HEPATITIS C GUIDANCE: AASLD-IDSA RECOMMENDATIONS FOR TESTING, MANAGING, AND TREATING ADULTS INFECTED WITH HEPATITIS C VIRUS

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These recommendations have been approved by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA).

PREAMBLE

The pace of hepatitis C virus (HCV) drug development in recent years has accelerated dramatically. For patients to benefit from these impressive advances, practitioners need access to the most up-to-date data, and to advice from experienced experts. Such information and advice can be difficult to access readily given the diverse sources from which information is available, and the sometimes lengthy time needed for publication of original articles and scholarly perspectives. Traditional practice guidelines for more established areas of medicine and care often take years to develop and bring to publication. In the new era in hepatitis C treatment, such a process would not be nimble or timely enough to address the needs of patients with HCV infection, practitioners caring for these patients, or payers approving therapies for use. A living document made available in a web-based system, such as that used by the United States Department of Health and Human Services (HHS) for HIV treatment recommendations (http://aidsinfo.nih.gov/guidelines), was selected as the best model to provide timely recommendations for hepatitis C management. In 2013, the two major membership societies supporting liver and infectious diseases specialists (AASLD and IDSA) joined forces to develop guidance for the management of hepatitis C in this rapidly moving field. The International Antiviral Society-USA (IAS-USA), which has experience in developing treatment guidelines in

HIV disease, was invited to join the effort as a collaborating partner responsible for managing the Panel and the Guidance development process.

The goal of the hepatitis C guidance is to provide up-to-date recommendations for HCV care practitioners on the optimal screening, management, and treatment for adults with HCV infection in the United States, using a rigorous review process to evaluate the best available evidence. This review provides a condensed summary of recommendations from the Guidance. The complete Guidance, which is updated regularly, is available at <www.HCVGuidelines.org>.

PROCESS

This document was conceived to be a living document that would reside online and undergo realtime revisions as the field evolved. To lead the process, two co-chairs selected by the Governing Boards of each founding society were joined by a fifth co-chair representing IAS-USA. These co-chairs selected ten panel members from each society. The panel members were chosen to represent expertise in the diagnosis, management, treatment, research and patient care from the fields of hepatology and infectious diseases. At least 51% of the panelists could have no substantive industry support other than research advisory boards, data safety monitoring boards, or research funding that went to the member's employer.

The panel first convened in person meeting in October, 2013. Panel members were divided into teams to review available data and to propose preliminary guidance in three areas: 1) Testing and linkage to care, 2) Initial treatment of HCV infection, and 3) Retreatment of patients in whom prior HCV treatment had failed. The treatment section teams also reviewed data for special considerations in patients with hepatitis C, including those with HCV/HIV coinfection, decompensated cirrhosis, and those who had undergone liver transplantation. The teams and co-chairs met regularly by conference call. All panel members reviewed and approved the final recommendations. Each society Governing Board peer reviewed the final recommendations. The first version of the Guidance was uploaded (www.HCVguidelines.org) on January 29, 2014. By September, 2014, three additional sections were developed including: 1) Treatment of acute HCV infection, 2) Monitoring during and after therapy, and 3) When and in whom to treat. In October, 2014, the panel reconvened in person to update recommendations to consider data on pending new treatments. The updated recommendations (and appropriate revisions of all current guidance) were uploaded on December 20, 2014. This report was prepared on May 20, 2015.

Funding for the guidance itself was provided by the AASLD and the IDSA. No industry funding was solicited or accepted. The Centers for Disease Control and Prevention provided separate funding for identifying and reviewing data pertaining to testing and linkage to care.

COLLECTING, EVALUATING AND RATING THE EVIDENCE

The panel, comprising experts in the fields of hepatology and infectious diseases used an evidence-based approach to review available information for the guidance. Information sources considered are: research published in peer-reviewed journals or presented at major national or international research conferences; safety warnings from the US Food and Drug Administration (FDA) or other regulatory agencies or the manufacturer; drug interaction data; prescribing information from FDA-approved products; and registration data for new products under FDA review. An initial search of the literature yielded 3939 unique citations on November 4, 2013. To be considered, articles needed to be published in English from 2010 to the present. Review studies; those using mice or rats; and in vitro studies were excluded. Panel members monitor the literature and other sources regularly and update the Guidance as new evidence warrants.

Each recommendation is rated in terms of the level of evidence (depicted by a Roman numeral I, II, or III) and the strength of the recommendation (depicted by a letter A, B or C) using a scale (**Table 1**) adapted from the American College of Cardiology and the American Heart Association Practice Guidelines [1,2].

HCV TESTING AND LINKAGE TO CARE

Of the estimated 2.2 to 3.2 million persons [3] chronically infected with HCV in the United States, half are unaware that they are infected [4]. Identification of those with active infection is the first step toward improving health outcomes and preventing transmission [5-7]. Accordingly, HCV testing is recommended in select populations based on demography, prior exposures, risk

behaviors, and medical conditions (**Table 2).** In 2012, the Centers for Disease Control and Prevention (CDC) expanded its risk-based HCV testing guidelines originally issued in 1998 [7] with a recommendation to offer a one-time HCV test to all persons born from 1945 through 1965, regardless of whether HCV risk factors have been identified. This recommendation was supported by the failure of the risk-based screening strategy to identify more than 50% of HCV infections. 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 cohorts. A 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 [8]. The cost-effectiveness of one-time birth cohort testing is comparable to that of current risk-based screening strategies [5].

Recommendation:

1. Consistent with CDC and the US Preventive Services Task Force (USPSTF) a one time HCV test is recommended in asymptomatic persons in the 1945 to 1965 birth cohort and other persons based on exposures, behaviors, and conditions that increase risk for HCV infection. (I-B)

HCV antibody testing should be performed using FDA-approved methods such as testing for HCV antibody (anti-HCV) [9,10] with laboratory-based assays or a point-of-care assay [11]. A positive anti-HCV test result indicates current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result [12]. Therefore, FDA-approved quantitative or qualitative nucleic acid testing (NAT) with a detection level of 25 IU/mL or lower

should be used to detect HCV RNA to confirm active HCV infection and guide clinical management. HCV RNA testing should also be performed in persons with a negative anti-HCV test who are immunocompromised (eg, persons receiving chronic hemodialysis) [13] or who might have been exposed to HCV in the prior 6 months, because these persons may be anti-HCV negative. An HCV RNA test is also needed to detect reinfection in anti-HCV–positive persons after previous spontaneous or treatment-related viral clearance. Further details for interpreting results of different antibody and NAT results can be found in the CDC testing algorithm at www.HCVGuidelines.org.

Recommendation:

2. All persons recommended for HCV testing should first be tested for HCV antibody using an FDA-approved test. Positive results should be confirmed by nucleic acid testing for HCV RNA. (I-A)

Evidence regarding the optimal 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 men who have sex with men (MSM) who have unprotected sex [14-19], at least annual HCV testing is recommended in these subgroups.

Recommendation:

3. 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 at ongoing risk of HCV exposure. (IIa-C)

HCV-infected persons should be educated about preventing further damage to their liver. Most important is prevention of the potential deleterious effect of alcohol, which may lead to more rapid progression of liver fibrosis and the development of hepatocellular carcinoma [20-26]. Persons with HCV should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) since coinfection with HBV and HIV have each been associated with poorer prognosis of HCV [27,28], they share overlapping risk factors, and additional benefits accrue from their diagnosis and treatment [29,30] (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.html).

Patients with obesity and metabolic syndrome who have underlying insulin resistance are more prone to have nonalcoholic fatty liver disease, which may accelerate fibrosis progression in HCV-infected persons [31,32]. Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index of 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 [33,34].

Recommendation:

4. HCV-infected persons should be educated about their disease and how to prevent further damage to their liver. (IIa-B)

Improvements in identification of current hepatitis C and advances in treatment will have limited impact on HCV-related morbidity and mortality unless patients have access to appropriate medical care. In the United States, it is estimated that only 13% to 18% of persons with chronic HCV infection receive treatment [35]. Indeed, in many cases referral to practitioners who are able and willing to evaluate such patients and provide treatment is delayed or never occurs [36-38]. Thus, it is crucial that all patients with current hepatitis C and a positive HCV RNA test result be referred to and evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Further, those with advanced fibrosis or cirrhosis require specialized management, including consideration of liver transplantation as indicated.

Recommendation:

5. 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. (IIa-C)

WHEN AND IN WHOM TO INITIATE HCV THERAPY

Successful hepatitis C treatment is achievable in nearly all infected patients and is reflected by a sustained virologic response (SVR), defined as the continued absence of detectable HCV RNA for 12 or more weeks after completion of therapy. SVR is a marker for virologic cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of

patients followed up for at least 5 years [39,40]. Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation, regression of fibrosis in most cases, and resolution of cirrhosis in half [41]. Among the latter group, portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improve. SVR is associated with a more than 70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]) and a 90% reduction in the risk of liver-related mortality and liver transplantation [42-44].

Cure of HCV infection may also reduce symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting up to 15% of HCV-infected individuals [45,46]. HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful HCV treatment [47-51]. These reductions in disease severity contribute to dramatic reductions in all-cause mortality [43,52]. Lastly, patients achieving SVR have substantially improved quality of life, including physical, emotional, and social health [53,54].

Evidence clearly supports treatment for all HCV-infected persons, except those with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. Although treatment is best administered early in the course of the disease before fibrosis progression and the development of complications, the most immediate benefits of treatment will be realized by populations at highest risk for liver-related complications. Thus, where resources limit the ability to treat all infected patients immediately as recommended, it is most appropriate to treat first those at greatest risk of disease complications, and those at risk for transmitting HCV or in

whom treatment may reduce transmission risk. Where such limitations exist, prioritization of immediate treatment for those listed in **Tables 3** and **4** is recommended, including patients with progressive liver disease (Metavir stage F3 or F4), transplant recipients, or those with clinically severe extrahepatic manifestations.

Recent reports suggest that initiating therapy in patients with lower stage fibrosis may extend the benefits of SVR. In a long-term follow-up study, 820 patients with Metavir stage F0 or F1 fibrosis confirmed by biopsy were followed for more than 20 years. The 15-year survival rate was significantly better in those who experienced an SVR than in those whose treatment had failed or those who were untreated (93%, 82% , and 88%, respectively; *P*=.003) and argues for consideration of earlier initiation of treatment [55]. Several other modeling studies suggest greater mortality benefit if treatment is initiated at stages prior to F3 [56-58].

Recommendation:

6. Antiviral treatment is recommended for all patients with chronic HCV infection, except those with limited life expectancy due to nonhepatic causes. (I-A)

Recommendation:

7. If resources limit the ability to treat all infected patients immediately as recommended, then it is most appropriate to treat those at greatest risk of disease complications before treating those with less advanced disease. (See Tables 3 and 4 for ratings).

An accurate assessment of fibrosis is vital in assessing the urgency for treatment, in some instances the duration of treatment, and the need for more intensive clinical monitoring. The degree of hepatic fibrosis is one of the most robust prognostic factors used to predict disease progression and clinical outcomes [59]. In addition to being in more urgent need for antiviral therapy, individuals with severe fibrosis require screening for hepatocellular carcinoma (HCC) and esophageal varices [60,61].

There are several acceptable approaches to staging. Individuals with clinically apparent cirrhosis such as those with endoscopic evidence of varices or imaging showing cirrhosis or portal hypertension do not require additional staging. However, the majority of patients require testing to determine stage. Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs [62]. 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. Recently, noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests such as aspartate transaminase [AST], alanine transaminase [ALT] and platelet count), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography [63-66]. No single method is recognized to have high accuracy alone and results of each test must be interpreted carefully. The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography [67].

Recommendation:

8. Use of noninvasive testing or liver biopsy is recommended in order to assess the degree of hepatic fibrosis, and hence the urgency of immediate treatment. (I-A)

INITIAL TREATMENT OF HCV INFECTION

This section addresses treatment of patients with chronic hepatitis C who are naive to any type of therapy. Although regimens containing peginterferon (PEG-IFN) and ribavirin (RBV) plus direct-acting antiviral (DAA) drugs are approved by the FDA for many HCV genotypes, the initial regimen for patients who are treatment naive with HCV genotype 1 generally has been superseded by treatments incorporating regimens using only DAAs. Recommended treatments are viewed as equivalent and the decision of which to use may involve consideration of drug interactions between the DAAs and concomitant medications. (See: http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection#drug-interactions)**.** For example, the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) has a potential interaction with proton pump inhibitors. Similarly, the daily fixed-dose combination of paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) (hereafter paritaprevir/ritonavir/ombitasvir plus dasabuvir or PrOD) has a substantial interaction with the long-acting inhaled beta-adrenoceptor agonist salmeterol and other drugs that interface with the CYP 3A4 isoenzyme.

Genotype 1a

Patients with HCV genotype 1a tend to have higher relapse rates than patients with HCV genotype 1b with certain regimens. Genotype 1 HCV infection that cannot be subtyped should be treated as genotype 1a infection.

For HCV genotype 1a–infected, treatment-naive patients, there are 3 regimens of comparable efficacy: ledipasvir/sofosbuvir [68,69]; PrOD and weight-based RBV [70,71]; and sofosbuvir plus simeprevir [72]. For PrOD, the use of RBV and the length of therapy differ for those with compensated cirrhosis versus those who do not have cirrhosis. The standard weight-based dosing of RBV is 1000 mg for individuals who weigh less than 75 kg to 1200 mg for those who weigh 75 kg or more. The known safety profiles of each of these recommended regimens are excellent. Across numerous phase III studies, less than 1% of patients without cirrhosis discontinued treatment early and adverse events were mild. Most adverse events occurred in RBV-containing arms. Patients with cirrhosis and HCV genotype 1a who were harboring the non-structural protein 3 (NS3) Q80K polymorphism had lower SVR rates after treatment with sofosbuvir and simeprevir than those who did not harbor the Q80K polymorphism[73]; in these patients, one of the other recommended regimens for cirrhosis should be used.

Recommendation:

9. Treatment options for treatment-naive patients with HCV genotype 1a who are initiating therapy (regimens are listed in alphabetic order).

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (1-A)***
- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis). (I-A)***
- ***Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) for patients with a negative test result for the Q80K variant using commercially available resistance assays. In patients with HCV genotype 1a and cirrhosis who have the Q80K variant, one of the other regimens for cirrhosis detailed above is recommended. (IIa-B)***

Genotype 1b

For HCV genotype 1b–infected, treatment-naive patients, there are 3 regimens of comparable efficacy: ledipasvir/sofosbuvir for 12 weeks; PrOD for 12 weeks (plus RBV for patients with cirrhosis) [70,71]; and sofosbuvir plus simeprevir with or without weight-based RBV for 12 weeks (or 24 weeks for patients with cirrhosis) [72,74,75].

Recommendation:

10. Treatment options for treatment-naive patients with HCV genotype 1b who are initiating therapy (regimens are listed in alphabetic order).

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (I-A)***

- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks, with the addition of weight-based RBV for patients with cirrhosis. (I-A)***
- ***Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis). (IIa-B)***

Genotype 2

Sofosbuvir plus weight-based RBV is the recommended therapy for treatment-naive patients with HCV genotype 2 infection [75-78]. Until more data are available, extending treatment to 16 weeks in HCV genotype 2–infected patients with cirrhosis is recommended**.**

Recommendation:

11. Regimen for treatment-naive patients with HCV genotype 2 infection.

- ***Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks. (I-A)***
- ***Extending treatment to 16 weeks is recommended for patients with cirrhosis. (IIb-C)***

Genotype 3

HCV genotype 3 is the most difficult genotype to treat with available DAAs. Sofosbuvir plus weight-based RBV for 24 weeks is the recommended DAA-only regimen in the United States

[76,79]. Based on recent data from a randomized trial demonstrating higher SVR rates than those seen with sofosbuvir and RBV for 24 weeks, the combination of sofosbuvir plus PEG-IFN and RBV for 12 weeks is recommended for IFN-eligible patients[80], although the adverse effects and increased monitoring requirements of PEG-IFN may make this a less attractive therapeutic option. Daclatasvir plus sofosbuvir for 12 weeks has been studied, but daclatasvir is not FDA approved [81].

Recommendation:

12. Treatment for treatment-naive patients with HCV genotype 3 infection.

- ***Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks for IFN-eligible patients. (I-A)***
- ***Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks for IFN-ineligible patients. (I-B)***

Genotype 4

For the treatment of therapy-naive patients with HCV genotype 4, three therapeutic options are recommended: daily combination of paritaprevir/ritonavir/ombitasvir (PrO) with weight-based RBV [82]; ledipasvir/sofosbuvir [83,84]; or sofosbuvir plus weight-based RBV [85-87]. Given the demonstrated activity *in vitro* and *in vivo* of simeprevir against HCV genotype 4, simeprevir plus sofosbuvir may be considered, but supportive clinical data are limited.

Recommendation:

13. Treatment options for treatment-naive patients with HCV genotype 4 infection (listed in alphabetic order).

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (IIb-B)***
- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks. (I-B)***
- ***Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks. (IIa-B)***
- ***Alternatives:***
  - ***Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks. (II-B)***
  - ***Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV for 12 weeks. (IIb-B)***

Genotype 5 or 6

Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. Nonetheless, based on emerging data, sofosbuvir plus ledipasvir is recommended [83,84,88].

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Recommendation:

14. Treatment for treatment-naive patients with HCV genotype 5 or 6 infection.

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (IIa-B)***
- ***Alternative:***
  - ***Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks for patients who are IFN eligible. (IIa-B)***

RETREATMENT OF PERSONS IN WHOM PRIOR THERAPY HAS FAILED

Prior Failure of PEG-IFN and RBV without a DAA

Genotype 1a

Three regimens are recommended in this setting: ledipasvir/sofosbuvir [89], PrOD and RBV [79], and simeprevir plus sofosbuvir [74-76,90]. In patients with cirrhosis, treatment with ledipasvir/sofosbuvir for 24 weeks produced higher SVR rates than did for 12 weeks of treatment, supporting the recommendation that HCV treatment–experienced patients with cirrhosis receive 24 weeks of treatment [89,91]. However, ledipasvir/sofosbuvir with weight-based RBV given for 12 weeks produced equivalent SVR rates to 24 weeks of ledipasvir/sofosbuvir in patients with cirrhosis in whom a prior course of PEG-IFN and RBV plus telaprevir or boceprevir had failed. For patients with cirrhosis who are treated with PrOD and RBV, 24 weeks of therapy is recommended [71]. Similarly, patients with cirrhosis who are being treated with simeprevir plus sofosbuvir should receive 24 weeks of therapy [92,93].

Genotype 1b

The recommended treatment options in this setting are ledipasvir/sofosbuvir [89], PrOD [94]; or simeprevir plus sofosbuvir [74-76,90]. For those with cirrhosis in whom a prior PEG-IFN-based regimen has failed, the recommendations for treatment are the same as those recommended for genotype 1a patients with cirrhosis, except the treatment duration of PrOD and RBV can be reduced to 12 weeks [71].

Recommendation:

15. Options for retreatment of patients with genotype 1 HCV in whom previous PEG-IFN and RBV treatment had failed (regimens listed in alphabetical order).

HCV Genotype 1a infection without cirrhosis -

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (I-A)***
- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dasabuvir (250 mg) and weight-based RBV for 12 weeks. (I-A)***
- ***Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks. (IIa-B)***

HCV Genotype 1b infection without cirrhosis -

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (I-A)***

- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks. (I-A)***
- ***Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks. (IIa-B)***

HCV Genotype 1a or 1b infection with compensated cirrhosis

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks, regardless of subtype. (I-A)***
- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV for 12 weeks, regardless of subtype. (I-B)***
- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 24 weeks (HCV genotype 1a) or 12 weeks (HCV genotype 1b). (I-A)***
- ***Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV for 24 weeks for patients with a negative test result for the Q80K variant using commercially available resistance assays, and for HCV genotype 1b infection. In patients with HCV genotype 1a and cirrhosis who have the Q80K variant, one of the other regimens for cirrhosis detailed above is recommended. (IIa-B)***

Prior Failure of PEG-IFN, and RBV, and a DAA

<u>Genotypes 1a and 1b</u>

Prior failure of telaprevir or boceprevir-containing regimens

The recommended treatment for patients without cirrhosis with HCV genotype 1 in whom a prior regimen that contained telaprevir or boceprevir has failed is ledipasvir/sofosbuvir for 12 weeks [89]. For patients with cirrhosis, relapse rates were higher in the 12-week than the 24-week treatment group [89]; thus, those patients with cirrhosis should have ledipasvir/sofosbuvir treatment duration extended to 24 weeks [89]. In a randomized retreatment study of patients with cirrhosis whose treatment with PEG-IFN and RBV plus telaprevir or boceprevir failed [95], SVR12 rates were identical between those receiving 12 weeks of ledipasvir/sofosbuvir and RBV and those receiving 24 weeks of ledipasvir/sofosbuvir. Thus, ledipasvir/sofosbuvir and RBV for 12 weeks is another recommended regimen for patients with cirrhosis in whom prior treatment with PEG-IFN and RBV and telaprevir or boceprevir failed [95].

There are few data for PEG-IFN, RBV and simeprevir treatment failures. However, based on expected patterns of resistance, treatment with ledipasvir/sofosbuvir may be given to this group of patients as well. Treatment with sofosbuvir and simeprevir or PrOD should be avoided.

Recommendation:

16. Options for retreatment of patients with genotype 1 HCV in whom a previous interferon-based and protease inhibitor containing regimen had failed (regimens listed in alphabetical order in each subgroup).

Patients without cirrhosis -

- ***Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks, regardless of subtype. (I-A)***

Patients with cirrhosis (and any subtype) -

- ***Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks, regardless of subtype. (I-A)***
- ***Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based RBV for 12 weeks, regardless of subtype. (IIa-B)***

Prior failure of sofosbuvir-containing regimens

Treatment failure with sofosbuvir-containing regimens appears to be more common in persons infected with HCV genotype 1a than with 1b, and more common in those with cirrhosis than those without cirrhosis. Treatment failure of simeprevir plus sofosbuvir is associated with resistance to simeprevir and other HCV NS3/4A protease inhibitors such as paritaprevir. Conversely, sofosbuvir resistance-associated variants (RAVs) are uncommon [74-76,90]. Some data exist for retreatment after a sofosbuvir-containing treatment failure with a regimen of sofosbuvir plus other drugs. Treatment with ledipasvir/sofosbuvir plus weight-based RBV is recommended for either prior sofosbuvir and RBV failures [96,97] or prior sofosbuvir plus PEG-IFN and RBV failures [97] Owing to the paucity of data in this setting, referral to a clinical trial may be appropriate for some patients. For patients with minimal liver disease, consideration should be given to deferral of retreatment until more information is available. In patients who

have cirrhosis and require retreatment more urgently, treatment with ledipasvir/sofosbuvir with RBV for 24 weeks is recommended until more data are available.

In the absence of data, for patients in whom prior treatment with simeprevir plus sofosbuvir failed, strong consideration should be given to enrollment in a clinical trial. For patients with minimal liver disease, consideration should be given to deferral of retreatment pending the availability of data. In patients who require retreatment more urgently, based on emerging data and the expected pattern of HCV drug resistance, ledipasvir/sofosbuvir with or without RBV is recommended.

Recommendation:

17. Options for retreatment of patients with genotype 1 HCV who failed a previous sofosbuvir-containing regimen (regimens listed in alphabetical order in each subgroup) -

- ***Based on the limited data available for effective therapy, it is recommended that patients without an urgent need for HCV treatment, regardless of subtype, should defer antiviral therapy until additional data are available or consider enrollment in a clinical trial. (IIb-C)***
- ***Patients without cirrhosis who have an urgent need for treatment should receive a daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based RBV for 12 weeks, regardless of subtype. (IIa-C)***

- ***Patients with cirrhosis who have an urgent need for treatment should receive a daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based RBV for 24 weeks, regardless of subtype. (IIa-C)***

Prior failure of NS5A regimen (including ledipasvir/sofosbuvir and PrOD)

There are limited data to guide retreatment of patients whose treatment with NS5A inhibitor–containing regimens has failed. Retreatment of those whose prior treatment with sofosbuvir/ledipasvir failed with sofosbuvir/ledipasvir for 24 weeks resulted in a high frequency of failure, which was predicted by the presence of NS5A RAVs [73]. Thus, those patients with minimal liver disease should defer therapy pending further data. Those who have cirrhosis or who require urgent retreatment should undergo RAV testing.

Recommendation

18. Options for retreatment of patients with HCV genotype 1 whose previous NS5A inhibitor–containing regimen failed

- *For patients without an urgent need for treatment, deferral of retreatment is recommended pending the availability of additional data. (III-C)*
- *For patients with cirrhosis or an urgent need for retreatment, testing for resistance-associated variants (RAVs) which confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays. (IIb-C)*
- *For patients with no NS5A RAVs detected, retreatment with a daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with RBV for 24 weeks is recommended. (IIb-C)*

- *For patients who have NS5A RAVs detected but do not have NS3 RAVs detected, treatment with sofosbuvir (400 mg) and simeprevir (150 mg) with RBV for 24 weeks is recommended. (IIb-C)*
- *For patients who have both NS3 and NS5A RAVs detected, referral to a clinical trial is recommended. (IIb-C)*

Genotype 2

Individuals with genotype 2 HCV infection who have failed a prior course of interferon-based therapy should receive sofosbuvir plus weight-based RBV for 12 weeks [78,90]. Extending treatment from 12 weeks to 16 weeks in HCV genotype 2–infected patients with cirrhosis is recommended**.** Recent data also suggest that sofosbuvir plus PEG-IFN and RBV for 12 weeks produces high rates of SVR compared with sofosbuvir plus RBV for 24 weeks and is an alternative for patients who are IFN eligible [80].

There are currently no data available to support a recommendation for patients who have failed previous treatment with a sofosbuvir-containing regimen. Consideration should be given to deferral of retreatment until more information is available.

Recommendation:

19. Patients with HCV genotype 2 infection in whom prior PEG-IFN and RBV treatment has failed should be treated with daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks (in noncirrhotic patients) to 16 weeks (in cirrhotic patients). (I-A)

Alternative:

Retreatment with daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is an alternative for patients in whom prior PEG-IFN and RBV treatment failed who are eligible to receive IFN.

Genotype 3

Individuals with genotype 3 HCV infection who have failed a prior course of interferon-based therapy should receive sofosbuvir plus weight-based RBV for 24 weeks [78,90]. Retreatment with daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is also highly effective, particularly among those with cirrhosis. It is recommended for those eligible to receive PEG-IFN [80]. This regimen may also be effective in those patients with HCV genotype 3 infection who have failed a prior course of sofosbuvir and ribavirin.

Recommendation:

20. Patients with HCV genotype 3 infection in whom prior PEG-IFN and RBV treatment has failed should receive -

- ***Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks for patients who are eligible to receive IFN. (I-A)***
- ***Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks for IFN-ineligible patients. (I-B)***

Genotype 4

Data are limited to help guide retreatment decision making for patients infected with HCV genotype 4. Nonetheless, for patients in whom retreatment is required after prior failure of PEG-IFN and RBV, four equivalent regimens are recommended: ledipasvir/sofosbuvir for 12 weeks [83]; PrO and weight-based RBV for 12 weeks for patients without cirrhosis [98]; sofosbuvir plus weight-based RBV and weekly PEG-IFN for 12 weeks [76]; or sofosbuvir plus weight-based RBV for 24 weeks [86]. Patients with cirrhosis who were treated with ledipasvir/sofosbuvir for 24 weeks had higher SVR rates than those treated for 12 weeks. Thus, for those with cirrhosis, 24 weeks of treatment without RBV is recommended [91,95].

Recommendation:

21. Options for retreatment of patients with genotype 4 who failed a previous interferon-based regimen (regimens listed in alphabetical order)

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks (no cirrhosis) or 24 (cirrhosis). (IIa-B)***
- ***Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks (no cirrhosis). (IIa-B)***
- ***Daily sofosbuvir (400 mg) for 12 weeks and daily weight-based RBV plus weekly PEG-IFN for 12 weeks for patients who are eligible to receive IFN. (IIa-B)***
- ***Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks. (IIa-B)***

Genotypes 5 and 6

Few data are available to help guide decision-making for patients infected with HCV genotype 5 or 6 in whom prior therapy has failed. Nonetheless, based on emerging data sofosbuvir plus ledipasvir is recommended [83,84,88].

Recommendation:

22. Patients with HCV genotype 5 or 6 infection in whom prior PEG-IFN and RBV treatment has failed should receive -

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. (IIa-B)***
- ***Alternative:***
  - ***Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks for patients who are IFN-eligible. (IIa-B)***

MONITORING PATIENTS BEFORE, DURING, AND AFTER ANTIVIRAL THERAPY

Recommendation:

23. Patients should be evaluated prior to starting therapy, during treatment, and following discontinuation of treatment in order to determine the severity of their liver disease and the efficacy and safety of their HCV treatment. The recommended evaluations (and ratings) are listed in Tables 5, 6, and 7.

Patients who do not achieve SVR because of failure of the treatment, or who relapse or are reinfected after treatment completion, may have continued liver injury and will have the potential to transmit HCV. Such patients should be monitored for progressive liver disease, counseled to prevent transmission, and considered for retreatment.

Patients in whom treatment fails should be monitored for signs and symptoms of cirrhosis and should be considered for treatment when alternative effective treatment is available [72,99]. Such patients may have a virus that is resistant to one or more of the antivirals used at the time of virologic "breakthrough" [72,100]. However, there is no evidence to date that the presence of RAVs causes more liver injury than does wild-type virus. Further, the long-term persistence of such RAVS remains unknown. Subsequent retreatment with combination antivirals may overcome the presence of resistance to one or more antivirals. However, with the exception of testing for the Q80K polymorphism at baseline in patients with HCV genotype 1a infection before treatment with simeprevir plus PEG-IFN and RBV, or treatment with sofosbuvir plus simeprevir in patients with cirrhosis, routine testing for RAVs before initial treatment is not recommended. Emerging data suggest that assessment for RAVs in patients whose treatment with NS5A-containing regimens failed is warranted for those who require retreatment.

Recommendation:

24. Patients who fail to achieve SVR should receive the following -

- ***Disease progression assessment every 6 months to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ration (INR).(I-C)***

- ***Surveillance for HCC with ultrasound testing every 6 months for patients with advanced fibrosis (ie, Metavir stage F3 or F4).(I-C)***
- ***Endoscopic surveillance for esophageal varices if cirrhosis is present. (I-A)***
- ***Evaluation for retreatment as effective alternative treatments become available. (I-C)***
- ***Routine monitoring for HCV drug RAVs during or after therapy is NOT recommended except prior to treatment of (1) persons with HCV genotype 1a infection who are being considered for treatment with simeprevir with PEG-IFN and RBV, or simeprevir or sofosbuvir (cirrhosis); or (2) persons with HCV genotype 1 infection who were previously treated with an NS5A inhibitor and are being considered for retreatment (III-C)***

Patients who have undetectable HCV RNA in the serum when assessed 12 or more weeks after completion of treatment are deemed to have achieved an SVR. In these patients, hepatitis C-related liver injury stops, although they remain at risk for non-hepatitis C-related liver disease, such as fatty liver or alcoholic liver disease. Patients with cirrhosis remain at risk for developing HCC.

SVR typically aborts progression of liver injury with regression of liver fibrosis in most but not all patients with an SVR [42,101-104]. Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0-F2) who achieve an SVR should receive standard medical care that is recommended for patients who were never infected with HCV.

Among patients with advanced liver fibrosis (ie, Metavir stage F3 or F4) who achieve an SVR, decompensated liver disease (with the exception of HCC) rarely develops during follow-up, and overall survival is prolonged [42,101-104]. Patients who have advanced fibrosis or cirrhosis continue to be at risk for development of HCC even after achieving an SVR, although their risk is much lower than the risk associated with persistent viremia [42,101-104]. Although liver fibrosis regresses in most patients who achieve an SVR [42,101-104] and bleeding from esophageal varices is rare [42,101-104], patients with cirrhosis should undergo screening endoscopy for detection of esophageal varices and these should be treated or monitored as indicated [60].

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 confirmed fatty liver disease, iron overload, or HBV) 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. Periodic testing is recommended for patients with ongoing risk for HCV infection (eg, illicit drug use or high-risk sexual exposure) or HCV reinfection. Flares in liver enzyme test results should prompt evaluation of possible de novo reinfection with HCV through a new exposure. Anti-HCV remains positive in most patients following an SVR. Thus, testing for HCV reinfection should be performed with an assay that detects HCV RNA (eg, a quantitative HCV RNA test).

Individuals with inactive (no detectable virus) or past hepatitis B virus infection may experience reactivation and clinically apparent hepatitis during immunosuppressive treatment or chemotherapy. This does not occur with hepatitis C infection. Thus, routine HCV RNA testing

during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

Recommendation:

25. Patients who achieve an SVR should receive the following -

- ***For patients without advanced fibrosis (ie, Metavir fibrosis stage F0-F2), no additional follow-up is recommended. (I-B)***
- ***Patients with advanced fibrosis (ie, Metavir fibrosis stage F3 or F4) should undergo surveillance for HCC with twice-yearly abdominal imaging. (I-C)***
- ***Continue endoscopy to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed up as indicated. (I-C)***
- ***Assessment of other causes of liver disease for patients who have persistently abnormal liver function test results after achieving an SVR. (I-C)***
- ***Assessment for HCV recurrence or reinfection is only necessary if the patient has ongoing risk for HCV infection or experiences otherwise unexplained hepatic dysfunction. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection. (I-A)***
- ***Routine prospective monitoring for HCV infection recurrence among patients who achieved SVR and who are receiving immunosuppressive treatment (e.g. systemic corticosteroids, antimetabolites, chemotherapy, etc) is NOT recommended. (III-C)***

UNIQUE PATIENT POPULATIONS

Decompensated Cirrhosis

Recommendation:

26. Patients with HCV who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner who is highly experienced in the management of advanced liver disease and HCV treatment (ideally in a liver transplant center). (I-C)

Genotypes 1 and 4

Emerging data support the use of DAA combinations in patients with decompensated cirrhosis. Treatment-naive or -experienced patients with HCV genotype 1 or 4 with CTP class B or C cirrhosis who received daily ledipasvir/sofosbuvir and RBV (600 mg, increased as tolerated) for 12 weeks or 24 weeks had similar SVR12 rates. Thus, a 12-week course of ledipasvir/sofosbuvir and RBV is an appropriate regimen for patients with decompensated cirrhosis who are infected with HCV genotype 1 or 4. For patients with decompensated cirrhosis who are awaiting liver transplant, the impact of SVR on their priority for transplantation is unknown; analysis of outcomes in this population is required. As of December 2014, there are no data from studies of ledipasvir/sofosbuvir without RBV in patients with decompensated cirrhosis.

Recommendation:

27. Recommended treatment for patients with genotype 1 or 4 HCV and 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 HCC -

- ***Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 12 weeks. (IIb-C)***
- ***For patients with anemia or RBV intolerance, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks. (IIb-C)***
- ***Alternative –***
  - ***For patients in whom prior sofosbuvir-based treatment has failed, daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) and RBV (initial dose of 600 mg, increased as tolerated) for 24 weeks. (IIb-C)***

Genotype 2 and 3

In one study, 61 patients with HCV infection and HCC meeting Milan criteria for liver transplant were treated with sofosbuvir plus RBV for up to 48 weeks [105]. At 12 weeks posttransplant, 30 of the 43 patients who had undergone liver transplant, (70%) had undetectable HCV RNA, consistent with prevention of HCV recurrence. Ten patients experienced recurrent HCV, 9 of whom had undetectable HCV RNA levels for less than 30 days pretransplant. Ten of the 11 (91%) patients with HCV genotype 2 or 3 achieved SVR12. These data suggest that sofosbuvir and RBV can be given to liver transplant candidates with HCC and mildly decompensated cirrhosis.

Recommendation:

28. Recommended treatment for patients with genotype 2 or 3 and decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with HCC -

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

Patients Who Develop Recurrent HCV Infection after Liver Transplantation

Genotypes 1 and 4

In a randomized controlled trial of 222 liver transplant recipients with recurrent genotype 1 or 4 HCV, participants were randomized to ledipasvir/sofosbuvir and RBV for 12 or 24 weeks [106]. SVR12 was achieved in 96% of patients with Metavir stage F0 to F3 fibrosis and compensated cirrhosis, in both the 12-week and 24-week arms. Efficacy was lower in CTP class B (85% SVR12) or C cirrhosis (60% SVR12), with no increase in SVR with 24 weeks duration. Since all patients received RBV, the safest presumption is that RBV contributes to the high SVR12 rates. However, based on other data [91], 24 weeks of ledipasvir/sofosbuvir is an alternative for RBV intolerant patients.

In a study of liver transplant recipients with mild recurrence of HCV genotype 1, PrOD plus weight-based RBV for 24 weeks achieved an SVR24 rate of 96% [107]. Because of the

interaction between ritonavir and calcineurin inhibitors, prospective dose adjustments are required for cyclosporine and tacrolimus. In a retrospective analysis of sofosbuvir plus simeprevir with or without RBV in liver transplant recipients, the SVR4 rate was 92% [108]. Simeprevir should not be coadministered with cyclosporine, but may be coadministered with tacrolimus with careful monitoring.

Recommendation:

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

- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based RBV for 12 for patients with HCV genotype 1 or 4 infection in the allograft.(I-B)***
- ***Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended for those who are RBV intolerant or ineligible. (I-B)***
- ***Alternatives: (for patients who were not previously treated with telaprevir- or boceprevir-containing regimens)***
    - ***For patients with HCV genotype 1 in the allograft, including those with compensated cirrhosis: Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based RBV for 12 weeks. (I-B)***
    - ***For patients with genotype 1 HCV in the allograft, including early (Metavir fibrosis stage F0-F2) recurrence: Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based RBV for 24 weeks. (I-B)***

Non-1 Genotypes

Few data are available to guide treatment of patients with HCV genotype 2 or 3 in the posttransplant setting; recommendations largely mirror those in the non-transplant population.

Recommendation:

30. Treatment-naive and -experienced patients with HCV genotype 2 in the allograft, including those with compensated cirrhosis should receive daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks. (IIb-C)

Recommendation:

31. Treatment-naive and -experienced with HCV genotype 3 in the allograft should receive the following –

Compensated cirrhosis:

- ***Daily sofosbuvir (400 mg) and weight-based RBV for 24 weeks (I-B)***

Decompensated cirrhosis (Child Turcotte Pugh class B or C):

- ***Daily sofosbuvir (400 mg) and low initial dose of RBV (600 mg, increasing as tolerated) for 24 weeks.(I-B)***

Patients with Renal Impairment

The currently approved DAAs can be safely dosed in persons with mild-to-moderate renal impairment (CrCl rate, 30-80 mL/min). However, there are few data to guide dosing of these agents in severe renal impairment/ESRD (CrCl < 30 mL/min). Studies of PrOD with or without

RBV (for HCV genotype 1a or 1b) in treatment-naïve, patients without cirrhosis with severe renal impairment show early promising efficacy [109]. Caution is warranted in managing anemia related to RBV, and RBV should not be given if the baseline hemoglobin level is less than 10 g/dL.

Recommendation:

32. For patients with mild to moderate renal impairment (CrCl rate >30-80 mL/min), no dosage adjustment is required when using sofosbuvir, simeprevir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) to treat or retreat HCV infection in patients with appropriate genotypes. (I-A)

Recommendation:

33. For treatment-naive patients with HCV genotype 1 without cirrhosis with CrCl rates less than 30 mL/min, treatment with the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with (1a) or without (1b) RBV (200 mg) once daily is recommended. RBV should only be given if the baseline hemoglobin level is greater than 10 g/dL. For patients with moderate renal impairment (eGFR 30-50mL/min), initial RBV dosing should be 200 mg or 400 mg alternating every other day. For patients with severe renal impairment or who are on hemodialysis (eGFR <30mL/min), initial RBV dosing should be 200 mg daily. (II-B)

HIV/HCV COINFECTION

Compared with those with HCV infection alone, persons with HCV/HIV coinfection have a higher rate of HCV persistence, faster progression to cirrhosis and end stage liver disease, and higher HCV RNA levels [110-112]. HIV/HCV coinfected persons also had lower responses to PEG-IFN and RBV than those with HCV infection alone, an observation largely explained by the higher baseline HCV RNA levels [113,114]. However, with the advent of DAAs, differences in treatment responses between mono- and coinfected patients have not been detected [115,116]. Thus, the same HCV treatment recommendations for HIV/HCV coinfected persons as for those with just HCV infection, with consideration of potential drug-drug interactions with HIV medications.

In some instances pharmacokinetic testing has been done in HIV/HCV coinfected persons, and there is clinical experience with the combinations (see www.hcvguidelines.org). In others, the pharmacology is predicted or based on healthy volunteer studies. The chief concern with the combination of ledipasvir/sofosbuvir is potentiation of the nephrotoxicity of tenofovir disoproxil fumarate (tenofovir). Tenofovir levels are increased by ledipasvir/sofosbuvir and may be even higher with coadministration of other antiretroviral drugs that raises tenofovir levels, particularly ritonavir-boosted protease inhibitors. With PrOD, the inclusion of 100 mg of ritonavir in the fixed combination will also “boost” HIV protease inhibitors (and some other medications) and additional ritonavir should be discontinued, then restarted when HCV treatment is finished. In healthy volunteers, when PrOD was combined with efavirenz, emtricitabine, and tenofovir,

gastrointestinal and neurologic adverse events occurred along with elevations of ALT. When the regimen was combined with rilpivirine, exposures to rilpivirine were substantially increased. Therefore, rilpivirine and efavirenz should not be used with the PrOD regimen [117,118].

Clinical trials have demonstrated the safety and efficacy of ledipasvir/sofosbuvir in HIV-infected persons with HCV genotype 1 or 4 who were generally taking antiretroviral therapy that included tenofovir and emtricitabine with rilpivirine, raltegravir, or efavirenz [119,120]. Data are derived from studies that included 335 HCV treatment-naive and -experienced HIV/HCV coinfected persons as well as those with or without cirrhosis. Clinical trial data in HIV-infected individual with HCV genotype 1 and 4 infection have demonstrated the safety and efficacy of ledipasvir/sofosbuvir for 12 weeks [119,120] and of PrOD with or without RBV [121] for 12 weeks.

Data on treatment of HIV/HCV-coinfected persons with HCV genotypes 2 and 3 support use of similar regimens as are recommended for persons without HIV infection [115,122]. Antiretroviral regimens allowed included combinations of TDF and emtricitabine with efavirenz, raltegravir, ritonavir-boosted atazanavir, ritonavir-boosted darunavir, or rilpivirine. High SVR12 rates were observed for genotype 2 (89%) and genotype 3 (84%). Treatment was generally well tolerated.

Recommendation:

34. HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral

medications. (I-B)

Recommendation:

35. Antiretroviral treatment interruption to allow HCV therapy is NOT recommended. (III-A)

Recommendation:

36. Antiretroviral and HCV drug interactions should be assessed prior to initiating therapy. Drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended. (I-A)

Recommendation:

37. The following are recommendations related to specific drug combination which need to be considered in co-infected patients –

Ledipasvir*:*

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

Sofosbuvir and ledipasvir/sofosbuvir:

- ***Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) should not be used with cobicistat and elvitegravir, pending further data. (III-C)***
- ***Sofosbuvir or ledipasvir/sofosbuvir should not be used with tipranavir. (III-B)***

Paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD):

- ***PrOD should be used with antiretroviral drugs with which it does not have substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, and atazanavir. The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with PrOD and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination. (IIa-C)***
- ***PrOD should not be used with efavirenz, rilpivirine, darunavir, or ritonavir-boosted lopinavir. (III-B)***
- ***PrOD should not be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy. (III-B)***

Simeprevir:

- ***Simeprevir should not be used with efavirenz, etravirine, nevirapine, cobicistat, or any HIV protease inhibitor. (III-B)***

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

Ribavirin:

- ***RBV should not be used with didanosine, stavudine, or zidovudine. (III-B)***

ACUTE HCV INFECTION

HCV infection is considered to be acute during the first 6 months. Infections of less than six months duration spontaneously resolve in 15% to 50% of cases, whereas spontaneous resolution occurs in fewer than 5% once infection persists for several years [123-126]. Within the first months of HCV infection, there is also a transition to (particularly in patients with unfavorable *IL28B* genotypes and genotype 1 HCV infection) decreasing responsiveness of HCV infection to PEG-IFN [127,128].

Aside from instances in which there is a single exposure such as a health care worker with a needlestick injury, it is often impossible to know exactly when infection occurred. With the transition to IFN-free treatments, this determination is less crucial since acute HCV infection can now be managed like chronic infection. However, better methods of differentiating acute from chronic infection would be useful for public health surveillance.

The decision of when to treat acute HCV infection is largely based on the likelihood of spontaneous resolution, the possibility of transmission to others, the efficacy and safety of treatment in the acute compared with the chronic phase of infection, and patient preference. Previously when PEG-IFN was used, responses were better if genotype 1 HCV infection was treated within the first 12 to 16 weeks than a year after infection [127,128]. Since the majority of spontaneous resolutions also occur in the first 12 to 16 weeks, treatment was recommended within that window [129]. With 12-week PEG-IFN-sparing regimens, SVR rates for treatment of chronic infection are higher than 90% and much safer. Consequently, unless necessary to prevent transmission to others or strongly preferred by the patient or practitioner for other reasons, persons with acute HCV infection should be monitored for six or more months. If spontaneous clearance has not occurred, treatment should follow the same recommendations as for chronic infection. Likewise, even when treatment is provided earlier than six months after infection, it is recommended to monitor at least 12 weeks for spontaneous resolution and use the same regimens as with chronic infection until studies demonstrate the superiority (or non-inferiority) of alternatives.

The optimal timing and intensity of monitoring in acute infection varies depending on the treatment considerations described above and whether there is evidence of severe hepatitis. At a minimum HCV RNA should be assessed four to six months after the estimated onset of infection to establish if chronic infection occurred. Often, more frequent testing of HCV RNA and liver enzymes is preferred.

Recommendation:

38. The following are recommended in the diagnosis and initial management of acute hepatitis C -

- ***HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels. (I-C)***
- ***Regular laboratory monitoring (every 4 weeks to 8 weeks for 6 months to 12 months) is recommended in the setting of acute HCV infection until the alanine aminotransferase (ALT) level normalizes and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. (I-B)***
- ***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 detect spontaneous clearance before starting treatment. (IIa-C)***
- ***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. (IIa-C)***
- ***Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (e.g., acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others. (I-C)***
- ***Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to injection drug use. (I-B)***

Recommendation:

39. Treatment of individuals with acute hepatitis C should be the same as that recommended for chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Treat). (IIa-C)

Alternative –

- ***PEG-IFN with or without RBV for 16 weeks (for those with HCV genotype 2 or 3 who have a rapid virologic response) to 24 weeks (for those with HCV genotype 1). (II-A)***

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Table 1. Rating by Classification and Level of Evidence

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 [1,2].

*In some situations, such as for PEG-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.

1 **Table 2.** Summary of Recommendations for Screening for HCV Infection

1. Birth Cohort

- Those persons born between the years of 1945 and 1965

2. Risk behaviors

- Injection-drug use (current or ever, including those who injected once)
- Intranasal illicit drug use

3. Risk exposures

- Long-term hemodialysis (ever)
- Getting a tattoo in an unregulated setting
- Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
- Children born to HCV-infected women
- Prior recipients of transfusions or organ transplants, including persons who:
  - were notified that they received blood from a donor who later tested positive for HCV infection
  - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
  - received clotting factor concentrates produced before 1987
- Persons who were ever incarcerated

4. Other

- HIV infection
- Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)

2

Table 3. 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 recipients.
  Rating: Class I, Level B
- Type 2 or 3 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.

Table 4. Persons with Risk of HCV Transmission* or in Whom Treatment May Reduce Transmission

- Men who have sex with men (MSM) with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis
- HCV-infected women of child-bearing potential wishing to get pregnant
- Infected healthcare workers who perform exposure-prone procedures

Ratings: Class IIa, Level C

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

Table 5. Recommended Assessments Prior to Starting Antiviral Therapy

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

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

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

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

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

Ratings: Class I, Level C

Table 6. Recommended Monitoring During Antiviral Therapy

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

The following laboratory testing is recommended:

- Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated.
- Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN.
- More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated.
- Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. Antiviral drug therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.
- Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.

Ratings: Class I, Level B

Prompt discontinuation of therapy is recommended for any a) 10-fold increase in alanine aminotransferase (ALT) activity at week 4; or b) any increase in ALT of less than 10-fold at week 4 that is accompanied by any weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or international normalized ratio. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8.

Rating: Class I, Level B

Table 7. Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

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

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

Ratings: Class III, Level C

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