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens

Rating: Class III, Level A

PEG (2a) (180 µg weekly) or PEG (2b) (1.5 µg/kg weekly) plus RBV (800 mg daily) for 24 weeks was directly compared with sofosbuvir (400 mg daily) plus weight-based RBV (1000 mg to 1200 mg daily) in the

FISSION trial. (Lawitz, 2013b) The SVR12 achieved with PEG/RBV was lower than that achieved with sofosbuvir/RBV overall (78% and 95%, respectively) and in the subgroups of patients with or without cirrhosis. Safety and tolerability of PEG/RBV was inferior to the profile observed with sofosbuvir and RBV, with greater frequency of reported adverse events and laboratory abnormalities as well as a higher rate of treatment due to adverse events. Further, the duration of therapy with PEG/RBV is 12 weeks longer than that of sofosbuvir plus RBV.

Due to their poor in vitro and in vivo activity, boceprevir and simeprevir should not be used as therapy for patients with HCV genotype 2 infection. Although telaprevir combined with PEG/RBV has antiviral activity against HCV genotype 2, (Foster, 2011) the additional side effects and longer duration of therapy do not support use of this regimen.

III. Genotype 3

Recommended regimen for treatment-naive patients with HCV genotype 3, regardless of eligibility for IFN therapy:

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 assessed the efficacy and safety of sofosbuvir (400 mg daily) plus RBV for 24 weeks in 250 treatment-naive (42%) and treatment-experienced (58%) subjects with HCV genotype 3 infection. The overall SVR12 was 84% and was higher among treatment-naive than treatment-experienced patients (93% versus 77%, respectively). These results suggest higher response rates can be achieved with a 24-week duration of sofosbuvir plus RBV than those reported for the 12- or 16-week durations studied in the FISSION (Lawitz, 2013b) (12 weeks, SVR12: 63%), POSITRON, (Jacobson, 2013c) (12 weeks, SVR 12: 61%) and FUSION (12 weeks, SVR12: 30%, 16 weeks, SVR12: 62%) trials. The primary reason for the higher SVR with extended therapy among treatment-naive patients was a reduction in the relapse rate from 40% to 5%. In sub-analysis, 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 genotype 3 who are eligible to receive IFN.

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

Rating: Class IIa, Level A

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

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

PEG/RBV for 24 to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

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/RBV is an FDA-approved regimen for HCV genotype 3, its less acceptable adverse effect profile, requirement 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 genotype 3, boceprevir, telaprevir, and simeprevir should not be used as therapy for patients with HCV genotype 3 infection.

IV. Genotype 4

Few data are available to help guide decision-making in patients infected with HCV genotype 4. 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 4 who are eligible to receive IFN.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons

with HCV genotype 4 infection.

Rating: Class IIa, Level B

In the Phase 3 NEUTRINO trial, (Lawitz, 2013b) 28 treatment-naive patients with HCV genotype 4 infection were treated with sofosbuvir (400 mg daily) plus PEG (2a) (180 µg weekly) and weight-based RBV (1000 mg 1200 mg once daily) for 12 weeks. Of the 28 patients with genotype 4, 27 (96%) achieved SVR12. The one patient who did not achieve SVR had cirrhosis and relapsed after therapy. The adverse event profile was similar to that seen with PEG/RBV therapy.

Recommended regimen for treatment-naive patients with genotype 4 who are not eligible to receive IFN.

Daily sofosbuvir (400 mg) plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is recommended for 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL
• A history of preexisting cardiac disease **patients with HCV genotype 4 infection.**

Rating: Class IIb, Level B

In a small study of Egyptian patients in the United States treated with sofosbuvir plus weight-based RBV (1000 mg to 1200 mg), SVR12 was achieved in 11/14 (79%) and 14/14 (100%) in treatment-naive patients treated for 12 weeks and 24 weeks, respectively. In treatment-experienced patients treated for 12 weeks and 24 weeks, SVR12 was achieved in 10/17 (59%) and 13/15 (87%), respectively. (Ruane, 2014)

Alternative regimens for treatment-naive patients with HCV genotype 4 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 24 to 48 weeks is an alternative regimen for IFN-eligible persons with HCV genotype 4 infection.

Rating: Class IIb, Level B

A Phase 3 trial in patients with HCV genotype 4 is currently under way. This trial compares PEG and weight-based RBV (1000 mg to 1200 mg) for 48 weeks with a 12-week regimen of simeprevir 150 mg once daily plus PEG and weight-based RBV (1000 mg to 1200 mg) followed by an additional 12 or 36 weeks of PEG/RBV alone. (Moreno, 2013) In another study, the RESTORE trial, an RGT approach is used in place of the simeprevir arm. Patients who have HCV RNA below 25 IU/mL at week 4 and undetectable HCV RNA by week 12 continue PEG/RBV for an additional 12 weeks, and those who do not achieve this response continue PEG/RBV for an additional 36 weeks (total 48 weeks of therapy). The study has enrolled 107 patients, of whom 35 are treatment-naive, including 2 with cirrhosis. To date, 10 of 11 patients (91%) who met criteria for shortened therapy have achieved SVR4, and 3 of 3 have achieved SVR12. To date, therapy has failed in 4 patients: 3 had detectable virus at the end of treatment and 1 experienced virologic relapse. Anemia was reported in 8.4% and hyperbilirubinemia in 1.9% of all study participants (n=107) (including treatment-experienced patients). Four serious adverse events were attributed to simeprevir. No episodes of rash were reported. (Moreno, 2013)

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

PEG/RBV for 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

PEG/RBV for 48 weeks was the previously recommended regimen for patients with HCV genotype 4. The addition of sofosbuvir (400 mg daily) to PEG/RBV increases response rates and markedly shortens therapy with no apparent additional adverse effects. The addition of simeprevir to PEG/RBV increases response rates with a minimal increase in adverse events and can shorten therapy to 24 weeks.

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

V. Genotype 5 or 6

Few data are available to help guide decision-making in 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. No data are available to support the use of a non-PEG containing regimen for patients with HCV genotype 5 or 6 infection.

Recommended regimen for treatment-naive patients with HCV genotype 5 or 6.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level B

In the Phase 3 NEUTRINO trial (Lawitz, 2013b), treatment-naive patients with genotypes 1 (n=291), 4 (n=28), 5 (n=1), and 6 (n=6) were treated with sofosbuvir (400 mg daily) plus PEG (2a) (180 µg per week) and weight-based RBV (1000 mg 1200 mg once daily) for 12 weeks. All 6 patients with HCV genotype 6 and the 1 patient with genotype 5 achieved SVR12. The adverse event profile in these patients and in the larger study population was similar to that seen with PEG/RBV therapy.

Alternative regimens for treatment-naive patients with HCV genotype 5 or 6.

Daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 48 weeks is an acceptable regimen for persons infected with HCV genotype 5 or 6.

Rating: Class IIb, Level A

PEG/RBV for 48 weeks was the previously recommended regimen for patients infected with HCV genotype 5 or 6. Sofosbuvir has activity against genotypes 5 and 6, and when combined with PEG/RBV for 12 weeks led to SVR in the 6 patients in whom it was studied. (Lawitz, 2013b) The addition of sofosbuvir (400 mg daily) to PEG/RBV shortens duration of therapy with no apparent additional adverse effects and likely substantially increases response rates.

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

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Telaprevir- or boceprevir-based regimens

Rating: Class III, Level A

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

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

Genotype	Recommended	Alternative	NOT Recommended
1	**IFN eligible:** SOF + PEG/RBV x 12 weeks 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: SOF + SMV ± RBV x 12 weeks	**IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: SOF + RBV x 24 weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG/RBV x 24 weeks

			Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
4	**IFN eligible:** SOF + PEG/RBV x 12 weeks 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present.

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. In general, treatment responses of patients achieving an undetectable level of virus during a prior treatment course who relapse following cessation of therapy (**relapser**) are similar to those of treatment-naive persons (see Initial Treatment). Treatment responses are generally lower in prior **non-responders**, which includes null responders (those in whom serum HCV RNA levels declined less than 2 $\log_{10}$ IU/mL by week 12 during a prior treatment course) and partial responders (those with a $\geq$ 2 $\log_{10}$ IU/mL response whose virus remained detectable up to 24 weeks or the end of treatment). This section assumes that a ***decision to treat has been made*** and advises on the optimal treatment. In many instances, however, it may be advisable to delay treatment for some patients with documented early fibrosis stage (F 0-2), because waiting for future highly effective, pangenotypic, combinations in IFN-free regimens may be prudent. Potential advantages of waiting to begin to treatment will be provided in a future update to this guidance.

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 graded 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. Regimens are 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."

As always, patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients should have careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen.

I. Genotype 1

Recommended regimen for HCV genotype 1 PEG/RBV (without an HCV protease inhibitor) nonresponder patients:

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 retreatment of HCV genotype 1 infection, regardless of subtype or IFN eligibility.

Rating: Class IIa, Level B

Recommended regimen for HCV genotype 1 PEG/RBV (with an HCV protease inhibitor) nonresponder patients:

Daily sofosbuvir (400 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) and weekly PEG for 12 to 24 weeks is recommended for retreatment of HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

COSMOS is a phase 2a 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 to 1200 mg daily) for 12 or 24 weeks (Jacobson, 2013b). Of the 80 null responders with a Metavir fibrosis stage of 2 or less included in this trial, 79% to 96% achieved SVR (79%-96% in RBV-containing arms and 93% in both RBV-free arms). Among those null responders with a Metavir fibrosis stage of 3 or 4 (n=47) who received 12 weeks of sofosbuvir and simeprevir, SVR4 was observed in 14 (93%) of 15 patients in the ribavirin-containing arm and 100% (all 7 participants) in the RBV-free arm. Although benefit from RBV is not apparent from these preliminary results, it cannot be excluded before availability of SVR12 data. Post-treatment results are not yet available for the 24-week arms. Excluding nonvirologic failures, patients with HCV genotype 1a with Q80K mutations had slightly lower numeric response rates (fibrosis stage 0-2: SVR12=89% [n=27]; fibrosis stage 3 or 4: SVR4=91% [n=11]) than genotype 1a patients without Q80K and genotype 1b (fibrosis stage 2: SVR12 100%, n=47; fibrosis stage 3 or 4: SVR4=100% [n=29]). However, because the study was not powered to assess this comparison, insufficient evidence exists on the role of testing for the Q80K mutation at this time. These regimens were well tolerated, although adverse events (eg, anemia and hyperbilirubinemia) were seen more often in patients on RBV-containing regimens. (Jacobson, 2013b)

The safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The uncertain impact of cholestasis and the occasional association of SMV with elevated transaminases create potential for drug accumulation or impaired hepatic function during SMV use. Clinical trials with SMV have been limited to patients with compensated disease who have CTP class A, total bilirubin of 1.5 x ULN or lower, and transaminases 10 x ULN or lower. For these reasons, simeprevir use should be limited to patients with compensated liver disease. Use of simeprevir is not recommended in patients with moderate to severe hepatic impairment. The combination of PEG/RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Alternative regimen for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1.

Eligible to receive IFN:

Daily sofosbuvir (400 mg) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 to 24 weeks is an alternative for retreatment of IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

Ineligible to receive IFN:

Daily sofosbuvir (400 mg) for 24 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 24 weeks is an alternative for retreatment of IFN-ineligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

NEUTRINO is an open-label, single-arm trial that evaluated 12 weeks of sofosbuvir plus PEG/RBV in treatment-naive subjects with HCV genotypes 1, 4, 5, or 6; 89% had HCV genotype 1, and 17% had cirrhosis. The SVR was 89% (261 of 292) and was somewhat lower in patients with genotype 1b than 1a (82% and 92%, respectively) and those with cirrhosis versus those without (80% versus 92%, respectively). (Lawitz, 2013a) Treatment-experienced subjects who did not respond to PEG/RBV with or without an HCV protease inhibitor were not included in this study. There are no data available to estimate the response in patients who have been previously treated with a protease inhibitor. However, among patients who were previously treated with PEG/RBV, the FDA estimates that the response rate in such patients would approximate the observed response rate in those NEUTRINO subjects with baseline factors traditionally associated with a lower response to IFN-based treatment. (US FDA, 2013a) In the NEUTRINO trial, SVR rate was 71% among participants with HCV genotype 1 with IL28B non-C/C alleles, high HCV RNA levels, and METAVIR 1 fibrosis stage F3 or F4 (37 of 52 patients). (Gilead Sciences, 2013; Sovaldi package insert)

In a prospective, multicenter trial of sofosbuvir (400 mg/day) plus RBV (ascending dose of 400 mg/day, escalating based on hemoglobin level) including treatment-experienced patients with recurrent HCV infection after liver transplantation, SVR12 was 70% in this population. (Charlton, 2013a)

Alternative regimen for PEG/RBV (without an HCV protease inhibitor) nonresponder patients with HCV genotype 1 who are eligible to receive IFN.

Daily simeprevir (150 mg) for 12 weeks plus weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) and weekly PEG for 48 weeks is an alternative for IFN-eligible persons with HCV genotype 1 infection. (All patients with cirrhosis who are receiving simeprevir should have well compensated liver disease.)

Rating: Class IIa, Level A

Simeprevir was combined with PEG/RBV in patients who had previously failed to respond to PEG/RBV dual therapy in the Phase 2b ASPIRE trial. (Zeuzem, 2013a); (Janssen Therapeutics, 2013) (www.fda.gov; package insert). SVR24 after 48 weeks of triple therapy in the simeprevir 150 mg/day arm was 65% in patients with a previous partial response (n=23) and 53% in patients with a prior null response (n=17). Patients with HCV genotype 1a infection had inferior response rates compared with those with genotype 1b (SVR24: 47% vs 77% in patients with a partial response and 41% vs 47% in patients with a null response, respectively). Despite lower SVR in patients with HCV genotype 1a infection, SVR rates were similar with and without the presence of the Q80K mutations at baseline. SVR rates in patients with advanced fibrosis (METAVIR stage F3 or F4) treated with simeprevir (150 mg daily) plus PEG/RBV for 48 weeks were 59% in patients with a partial response (n=33) and 35% in patients with a null response (n=34). Safety in patients exposed to simeprevir was similar to that of persons in the placebo arms; however, there was a higher incidence of hyperbilirubinemia (8%) and photosensitivity/rash (5%). (Zeuzem, 2013a)

The safety and efficacy of simeprevir have not been studied in HCV-infected patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The uncertain impact of cholestasis and the occasional association of simeprevir with elevated transaminases pose potential for impaired hepatic function during simeprevir use. Clinical trials with simeprevir have been limited to patients with compensated disease who have CTP class A, total bilirubin level of 1.5 x ULN or lower, and transaminase level of 10 x ULN or lower. For these reasons, simeprevir use should be limited to patients with compensated liver disease. Use of simeprevir is not recommended in patients with moderate to severe hepatic impairment. Use of the drug in this population is not recommended at this time. The combination of PEG/RBV is contraindicated in patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

The following regimens are NOT recommended for PEG/RBV (with or without an HCV protease inhibitor) nonresponder patients with HCV genotype 1:

PEG/RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

For nonresponder patients with genotype 1 and a history of decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C), treatment is not indicated because of the risks of PEG and boceprevir and telaprevir in this population.

Triple therapy with boceprevir plus PEG/RBV for 48 weeks may result in SVR for up to 52% of PEG/RBV partial responders (RESPOND 2; (Bacon, 2011)) and 38% of null responders (PROVIDE; (Di Bisceglie, 2013)). Similarly, telaprevir plus PEG/RBV resulted in SVR24 of 54% to 59% among partial responders and an SVR24 of 29% to 33% among null responders (REALIZE; (Zeuzem, 2011)). Due to the relatively poor efficacy, prolonged duration of therapy (48 weeks), and poor tolerability, these regimens are no longer recommended.

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

Patients with advanced liver disease are at increased risk for sepsis, worsening decompensation, and death when treated with dual or triple IFN-based therapy. (Crippin, 2002); (Coilly, 2014) Simeprevir is primarily metabolized by the liver and should not be used in patients with advanced cirrhosis (CTP B or C), as the AUC is increased 2.4- to 5.2-fold. (Janssen Therapeutics, 2013) (Olysio package insert, Janssen).

II. Genotype 2

Recommended regimen for genotype 2 PEG/RBV nonresponders.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for retreatment of HCV genotype 2 infection. (Patients with cirrhosis may benefit by extension of treatment to 16 weeks.)

Rating: Class I, Level A

High SVR12 rates have been demonstrated in non-cirrhotic genotype 2 treatment-experienced patients who received 12 weeks of sofosbuvir plus RBV. Limited data are available in cirrhotic genotype 2 treatment experienced patients; 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, at this time definitive recommendations on the appropriate duration of sofosbuvir and RBV for treatment-experienced, HCV genotype 2-infected persons with cirrhosis cannot be made. The decision to extend therapy to 16 weeks should be made on a case-by-case basis.

Alternative regimen for PEG/RBV nonresponder patients with HCV genotype 2 infection who 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 for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 2 infection.

Rating: Class IIa Level B

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

The following regimens are NOT recommended for nonresponder patients with HCV genotype 2.

PEG/RBV with or without telaprevir, boceprevir or simeprevir

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

No HCV protease inhibitors have been approved or are indicated for the treatment of genotype 2 infection. Although PEG/RBV has been the mainstay of treatment of 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 HCV genotype 3 PEG/RBV nonresponders.

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 HCV genotype 3 infection.

Rating: Class IIa, Level A

The phase 3 FUSION trial compared 12 weeks (n=103) with 16 weeks (n=98) of daily sofosbuvir (400 mg) and weight-based RBV (1000 mg to 1200 mg) in genotype 2 or 3 HCV-infected patients in whom previous PEG/RBV therapy had failed. Of patients, 63% had genotype 3; 34% of all patients 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 genotype 3 patients in the 12-week arm was 30% (19% among patients with cirrhosis and 37% among those without cirrhosis). Extending therapy to 16 weeks increased the SVR rate among genotype 3 patients to 62% (61% among patients with and 63% in those without cirrhosis).

Based on results from FUSION, the phase 3 multicenter, randomized placebo-controlled VALENCE trial was amended to evaluate the effect 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 relapsed. The SVR12 rates after 24 weeks of therapy for treatment-experienced patients with genotype 3 was 79% (60% among patients with 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 in all genotype 3 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%). Although longer treatment duration with a well-tolerated regimen may potentially be more successful in these more difficult-to-treat patients, data remain limited. Either duration of treatment is considered acceptable at this time (see below).

Alternate regimen for HCV genotype 3 PEG/RBV nonresponder patients who 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 for 12 weeks is an alternative for IFN-eligible persons with HCV genotype 3 infection.

Rating: Class IIa Level B

Choice of specific regimen may be influenced by previous or anticipated tolerance to PEG or 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. 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 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 for 24 weeks. Of HCV genotype 3-infected patients with and without cirrhosis, 10 (83%) of 12 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 nonresponder patients with HCV genotype 3 infection.

PEG/RBV with or without telaprevir, boceprevir or simeprevir

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

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

IV. Genotypes 4, 5, and 6

***Recommended regimen for HCV genotype 4, PEG/RBV nonresponder patients*.**

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 4 infection

Rating: Class IIa, Level C

***Alternate regimen for HCV genotype 4, PEG/RBV nonresponder patients*.**

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 HCV genotype 4 infection.

Rating: Class IIa, Level B

The following regimens are NOT recommended for nonresponder patients with genotype 4

HCV infection.

PEG/RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Recommended regimen for HCV genotype 5 or 6, PEG/RBV nonresponder patients.

Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly PEG for 12 weeks is recommended for retreatment of IFN-eligible persons with HCV genotype 5 or 6 infection.

Rating: Class IIa, Level C

Alternate regimen for PEG/RBV nonresponder patients with HCV genotype 5 or 6.

None

The following regimens are NOT recommended for nonresponder patients with HCV genotype 5 or 6.

PEG/RBV with or without telaprevir or boceprevir

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

In the NEUTRINO trial, high SVR rates were seen in small numbers of treatment-naive patients with HCV genotypes 4, 5, and 6 treated with sofosbuvir plus PEG/RBV for 12 weeks (genotype 4: n=28, SVR=96%; genotype 5: n=1, SVR=100%; and genotype 6: n=6, SVR=100%). (Lawitz, 2013a) In a pilot study of treatment-experienced HCV genotype 4 patients of Egyptian ancestry, SVR12 was 59% in patients treated with sofosbuvir plus RBV for 12 weeks; SVR4 was 93% in patients treated for 24 weeks. In this cohort, 24% to 27% of patients had cirrhosis. (Ruane, 2013) The only available data with simeprevir for treatment-experienced patients with genotype 4 come from the ongoing RESTORE trial, in which patients (n=50) are receiving treatment with daily simeprevir 150 mg for 12 weeks plus PEG/RBV for a total of 48 weeks (10 prior partial responders, 40 prior null responders). Interim analysis revealed a 40% to 49% RVR rate using this regimen. Final SVR results are pending. (Moreno, 2013) Given the relative paucity of data, expert consultation is needed to determine optimal duration of therapy in patients with genotype 4, 5, or 6 treated with sofosbuvir.

Explanations of highlighted changes made on March 21, 2014 are available here.

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

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

Genotype	Recommended	Alternative	NOT Recommended
Patients in whom previous PEG/RBV has failed*			
1	SOF + SMV ± RBV x 12 weeks	SOF x 12 weeks + PEG/RBV x 12-24 weeks SOF + RBV x 24 weeks SMV x 12 weeks + PEG/RBV x 48 weeks**	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± telaprevir or boceprevir Monotherapy with PEG, RBV, or a direct-acting antiviral agent Do not treat decompensated cirrhosis with PEG
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV ± any current protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
4	SOF + PEG/RBV x 12 weeks	SOF + RBV x 24 weeks	PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a

			DAA Do not treat decompensated cirrhosis with PEG
5 or 6	SOF x 12 weeks + PEG/RBV 12 weeks		PEG/RBV ± any current HCV protease inhibitor Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG
Patients in whom previous treatment with PEG/RBV plus either telaprevir or boceprevir has failed* †† †††			
1	SOF x 12 weeks + PEG/RBV x 12-24 weeks	SOF + RBV x 24 weeks‡ SOF + PEG/RBV x 24 weeks‡‡	PEG/RBV ± telaprevir or boceprevir or SMV Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV

*Failure (non response) is defined as partial or null response to treatment with PEG/RBV. Relapse to prior therapy should be treated the same as treatment-naive (see Initial Treatment section)

**For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present

*** Failure (non response) is defined as partial or null response to treatment with PEG/RBV plus telaprevir or boceprevir. Relapse to prior therapy should be treated the same as treatment naive (see Initial Treatment section)

† Consideration should be given to postponing treatment, pending release of new drugs for patients with

limited (F 0-2) hepatic fibrosis

[††] A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure not provided due to potential risk of preexistant resistance to protease inhibitor treatment.

[†††] Given the lack of prior approval of protease inhibitor therapy for genotypes 2, 3, 4, 5, 6 and the lack of sufficient data, no recommendations are given for these genotypes at this time

[‡]IFN ineligible

[‡‡]IFN eligible

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, and is divided into 3 parts: pretreatment and on-treatment monitoring, post-treatment follow-up for persons in whom treatment has failed to clear virus, and post-treatment 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.

Rating: Class I, Level C

The following laboratory tests are recommended within 6 weeks prior to starting antiviral therapy:

> **Complete blood cell (CBC) count; 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)**

Rating: Class I, Level B

The following laboratory test is recommended within 12 weeks of starting antiviral therapy:

> **HCV genotype and quantitative HCV viral load**

Rating: Class I, Level B

Recommended monitoring during antiviral therapy

CBC count, creatinine level, calculated GFR, and hepatic function panel are recommended every 4 weeks during antiviral therapy. TSH is recommended every 12 weeks for patients on IFN. More frequent assessment for drug-related toxic effects (eg, CBC count for patients receiving RBV) is recommended as clinically indicated.

Rating: Class I, Level B

Quantitative HCV viral load testing is recommended after 4 weeks of therapy, at the end of treatment, and at 12 weeks following completion of therapy.

Rating: Class I, Level B

Quantitative HCV viral load monitoring at 4 weeks is recommended, but discontinuation of treatment because this test result is missing is NOT recommended.

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

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

Rating: Class III, Level C

Female patients 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**].

Individuals receiving antiviral therapy for chronic HCV infection should have careful monitoring for toxic effects, virologic response, and adherence to therapy. The assessment of HCV viral load at week 4 of therapy is useful to determine adherence or futility, and the end of treatment viral load will help to differentiate potential viral breakthrough versus relapse. Although HCV-RNA testing is recommended at week 4 of treatment, the absence of testing results at week 4 is not a reason to discontinue treatment. Some may choose to forego end of treatment viral load testing given the high rates of viral response with the newer regimens but to focus on the week 12 post-treatment viral load.

The availability of IFN-free treatment regimens has simplified hepatitis C therapy with shorter-duration, all-oral therapy for many patients. However, PEG/RBV-based regimens are still recommended for some patients and these require specific monitoring for the toxic effects (eg, anemia or neutropenia) associated with PEG or RBV use. (RBV prescribing information, 2014); (PEG prescribing information, 2014) In patients without 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 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. Thus, the pretreatment evaluation should explore potential drug-drug interactions (eg, http://www.hep-druginteractions.org/) for the selected antiviral medications, address potential drug adverse effects, and include laboratory testing. The purpose of on-treatment monitoring is to document viral response, evaluate for possible drug toxic effects, and assess adherence to the regimen.

RBV is reported to cause 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. The safety of newer antivirals during pregnancy is unknown. 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.

Monitoring patients who have completed treatment

Patients who do not achieve an SVR, because of failure of the treatment to clear or maintain clearance of HCV infection with relapse after treatment completion, have ongoing HCV infection and the possibility of continued liver injury. 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, hepatitis C-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.

Recommended monitoring for patients in whom treatment failed to achieve an SVR

Disease progression assessment every 6 months to 12 months with a hepatic function panel, CBC count, and INR is recommended.

Rating: Class I, Level C

Surveillance for hepatocellular carcinoma with ultrasound testing every 6 months is recommended for patients with more advanced fibrosis (ie, Metavir 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

Monitoring for HCV drug resistance-associated variants (RAVs) on and after 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, 2014) 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, 2014); (Schneider, 2014) However, there is no evidence to date that the presence of RAVs results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. 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-associated resistant mutations may impact simeprevir activity in vitro. However, there are currently no data on SVR rates when patients are retreated with sofosbuvir plus simeprevir after emergence of telaprevir- or boceprevir-associated resistance mutations. With the exception of testing for Q80K polymorphism at baseline in patients with HCV genotype 1a before treatment with simeprevir plus PEG/RBV, testing for RAVs prior to repeat antiviral treatment is not recommended. If in doubt, consultation with an expert in the treatment of HCV infection may be useful.

Recommended follow-up for patients who achieve an SVR

For patients who do not have advanced fibrosis (ie, those with Metavir F0, F1, or 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 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

Routine assessment for regression in liver fibrosis after achieving SVR is NOT recommended.

Rating: Class III, 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/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 F0, F1, or 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 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 fail to respond), but still may be at some risk of 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 least annually 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)

There is no evidence that monitoring for liver fibrosis regression after an SVR provides clinical benefit.

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.

Testing patients with ongoing risk for HCV infection (eg, illicit drug use, high-risk sexual exposure) periodically for HCV reinfection is recommended. Flares in liver enzyme test results should prompt evaluation of possible de novo re-infection 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, it is recommended that testing for reinfection with HCV 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 an SVR and who are receiving immunosuppressive treatment (eg, systemic

corticosteroids, antimetabolites, chemotherapy, etc.) is NOT routinely recommended.

Rating: Class III, Level C

In patients with inactive or past hepatitis B virus (HBV) infection, reactivation of infection and clinically apparent hepatitis during immunosuppressive treatment or chemotherapy can occur. 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) 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, routine testing of HCV RNA during immunosuppressive treatment, or prophylactic administration of antivirals during immunosuppressive treatment, is not routinely recommended. However, acute liver injury is common among patients receiving chemotherapy or potent immunosuppressive agents; quantitative HCV RNA testing should be included in the laboratory assessment of the cause of liver injury.

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.

Rating: Class I, Level C

The following laboratory tests are recommended within 6 weeks prior to starting antiviral therapy:

- **Complete blood cell (CBC) count; 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)**

Rating: Class I, Level B

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

HCV genotype and quantitative HCV viral load

Rating: Class I, Level B

Recommended monitoring during antiviral therapy

CBC count, creatinine level, calculated GFR, and hepatic function panel are recommended every 4 weeks during antiviral therapy. TSH is recommended every 12 weeks for patients on IFN. More frequent assessment for drug-related toxic effects (eg, CBC count for patients receiving RBV) is recommended, as clinically indicated.

Rating: Class I, Level B

Quantitative HCV viral load testing is recommended after 4 weeks of therapy, at the end of treatment, and at 12 weeks following completion of therapy.

Rating: Class I, Level B

Quantitative HCV viral load monitoring at 4 weeks is recommended, but discontinuation of treatment because this test result is missing is NOT recommended.

Rating: Class III, Level C

Recommended monitoring for pregnancy-related issues prior to and during antiviral therapy that includes RBV.

Women of child bearing 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 child bearing 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 child bearing potential, and for female partners of men who receive RBV treatment.

Rating: Class I, Level C

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

Rating: Class III, Level C

Female patients 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 an SVR

Disease progression assessment every 6 months to 12 months with a hepatic function panel, CBC count, and INR is recommended.

Rating: Class I, Level C

Surveillance for hepatocellular carcinoma with ultrasound testing every 6 months is recommended for patients with more advanced fibrosis (ie, Metavir 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

Monitoring for HCV drug resistance-associated variants (RAVs) on and after therapy is NOT recommended.

Rating: Class III, Level C

Recommended follow-up for patients who achieve an SVR

For patients who do not have advanced fibrosis (ie, those with Metavir F0, F1, or 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 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

Routine assessment for regression in liver fibrosis after achieving SVR is NOT recommended.

Rating: Class III, Level C

Monitoring for HCV during chemotherapy and immunosuppression

Prospective monitoring for HCV recurrence among patients who achieved an SVR and who are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc.) is NOT routinely recommended.

Rating: Class III, Level C

UNIQUE PATIENT POPULATIONS

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

1. Patients with HIV/HCV Coinfection

***The summary of recommendations for HIV-coinfected patients is in the* BOX.**

Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 infection who are eligible to receive IFN:

Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is recommended for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class I, Level B

Recommended regimen(s) for treatment-naive and prior relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN.

Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive HIV/HCV-coinfected patients with HCV genotype 1 infection.

Rating: Class I, Level B

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] daily) for 12 weeks is recommended for treatment-naive and prior PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.

Rating: Class IIa Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV nonresponse, regardless of IFN eligibility

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] daily) for 12 weeks is recommended for prior PEG/RBV nonresponder, HIV/HCV-coinfected patients with genotype 1 infection. Simeprevir should only be used with antiretroviral drugs with which it does not have significant interactions: raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir.

Rating: Class IIa, Level C

Recommended regimen(s) for treatment-experienced patients with HCV genotype 1 with a history of PEG/RBV plus telaprevir or boceprevir nonresponse

Treat as recommended for HCV-monoinfected individuals.

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 2 and 3 infection

Use the same regimens as is recommended for persons with HCV monoinfection; specifically:

For patients with genotype 2 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 12 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients. Patients who are prior nonresponders and have cirrhosis may benefit by extension of treatment to 16 weeks.

Rating: Class I, Level B

For patients with genotype 3 infection: sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is recommended for treatment-naive and treatment-experienced HIV/HCV-coinfected patients.

Rating: Class I, Level B

Recommended regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with genotype 4, 5, or 6 HCV:

Treat as recommended for persons with HCV monoinfection.

HIV/HCV coinfection results in increased liver-related morbidity and mortality, non-hepatic organ dysfunction, and overall mortality. Even in the potent antiretroviral era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection. (Thein, 2008); (de Ledinghen, 2008); (Fierer, 2013) Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with PEG/RBV have lower rates of hepatic decompensation, hepatocellular carcinoma, and liver related mortality. (Berenguer, 2009); (Limketkai, 2012); (Mira, 2013) Uptake of HCV therapy is limited in the HIV/HCV-coinfected population due to historically lower response rates, patient comorbidities, patient and practitioner perception, and the adverse events associated with IFN-based therapy. (Mehta, 2006); (Thomas, 2008) Due to the special population designation, the first 2 approved DAAs, telaprevir and boceprevir, remain off label for use in HIV/HCV-coinfected patients, further limiting access to treatment in this population. With the availability of the DAAs sofosbuvir and simeprevir, a milestone has been reached in HIV/HCV coinfected patients. Treatment of HIV/HCV-coinfected patients requires awareness and attention to the complex drug interactions that can occur between DAA and HIV antiretroviral medications.

Pharmacokinetics and Drug Interactions

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 OATP. Drug interaction studies with antiretroviral drugs (ie, efavirenz, tenofovir, emtricitabine, rilpivirine, darunavir/ritonavir, and raltegravir) in non-infected persons identified no clinically significant interactions (Kirby, 2013) making sofosbuvir an ideal therapy for patients with HIV/HCV coinfection. Sofosbuvir is not recommended for use with tipranavir because of the potential of this antiretroviral drug to induce P-gp (see package insert).

Simeprevir is metabolized primarily by cytochrome P450 3A4 (CYP3A4) and therefore is 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 non-infected 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 darunavir/ritonavir, resulting in their exclusion from the Phase III C212 clinical trial investigating simeprevir in combination with PEG/RBV in patients with HIV/HCV coinfection. (Ouwerkerk-Mahadevan, 2012)

Ribavirin has the potential for dangerous drug interactions with didanosine resulting in mitochondrial toxicity with hepatomegaly/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, and thus zidovudine is not recommended for use with RBV. (Alvarez, 2006)

Sofosbuvir (400 mg once daily) as part of a triple-therapy regimen with PEG (180 ?g weekly) and weight-based RBV (1000 mg to 1200 mg daily given in divided doses) is safe and efficacious in patients with HCV monoinfection, with an overall SVR12 of 89% in HCV genotype 1 patients. The P7977-1910 study was a single-center, single-arm trial (N=23) investigating this same 12-week triple therapy regimen in HIV-infected patients coinfected with HCV genotypes 1, 2 3, or 4. (Rodriguez-Torres, 2013) Allowable antiretrovirals included either efavirenz, atazanavir/ritonavir, darunavir/ritonavir, raltegravir, or rilpivirine in combination with tenofovir/emtricitabine. Of patients with HCV genotype 1 (N=19), 89% achieved SVR12; 2 patients discontinued the study early due to adverse events (ie, anemia and altered mood). This regimen is therefore recommended for persons with HIV/HCV genotype 1 coinfection who are eligible to receive IFN and are either treatment-naive or have had prior PEG/RBV relapse.

The Phase III PHOTON-1 study enrolled 182 treatment-naive patients with HIV/HCV coinfection (n=114 with genotype 1; n=26 with genotype 2; n=42 with genotype 3) in a single-arm clinical trial investigating sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily given in divided doses) for 24 (genotype 1) or 12 (genotypes 2 and 3) weeks. (Sulkowski, 2013c) The population had well-controlled HIV with mean CD4 counts of 559 to 636 cells/?L. The same ARVs were allowed as those in the P7977-1910 study. Of participants, 90% completed treatment and 3% discontinued treatment due to adverse events. SVR12 was achieved in 76%, 88%, and 67% of participants with HCV genotypes 1, 2, and 3, respectively. For the combination of sofosbuvir plus RBV, genotype 1b subtype was a predictor of poorer response. Cirrhosis and African American race also exhibited trends toward lower SVR12. Based on the potential for lower response in HIV/HCV-coinfected patients with cirrhosis, the use of sofosbuvir plus PEG/RBV should be considered over sofosbuvir plus RBV. This regimen is otherwise recommended for HIV/HCV genotype 1-coinfected patients who are treatment naive or have relapsed after receipt of PEG/RBV and are ineligible for IFN.

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 basis for the recommendation supporting the use of this all-oral combination as an alternative regimen for patients with HCV monoinfection who cannot tolerate the recommended regimens. Although sofosbuvir plus simeprevir has been used anecdotally in patients with HIV/HCV coinfection, this drug combination has never been studied in this population. Despite the absence of data, this regimen may be considered for the treatment of HCV genotype 1 infection in patients with HIV infection who are not eligible for IFN and who are receiving antiretroviral therapy that may be coadministered with simeprevir (ie, raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir).

Similarly, no data exist for the combination of sofosbuvir plus simeprevir for the (re)treatment of HCV infection in HIV-infected patients. However, preliminary results obtained in HCV-monoinfected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in coinfected patients receiving compatible antiretroviral therapy as described above (see Retreatment of HCV Monoinfected Patients). (Jacobson, 2013b) Given the lack of clinical data in this population, it may be prudent to reserve this regimen for the treatment of persons with advanced fibrosis in whom a delay of therapy may lead to adverse clinical outcomes.

No data with sofosbuvir currently exist to guide retreatment recommendations for coinfected patients with HCV genotype 2 or 3 HCV infection. The ongoing PHOTON-1 study enrolled 41 treatment-experienced patients coinfected with HCV genotype 2 or 3, receiving sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily given in divided doses) for 24 weeks. (Sulkowski, 2013b) Results are expected in early 2014. In the absence of data, current recommendations for the retreatment of HIV patients coinfected with HCV genotype 2 or 3 are the same as those for HCV-monoinfected patients. Data also are lacking regarding use of sofosbuvir among patients coinfected with HCV genotype 4, 5, or 6 and HIV. Similarly, with no current data on the use of sofosbuvir in patients with genotype 4, 5, or 6 HCV and HIV coinfection, but given evidence of safety and efficacy of sofosbuvir-based regimens in this population, the recommended regimens for treatment in treatment-naive and treatment-experienced patients with HIV/HCV coinfection are the same as those for HCV-monoinfected patients.

Alternative regimen(s) for treatment-naive or treatment-experienced (prior PEG/RBV relapse) HIV/HCV- coinfected patients with genotype 1 who are eligible to receive IFN

Simeprevir (150 mg once daily) for 12 weeks and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 24 weeks (for treatment-naive and treatment-experienced with prior relapse to PEG/RBV) is an acceptable regimen for IFN-eligible HIV/HCV-coinfected persons with either (1) HCV genotype 1b or (2) HCV genotype 1a infection in whom the Q80K polymorphism is not detected prior to treatment. Simeprevir can only be used with the following antiretroviral drugs: raltegravir, rilpivirine, maraviroc, enfuvirtide tenofovir, emtricitabine, lamivudine, and abacavir.

Rating: Class IIa, Level B

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponders) HIV/HCV-coinfected patients with genotype 1 who are eligible for IFN

Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for IFN-eligible persons with HCV genotype 1 infection, regardless of subtype.

Rating: Class IIb, Level C

Alternative regimen(s) for treatment-naive and PEG/RBV relapser HIV/HCV-coinfected patients with genotype 1 who are ineligible or unwilling to receive IFN.

None

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 1 who are ineligible to receive IFN.

Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) for 24 weeks is an acceptable regimen for treatment-experienced (nonresponder) HIV/HCV-coinfected patients with HCV genotype 1 infection.

Rating: Class IIb, Level C

Alternative regimen(s) for treatment-naive and PEG/RBV relapser, HIV/HCV-coinfected patients with genotype 2 or 3 infection.

None

Alternative regimen(s) for treatment-experienced (PEG/RBV nonresponder) HIV/HCV-coinfected patients with genotype 2 or 3 infection who are eligible to receive IFN.

Sofosbuvir (400 mg once daily) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg] daily) plus weekly PEG for 12 weeks is an acceptable regimen for treatment-experienced IFN-eligible persons with HCV genotype 2 or 3 infection.

Rating: Class IIa, Level C

Alternative regimen(s) for treatment-naive and treatment-experienced HIV/HCV-coinfected patients with HCV genotype 4, 5, or 6 infection.

None

The TMC435-C212 is a Phase III, open-label, single-arm study investigating simeprevir plus PEG/RBV (fixed-dose ribavirin) in treatment-naive and treatment-experienced patients coinfected with HCV genotype-1 and HIV. (Dieterich, 2013) The study used an RGT design for treatment-naive and prior PEG/RBV relapsers; prior partial and null responders and all patients with cirrhosis (regardless of treatment history) received 48 weeks of therapy (SMV x 12 weeks plus PEG/RBV x 48 weeks). The primary analysis reported an overall SVR12 of 74% (treatment naive: 79%; prior relapsers, 87%: prior partial responders: 70%; prior null responders: 57%). Most (89%) eligible patients met criteria for RGT and were able to shorten therapy to 24 weeks, after which time 78% achieved SVR12. Lower SVR12 was reported in several clinically relevant subgroups: genotype 1a (71% vs 89% in genotype 1b); genotype 1a with the Q80K mutation at baseline (67%); advanced fibrosis or cirrhosis (64%); IL28B unfavorable genetic polymorphisms (68% and 61% for the CT and TT variants vs 96% for the favorable CC variant); high baseline HCV RNA (70% for >800,000 IU/mL or 93% for <800,000 IU/mL); and patients not receiving antiretroviral therapy (62% vs 75% in subjects on antiretroviral drugs). As with patients with HCV monoinfection, baseline resistance testing for the Q80K polymorphism should be performed in all patients harboring the genotype 1a subtype and a different regimen considered if the polymorphism is present. Virologic failures occurred; most failures (79%) were associated with the emergence of resistant-associated mutations.

The adverse event profile was similar to that of patients with HCV monoinfection, with a higher frequency of pruritus, rash, photosensitivity, and increased bilirubin than is observed in patients receiving PEG/RBV alone. Due to the complexity of antiretroviral drug-associated drug interactions with simeprevir, the longer course of PEG/RBV, the adverse effect profile, and the risk of resistance emergence with treatment failure, simeprevir plus PEG/RBV is considered an alternative regimen for treatment-naive and prior PEG/RBV relapse patients with HIV coinfection with genotype HCV who cannot tolerate the recommended regimens. This regimen is not recommended in prior nonresponders or patients with cirrhosis because of observed lower response rates seen and the poor tolerability of 48 weeks of PEG/RBV. Due to diminished activity in vitro (for genotype 2 and 3) and insufficient data (for genotype 4) this regimen cannot be recommended for these genotypes.

Sofosbuvir plus PEG/RBV has not been studied in patients with HIV/HCV genotype 1 coinfection in whom previous IFN-based HCV therapy has failed. However, in a study of a limited number of patients (n=19), the efficacy of this regimen in treatment-naive subjects with HIV/HCV genotype 1 coinfection was equivalent to that in patients with HCV monoinfection. (Rodriguez-Torres, 2013) An exploratory FDA analysis estimated the SVR rate of this regimen to be 78% among a treatment-experienced population with HCV monoinfection, including 71% in those with multiple poor pretreatment response predictors. (US FDA, 2013b) These data, along with the absence of antiretroviral drug limitations, support inclusion of this regimen as a recommended option for treatment-experienced patients with HIV/HCV coinfection.

Sofosbuvir plus RBV has not been studied in prior HCV treatment-experienced patients with HIV/HCV genotype 1 coinfection. This regimen yielded an SVR12 rate of 76% among treatment-naive HIV/HCV genotype 1-coinfected patients. (Sulkowski, 2013b) However, responses to this regimen are expected to be lower in treatment-experienced coinfected subjects based on limited data in treatment-experienced HCV-monoinfected patients treated for 12 weeks with sofosbuvir (400 mg once daily) plus weight-based RBV (1000 mg to 1200 mg daily in divided doses). (Gane, 2013a) Further, response rates are expected to be lower than those associated with the recommended and alternative regimens. This regimen should be reserved for coinfected patients who cannot tolerate IFN and do not have antiretroviral regimen options compatible with simeprevir. These patients require expert consultation with careful consideration of fibrosis stage; in some cases, deferral of therapy may be a more appropriate action.

Sofosbuvir plus PEG/RBV has not been studied in patients with HIV/HCV genotype 2 or 3 coinfection in whom previous IFN-based HCV therapy has failed. However, recognizing the potential limitations of sofosbuvir plus RBV in more difficult to treat genotype 2 and 3 patients, particularly those with prior nonresponse and cirrhosis, the addition of IFN to the regimen can be considered for those patients who are eligible. The LONESTAR-2 (open-label, single-site, single-arm phase 2 trial) evaluated PEG (180 & #956;g weekly), sofosbuvir (400 mg once daily), and weight-based RBV (1000 mg to 1200 mg daily in divided doses) for 12 weeks in HCV-monoinfected treatment-experienced patients with genotype 2 or 3 infection. Cirrhosis was present at baseline in 55% of patients. Overall, SVR12 was achieved in 96% (22 of 23) of those with genotype 2 infection. SVR occurred in 93% (13/14) and 100% (9 of 9) of patients with and without cirrhosis, respectively. Because sofosbuvir is safe and effective when used to treat HIV/HCV-coinfected patients, the combination of sofosbuvir plus PEG/RBV for 12 weeks can be considered for appropriate genotype 2 and 3 HIV/HCV-coinfected patients.

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

PEG/RBV with or without telaprevir or boceprevir for 24 to 48 weeks

Rating: Class IIb, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Due to its prolonged treatment course, adverse effects, and poor response rates, PEG/RBV is no longer recommended for the treatment of patients with HCV genotypes 1, 2, 3, or 4 who are coinfected with HIV. Neither telaprevir nor boceprevir is approved for use in patients with HIV/HCV coinfection. However, when combined with PEG/RBV and used for 48 weeks, these drugs have reported efficacy and safety in patients with HIV/HCV genotype 1 coinfection similar to that in patients with HCV genotype 1 monoinfection. (Sulkowski, 2013d); (Sulkowski, 2013a) Ongoing Phase III trials will investigate the use of RGT for select patient groups. Telaprevir and boceprevir are each substrates and 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) Due to the adverse effect profile, prolonged required course of PEG/RBV, and substantial drug interactions, these agents 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 not enough data to support a recommendation for the use of simeprevir for genotype 4 infection in HIV/HCV-coinfected patients.

2. Patients with Cirrhosis

The summary of recommendations for patients with cirrhosis is in the BOX.

Compensated Cirrhosis

Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A

This statement is supported by a number of studies (described above) that included patients with compensated cirrhosis who were evaluated in sub-group analyses.

Decompensated Cirrhosis

Patients with decompensated cirrhosis (moderate or severe hepatic impairment; 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

If the decision to treat has been made, the recommended regimen for patients with any HCV genotype 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 providers

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks

Rating: Class IIb, Level B

In one study, 61 patients with HCV infection and hepatocellular carcinoma meeting MILAN criteria for liver transplant were treated with sofosbuvir plus RBV for up to 48 weeks. (Curry MP, 2013) At the time of treatment initiation, the median MELD score was 8 (range: 6-14), and 17 patients had CTP scores of 7 or 8 (CTP Class B). To date, 44 patients have undergone liver transplantation, of whom 41 (93%) had HCV RNA below the lower limit of quantification. At 12 weeks post-transplant, 23 of 37 (62%) had no detected HCV RNA consistent with prevention of recurrent HCV infection. In the post-transplant period, 10 patients experienced recurrent HCV infection. Among the 10 patients who experienced recurrent graft infection, 9 had HCV RNA not detected for less than 30 days pretransplant. The most common adverse effects were fatigue, anemia, and headache; adverse effects led to treatment discontinuation for 2 patients (3%).

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, (Forns, 2013b) 44 patients were treated with sofosbuvir plus RBV 32 patients were also given PEG. 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 achieved HCV RNA less than the lower limit of quantification. Of 27 patients evaluated at 12 weeks post-treatment, 15 patients (56%) achieved SVR. Overall, 75% had improved or stable clinical liver disease including improvement in hyperbilirubinemia and coagulopathy as well as decrease in MELD score. In this very sick population, 8 patients died, most from liver disease progression.

The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):

Any IFN-based therapy

Rating: Class III, Level A

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-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/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.

3. Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

The summary of recommendations for patients who develop recurrent HCV infection post-liver transplantation is in the BOX.

Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without 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] 1200 mg), for 12 weeks to 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis

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] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks is recommended for patients with compensated allograft HCV genotype 2 or 3 infection.

Rating: Class IIb, Level C

Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.

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] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level, with or without PEG (in the absence of contraindication to its use), for 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Simeprevir has not been studied with sofosbuvir in the post-transplant setting. However, the [illegible] cyclosporine. Simeprevir should not be coadministered with cyclosporine.

The coadministration of simeprevir with tacrolimus at steady-state resulted in an 85% increase in plasma concentration of simeprevir compared with historical data and no substantial change in tacrolimus plasma concentration. (Janssen R&D, 2013b; see also product prescribing information) Based on phase I studies, an 85% increase in simeprevir concentration is unlikely to be clinically significant and therefore, no dose adjustment is required for either drug when tacrolimus and simeprevir are coadministered. Clinicians may consider the use of sofosbuvir plus simeprevir in patients receiving tacrolimus, with therapeutic drug monitoring of tacrolimus level, particularly in those expected to have difficulty tolerating RBV (eg, patients with impaired renal function or anemia). Consideration should be given to pretreatment resistance testing for the Q80K polymorphism in patients infected with genotype 1a HCV.

In addition to the sofosbuvir compassionate-use program (Forns, 2013a), 40 patients with recurrent HCV [illegible] discontinued therapy due to adverse events. No deaths, graft loss, or episodes of rejection were reported.

The addition of PEG to sofosbuvir plus RBV may also be considered in the absence of contraindications.

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

Monotherapy with PEG, RBV, or a DAA

Rating: Class III, Level A

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

Rating: Class III, Level A

Telaprevir or boceprevir should not be used in the post-liver transplant population because of surrounding toxicity and drug interactions with calcineurin inhibitors**.**

Decompensated Cirrhosis

Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Rating: Class I, Level C

4. Patients with Renal Impairment, Including Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis

Summary of Recommendations for Patients with Renal Impairment Including, Severe Renal Impairment (CrCl <30 mL/min) or ESRD Requiring Hemodialysis or Peritoneal Dialysis is found in the BOX.

When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population.

Rating: Class IIa, level B

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 2 and 3 sofosbuvir clinical trials have excluded patients with serum Cr level above 2.5 and/or CrCl level below <60 mL/min. The pharmacokinetics of a single dose of sofosbuvir 400 mg was assessed in persons not infected with HCV (study P7977-0915) with mild (estimated glomerular filtration rate [eGFR] ≥50 and <80 mL/min/1.73m^2), moderate (eGFR ≥30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR <30 mL/min/1.73m^2) and persons with ESRD requiring hemodialysis. Relative to persons with normal renal function (eGFR>80 mL/min/1.73m^2), the sofosbuvir AUC(0-inf) was 61%, 107%, and 171% higher in subjects with mild, moderate, and severe renal impairment, respectively. The GS-331007 AUC(0-inf) was 55%, 88%, and 451% higher, respectively. No safety signals have been seen under similar conditions. In subjects with ESRD (relative to subjects with normal renal function), sofosbuvir and GS-331007 AUC (0-inf) was 28% and 1280% higher, respectively, when sofosbuvir was dosed 1 hour before hemodialysis, compared with 60% and 2070% higher, respectively, when sofosbuvir was dosed 1 hour after hemodialysis. No dose 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.

When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis.

Rating: Class IIa, level B

Simeprevir is primarily metabolized by liver CYP3A4, and renal clearance plays an insignificant role (<1%) in the elimination of simeprevir and its metabolites.

Simeprevir 150 mg daily for 7 days has been studied in non-HCV infected patients with severe renal impairment (eGFR<30 mL/min/1.73m^2) and healthy volunteers (eGFR> mL/min/1.73 m^2). For persons with severe renal impairment, simeprevir C_{min}, C_{max}, and AUC(24 hour) were 71%, 34%, and 62% higher, respectively, compared with matched healthy controls. Simeprevir exposure was higher in patients with severe renal impairment (steady-state by day 7), but no significant difference was observed in simeprevir plasma protein binding. Simeprevir was generally safe and well tolerated in subjects with severe renal impairment. Therefore, no dose adjustment of simeprevir is required in these patients. No clinically significant differences in pharmacokinetics were observed in HCV-uninfected participants with mild, moderate, or severe renal impairment. CrCl level was not identified as a significant covariate of simeprevir population pharmacokinetics in HCV-infected patients.Simeprevir has not been evaluated in patients receiving hemodialysis.

In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required.

Rating: Class IIa, level B

HCV infection is a major health problem in patients with ESRD. The incidence of acute HCV infection during maintenance dialysis is much higher than that in the general population because of the risk for nosocomial transmission. The kidney is important for the catabolism and filtration of both IFN and RBV, and therefore, reduced doses of both PEG and RBV are warranted in patients with ESRD.

Impaired excretion of RBV occurs in patients with chronic kidney disease, as RBV is mostly eliminated by the kidney. Very little RBV is removed via dialysis. Thus, the drug can accumulate, exacerbating hemolysis in the dialysis population already at substantial risk for anemia. If a decision is made to use RBV in patients on maintenance hemodialysis, it should be used only after the implementation of several safety precautions, including (1) administering very low doses of RBV (200 mg daily), (2) monitoring hemoglobin levels on a weekly basis, (3) titrating epoetin alfa to treat anemia, and (4) providing intravenous iron supplementation to boost erythropoietin activity.

Dose adjustments needed for patients with renal impairment are summarized in the Renal Impairment Table.

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

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

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
1	**Treatment-naive and prior PEG/RBV relapsers** **IFN eligible:** SOF + PEG/RBV x 12 weeks 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/?L, a baseline platelet count below 90,000/?L or	**Treatment naive and prior PEG/RBV relapsers** **IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* 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/?L, a baseline platelet count below	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks SMV x 12 weeks + PEG/RBV x 48 wks	**For SOF use:** ALL except didanosine, zidovudine, or tipranavir **For SMV use:** LIMITED to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir

baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: SOF + RBV x 24 weeks SOF + SMV ± RBV x 12 weeks **Treatment experienced (prior PEG/RBV nonresponders) regardless of IFN eligibility:** SOF + SMV ± RBV x 12 weeks	90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: None **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV x 12 Weeks 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: SOF + RBV x 24 Weeks

2	SOF + RBV x 12 weeks regardless of treatment history	**Treatment naive and prior PEG/RBV relapsers**: None **Treatment experienced (prior PEG/RBV nonresponders)** **IFN eligible:** SOF + PEG/RBV X 12 Weeks 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: None	PEG/RBV x 24-48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine, or tipranavir
3	SOF + RBV x 24 weeks regardless of treatment history	**Treatment naive and PEG/RBV relapsers:** None **Treatment**	PEG/RBV x 24 - 48 weeks Any regimen with TVR, BOC, or	ALL except didanosine, zidovudine, or tipranavir

		experienced (prior PEG/RBV nonresponders) **IFN eligible:** SOF + PEG/RBV X 12 Weeks 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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: None	SMV	
4	**Regardless of treatment history:** **IFN eligible:** SOF + PEG/RBV x 12 weeks IFN ineligible IFN ineligible is defined as one or more of the below: • Intolerance to	None	PEG/RBV x 48 weeks Any regimen with TVR or BOC	ALL except didanosine, zidovudine, or tipranavir

	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/?L, a baseline platelet count below 90,000/?L or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease: SOF + RBV x 24 weeks			
5 or 6	**Regardless of treatment history:** SOF + PEG/RBV x 12 weeks	None	PEG/RBV x 48 weeks Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine, or tipranavir

*For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments should be considered if this mutation is present.

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

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

Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.

Rating: Class I, Level A

Patients with decompensated cirrhosis (moderate or severe hepatic impairment; 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

The recommended regimen for patients with any HCV genotype 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 providers

Daily sofosbuvir (400 mg) plus weight-based RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks

Rating: Class IIb, Level B

The following regimens are NOT recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):

> **Any IFN-based therapy**
>
> **Rating:** Class III, Level A
>
> **Monotherapy with PEG, RBV, or a DAA**

Rating: Class III, Level A

Telaprevir-, boceprevir-, or simeprevir-based regimens

Rating: Class III, Level A

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. Summary of Recommendations for Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation

Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis

Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without 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] 1200 mg), for 12 weeks to 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis

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] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks is recommended for patients with compensated allograft HCV genotype 2 or 3 infection.

Rating: Class IIb, Level C

Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.

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] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level,

with or without PEG (in the absence of contraindication to its use), for 24 weeks is recommended for patients with compensated allograft HCV genotype 1 infection.

Rating: Class IIb, Level C

The following regimens are NOT recommended for treatment-naive patients with compensated allograft hepatitis C infection

> **Monotherapy with PEG, RBV, or a DAA**
>
> **Rating:** Class III, Level A
>
> **Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C infection.**
>
> **Rating:** Class III, Level A

Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C).

Rating: Class I, Level C

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

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

Renal Impairment	eGFR/CrCl level (mL/min/ 1.73 m^2)	Interferon	Ribavirin	Sofosbuvir	Simeprevir
Mild	50-80	180 µg PEG (2a); PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
Moderate	30-50	180 µg PEG (2a); PEG alfa-2b1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
Severe	<30	135 µg PEG (2a); PEG (2b)1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
ESRD/HD		PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

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

When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ?30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population.

Rating: Class IIa, level B

When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis.

Rating: Class IIa, level B

In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required.

Rating: Class IIa, level B

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).

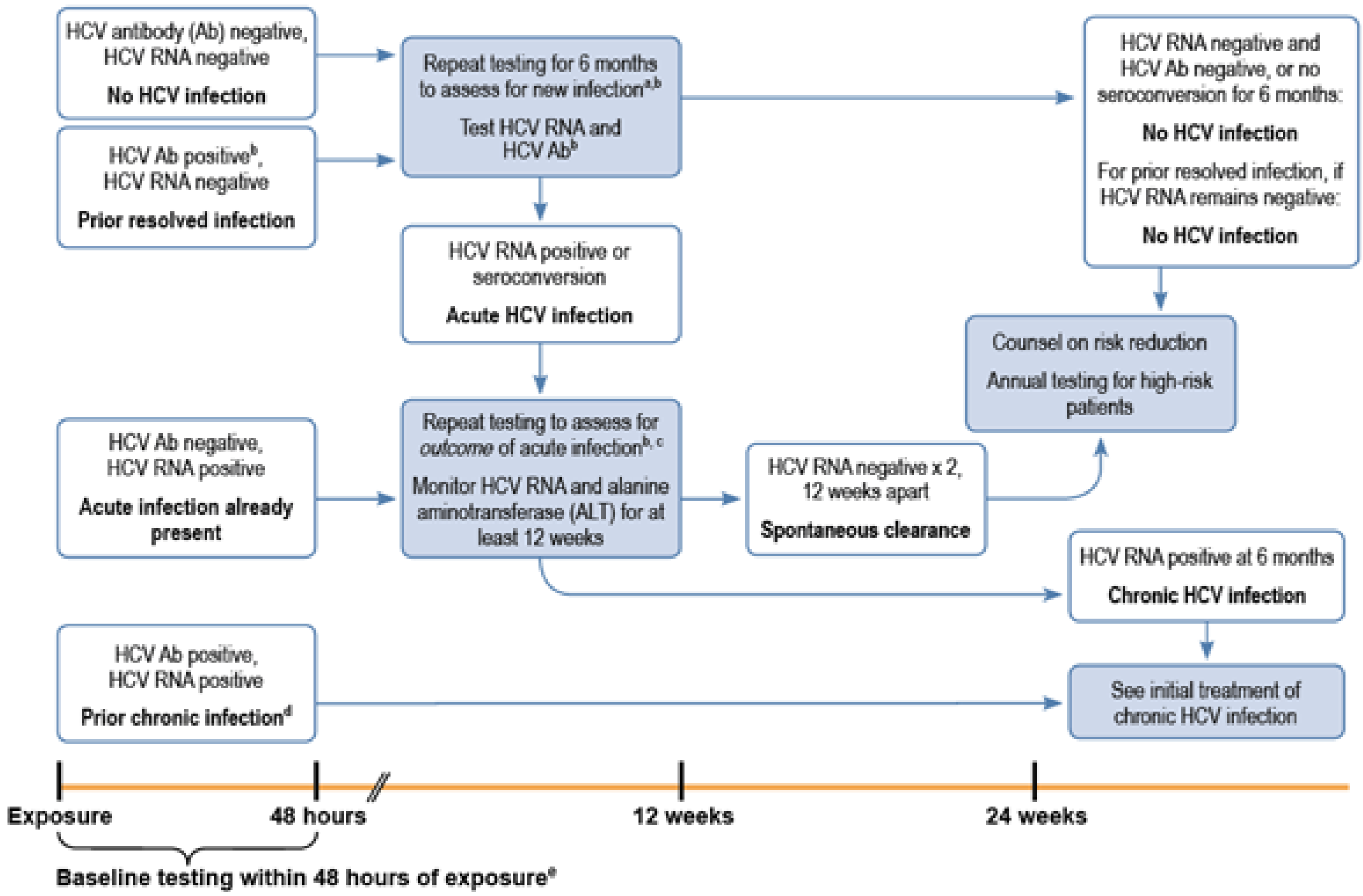
Rating: Class II, Level A

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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