The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

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www.hcvguidelines.org

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

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- Treatment-Experienced Genotype 5 or 6
- Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis
- DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Unique Populations

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References

- Reference list sorted by first author

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version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this.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 has increased rapidly as numerous new drugs with different mechanisms of action have become available over the past few years. To provide healthcare professionals with timely guidance as new therapies become available and are integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD), developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

The AASLD/IDSA guidance on hepatitis C addresses management issues ranging from testing and linkage to care, the crucial first steps toward improving health outcomes for HCV-infected persons, to the optimal treatment regimen in particular patient situations. Recommendations are evidence based and rapidly updated as new data from peer-reviewed research become available. For each treatment option, recommendations reflect the best possible management for a given patient and a given point of disease progression. Recommendations are rated with regard to the level of the evidence and strength of the recommendation. The AASLD/IDSA guidance on hepatitis C is supported by the membership-based societies and not by pharmaceutical companies or other commercial interests. The governing boards of AASLD and IDSA have appointed an oversight committee of 4 co-chairs and selected panel members from the societies.

This guidance should be considered a living document in that the recommendations are 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 the FDA. Readers should consult prescribing information and other resources for further information. In the future, treatment recommendations may be further guided by data from cost-effectiveness studies.

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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 processes and detailed methods for developing the guidance are detailed in Methods Table 1. Recommendations are rated according to the strength of the recommendation and quality of the supporting evidence (see Methods Table 2) (AASLD-IDSA, 2015). Commonly used abbreviations are defined in Methods Table 3.

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

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

Topic	Description
Statement of need	Increased awareness of the rising number of complications of hepatitis C virus (HCV) infection, the recent screening initiatives by the Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force (USPSTF), and the rapid evolution of highly effective antiviral therapy for HCV infection have driven a need for timely guidance on how new developments change practice for healthcare professionals.
Goal of the guidance	The goal of the guidance is to provide up-to-date recommendations to healthcare practitioners on the optimal screening, management, and treatment for persons with HCV infection in the United States, considering the best available evidence. The guidance is updated regularly as new data, information, and tools and treatments become available.
Panel members	Panel members are chosen based on their expertise in the diagnosis, management, and treatment of HCV infection. Members from the fields of hepatology and infectious diseases are included, as well as HCV community representatives. Members are appointed by the sponsor societies after vetting by an appointed sponsor society committee. The panel chairs are appointed by the society boards, 2 each from the sponsor societies. All panel chairs and members serve as uncompensated volunteers for defined terms (2 to 3 years), which may be renewed based on panel needs.
Conflict of interest management	The panel was established with the goal of having no personal (ie, direct payment to the individual) financial conflicts of interest among its chairs and among fewer than half of its panel members. All potential panel members are asked to disclose any personal relationship(s) with pharmaceutical, biotechnology, medical device, or health-related companies or ventures that may result in financial benefit. Disclosures are obtained prior to the panel member appointments and for 1 year prior to the initiation of their work on the panel. Full transparency of potential financial conflicts is an important goal for the guidance that best ensures the credibility of the process and the recommendations. Individuals are also asked to disclose funding of HCV-related research activities to their institutional division, department, or practice group. Disclosures are reviewed by the HCV guidance chairs, who make assessments based on the conflict-of-interest policies of the sponsoring organizations (AASLD and IDSA). Personal and institutional financial relationships with commercial entities that have products in the field of hepatitis C are assessed. The following relationships are prohibited during membership on the guidance panel and are grounds for exclusion from the panel: • Employment with any commercial company with products in the field of hepatitis C • An ownership interest in a commercial entity that produces hepatitis C products • Participation in/payment for promotional or marketing activities sponsored by companies

Topic	Description
	with HCV-related products including non-CME educational activities or speakers bureaus for audiences outside of the company • Participation in any single-funder CME activity • Participation on a marketing or medical affairs advisory board The following relationships or activities are reportable but do not merit exclusion: • Commercial support of research that is paid to an organization or practice group Due to the rapidly evolving nature of the subject matter, having individuals with expertise in the particular clinical topic is crucial to developing the highest-quality and most-informed recommendations. To that end, research support from commercial entities is not considered grounds for panel exclusion (an unresolvable conflict) if the funding of the research was paid to the institution or practice group, as opposed to the individual. In the instance of someone conducting clinical research in a community practice, research funds to the group practice are acceptable. • Participation on commercial company scientific advisory boards Participation in advisory boards, data safety monitoring boards, or in consultancies sponsored by the research arm of a company (eg, study design or data safety monitoring board) is considered a potential personal conflict that should be reported but is not considered a criterion for exclusion. • CME honorarium earned in excess of $5000 (total per year, including travel costs) No need to report if total honorarium is less than $5000. The HCV guidance chairs achieved a majority of panel members with no personal financial interests. Panel members are asked to inform the group of any changes to their disclosure status and are given the opportunity to recuse themselves (or be recused) from the discussion where a perceived conflict of interest that cannot be resolved exists. Financial disclosures for each panel member can be accessed here.
Intended audience	Medical practitioners, especially those who provide care to or manage patients with hepatitis C, are the intended audience of the guidance.
Sponsors, funding, and collaborating partner	AASLD and IDSA are the sponsors of the guidance and provide ongoing financial support. Grant support was sought and obtained from CDC for the initial gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings.
Evidence identification and collection	The guidance is developed using an evidence-based review of information that is largely available to healthcare practitioners. Data from the following sources are considered by panel members when making recommendations: research published in the peer-reviewed literature or presented at major national or international scientific conferences; safety warnings from the US Food and Drug Administration (FDA) or other regulatory agencies or from manufacturers; drug interaction data; prescribing information from FDA-approved products; and registration data for

Topic	Description
	new products under FDA review. Press releases, unpublished reports, and personal communications are generally not considered. Literature searches are conducted regularly and before each major revision to ensure that the panel addresses all relevant published data. Medical subject headings and free text terms are combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases. To be considered for inclusion, articles are required to have been published in English from 2010 to the present. Data from abstracts presented at national or international scientific conferences are also considered.
Rating of the evidence and re commendations	The guidance is presented in the form of recommendations. Each recommendation is rated in terms of the level of the evidence and strength of the recommendation using a modification of the scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (AHA, 2011); (Shiffman, 2003). A summary of the supporting (and conflicting) evidence follows each recommendation or set of recommendations.
Data review and synthesis and preparation of r ecommendation s and supporting information	Draft recommendations are developed by subgroups of the full panel with interest and expertise in particular sections of the guidance. Following development of supporting text and references, the sections are reviewed by the full panel and chairs. A penultimate draft is submitted to the AASLD and IDSA governing boards for final review and approval before posting online on the website, www.hcvguidelines.org. Subgroups of the panel meet regularly by conference call as needed to update recommendations and supporting evidence. Updates may be prompted by new publications or presentations at major national or international scientific conferences, new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety warnings, or other information that may have a substantial impact on the clinical care of patients. Updates and changes to the guidance are indicated by a notice of update posted on the home page.
Abbreviations	Commonly used abbreviations in the text are defined in Methods Table 3.
Opportunity for comments	Evidence-based comments may be submitted to the panel by email to stynes@aasld.org or by clicking on the “Submit” button on the site contact form. The panel considers evidence-based comments about the recommendations, ratings, and evidence summaries but should not be contacted for individual patient management questions.

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Table 2. Rating System Used to Rate Level of Evidence and Strength of Recommendation

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

Class	
I	Evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective.
II	Conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment.
IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy.
IIb	Usefulness and efficacy are less well established by evidence and/or opinion.
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	
A	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent.
B	Data derived from a single randomized trial, nonrandomized studies, or equivalent.
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 (AHA, 2011); (Shiffman, 2003).

In some situations, such as for interferon-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 predetermined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B.

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Table 3. Commonly Used Abbreviations

Abbreviation	Definition and Notes
ACA	Patient Protection and Affordable Care Act
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AMP	average manufacturer price
Anti-HCV	HCV antibody
APRI	AST-to-platelet ratio index
AST	aspartate aminotransferase
AUC	area under the curve
AWP	average wholesale price[a]
BOC	boceprevir
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CTP	Child-Turcotte-Pugh (see below)
CYP	cytochrome P450
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	US Food and Drug Administration
GFR	glomerular filtration rate
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus Hepatitis C virus and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the disease entity.

Abbreviation	Definition and Notes
ICER	incremental cost-effectiveness ratio
IDU	injection drug use or user
INR	international normalized ratio
MELD	model for end-stage liver disease
MSM	men who have sex with men
NASH	nonalcoholic steatohepatitis
NAT	nucleic acid testing
NIH	National Institutes of Health
NS3	HCV nonstructural protein 3
NS5A	HCV nonstructural protein 5A
OATP	organic anion-transporting polypeptide
PBM	pharmacy benefit manager
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PreP	preexposure prophylaxis
PWID	people who inject drugs
QALY	quality-adjusted life-year
RAS	resistance-associated substitution
RBC	red blood cell(s)
RBV	ribavirin
RGT	response-guided therapy
sAg	surface antigen
SMV	simeprevir
SOF	sofosbuvir
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

Abbreviation	Definition and Notes
ULN	upper limit of normal
USPSTF	US Preventive Services Task Force
WAC	wholesale acquisition cost[b]

[a] "List price" for wholesale pharmacies to purchase drugs
[b] Typically, approximately 17% off of AWP

Child-Turcotte-Pugh (CTP) Classification of the Severity of Cirrhosis			
	CLASS A	CLASS B	CLASS C
Total Points	5-6	7-9	10-15
Factor	1 Point	2 Points	3 Points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
Prothrombin time / international normalized ratio	<1.7	1.71-2.3	>2.3
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or supressed with medication)	Grade III-IV (or refractory)

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Testing, Evaluation, and Monitoring of Hepatitis C

The following pages address testing, evaluation, and monitoring of patients with HCV before, during and after antiviral therapy.

- HCV Testing and Linkage to Care
- When and in Whom to Initiate HCV Therapy
- Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens
- Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy
- HCV Resistance Primer

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HCV Testing and Linkage to Care

One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time hepatitis C testing is recommended for persons born[a] from 1945 through 1965 without prior ascertainment of risk.	I, B

Other persons should be screened for HCV infection risk factors. One-time testing should be performed for all persons with behaviors, exposures, and conditions or circumstances associated with an increased risk of HCV infection.
 	
Risk Behaviors
 	
• Injection-drug use (current or ever, including those who injected only once)
• Intranasal illicit drug use
 	
Risk Exposures
 	
• Persons on long-term hemodialysis (ever)
• Persons with percutaneous/parenteral exposures in an unregulated setting
• Healthcare, emergency medical, and public safety workers after needle-stick, 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
  ◦ 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
 	
Other Conditions and Circumstances
 	
• HIV infection
• Sexually-active persons about to start pre-exposure prophylaxis (PreP) for HIV
• Unexplained chronic liver disease and/or chronic hepatitis, including elevated alanine aminotransferase (ALT) levels
• Solid organ donors (deceased and living)
	I, B

[a] Regardless of country of birth	

There are an estimated 3.5 million HCV-infected persons in the United States, including 2.7 million in the general noninstitutionalized population (Denniston, 2014) and 800,000 incarcerated, institutionalized, or homeless persons (Edlin, 2015). Approximately 50% of all infected people are unaware that they have HCV (Denniston, 2012); (Holmberg, 2013).

HCV testing is recommended in select populations based on demographics, possible exposures, high-risk behaviors, and medical conditions. Testing recommendations 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); (USPSTF, 2013); (CDC, 1998).

HCV is primarily transmitted through percutaneous exposure to infected blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection drug use. Sexual transmission also occurs but generally seems inefficient except among HIV-infected men who have unprotected sex with men (Schmidt, 2014).

Injection drug use poses the most significant risk for HCV infection, accounting for at least 60% of acute HCV infections in the United States. Healthcare exposures are important sources of transmission, including the receipt of blood products prior to 1992 (after which routine screening of the 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 percutaneous or parenteral exposures in an unregulated setting. Examples of these settings include tattoos received outside of licensed parlors and medical procedures done internationally or domestically where strict infection control procedures may not have been followed (eg, surgery before implementation of universal precautions) (Hellard, 2004).

The importance of these risk factors might differ based on geographic location and population (USPSTF, 2013); (CDC, 1998). An estimated 29% of incarcerated persons in North America are HCV-antibody–positive, supporting the recommendation to screen this population for HCV (Larney, 2013).

Because of shared transmission modes, persons with HIV infection are at risk for HCV. Sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men (Hosein, 2013); (van de Laar, 2010). Screening sexually active, non-HIV-infected persons before they start pre-exposure prophylaxis (PreP) for HIV infection prevention should also be considered (Volk, 2015).

Recent data support testing in all deceased and living solid organ donors because of the risk of HCV infection posed to the recipient (Seem, 2013); (Lai, 2013). Although hepatitis C testing guidelines from the US Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) do not specifically recommend testing immigrants from countries with a high prevalence of HCV infection (eg, Egypt and Pakistan), such persons should be tested if they were born from 1945 through 1965, or if they have risk factors for infection (see One-Time Testing Recommendations).

CDC established risk-based HCV testing guidelines in 1998 (CDC, 1998). These guidelines were expanded in 2012 with a recommendation to offer a one-time HCV testing to all persons born from 1945 through 1965 without prior ascertainment of HCV risk factors (see One-Time Testing Recommendations). This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections, due in part to patient underreporting of their risk and provider limitations in ascertaining risk factor information. Furthermore, persons in the 1945 through 1965 birth cohort account for nearly 75% of all HCV infections, with a 5-fold higher prevalence (3.25%) than other adults. This reflects a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000 annually in the US, compared to an estimated 30,500 in 2014) (CDC, 2016). A retrospective analysis published in 2013 showed that 68% of persons with HCV infection would have been identified with a birth cohort testing strategy, whereas only 27% would have been screened with the risk-based approach (Mahajan, 2013). The cost-effectiveness of one-time birth cohort testing is comparable to that of current risk-based screening strategies (Smith, 2012).

Both CDC and the USPSTF recommend a one-time HCV test in asymptomatic persons belonging to the 1945 through 1965 birth cohort, as well as other individuals based on exposures, behaviors, and conditions or circumstances that

increase HCV infection risk.

HCV Testing for Persons With Ongoing Risk Factors

Recommendation for HCV Testing for Persons With Ongoing Risk Factors	
RECOMMENDED	RATING
Annual HCV testing is recommended for persons who inject drugs and for HIV-infected men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for HCV exposure.	IIa, C

Evidence regarding the frequency of testing in persons at risk for ongoing exposures to HCV is lacking. Therefore, clinicians should determine the periodicity of testing based on the risk of infection or reinfection. Because of the high incidence of HCV infection among persons who inject drugs and HIV-infected men who have unprotected sex with men, HCV testing at least annually is recommended for these populations (Aberg, 2014); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011).

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

Initial HCV Testing and Follow-Up

Recommendations for Initial HCV Testing and Follow-Up	
RECOMMENDED	RATING
An HCV-antibody test is recommended for initial HCV testing. If the result is positive, current infection should be confirmed by a sensitive HCV-RNA test.	I, A
Among persons with a negative HCV-antibody 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 for persons who are immunocompromised.	I, C
Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an HCV-antibody test is expected to be positive.	I, C
Quantitative HCV-RNA testing is recommended prior to initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).	I, A
HCV genotype testing is recommended to guide selection of the most appropriate antiviral regimen.	I, A
Persons found to have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have evidence of current (active) HCV infection.	I, A

All persons recommended for HCV screening should initially be tested for HCV antibody (CDC, 2013); (Alter, 2003) using an assay approved by the US Food and Drug Administration (FDA). 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 laboratory-based HCV-antibody assays.

A positive test result for HCV antibody indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive result (Pawlotsky, 2002). Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm active HCV infection and guide clinical management, including initiation of HCV treatment. HCV-RNA testing should also be performed in persons with a negative HCV-antibody 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 because these persons may be HCV-antibody–negative. An HCV-RNA test is also needed to detect reinfection in HCV-antibody–positive persons after previous spontaneous or treatment-related viral clearance.

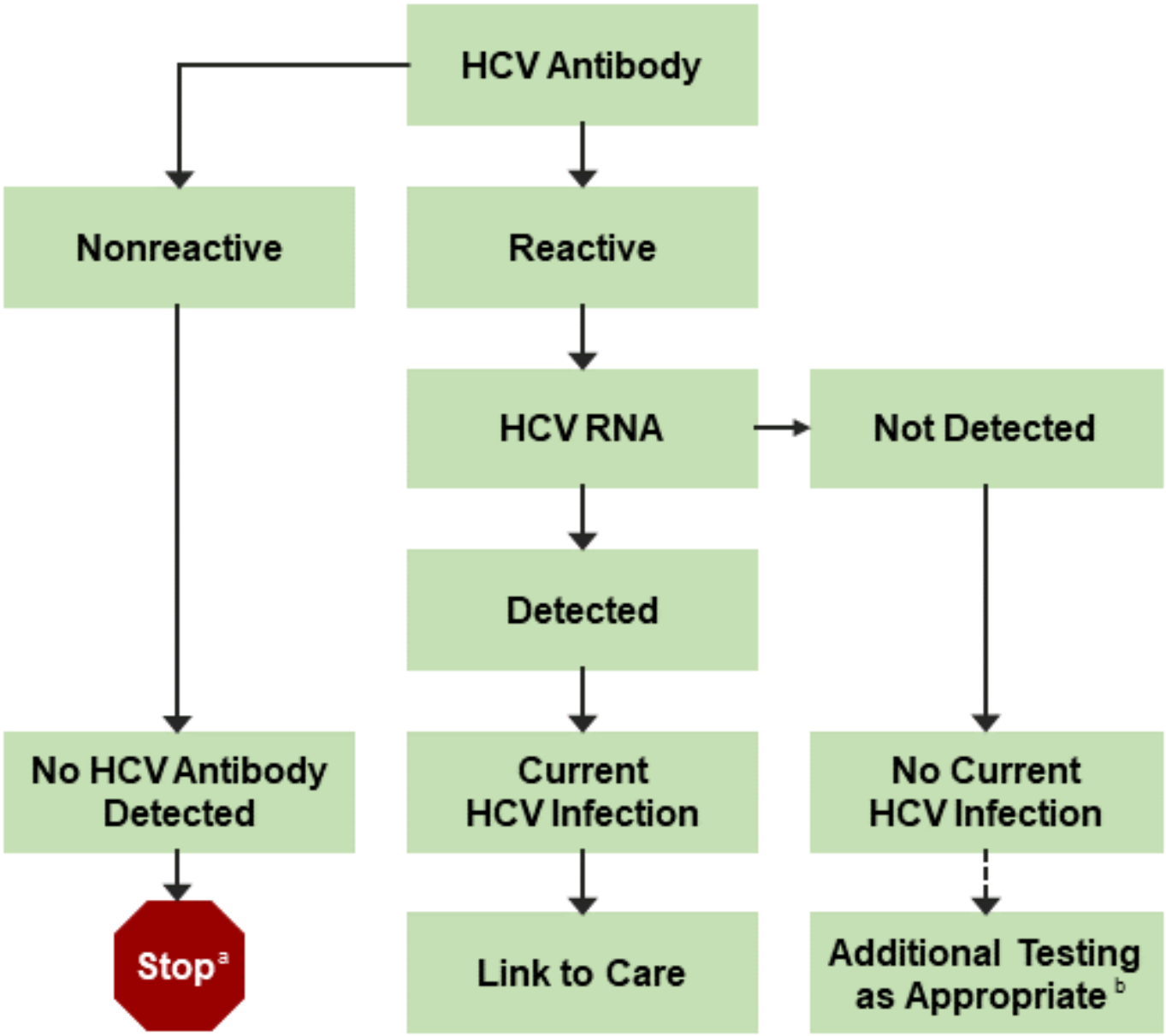
An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. Table 1 lists FDA-approved, commercially available HCV-antibody screening assays. Figure 1 shows the CDC-recommended testing algorithm.

Table 1. FDA-Approved HCV-Antibody Screening Assays

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott Laboratories Abbott Park, IL, USA	EIA[a] (manual)
Advia Centaur HCV	Siemens Healthcare Malvern, PA, USA	CIA[b] (automated)
Architect Anti-HCV	Abbott Laboratories Abbott Park, IL, USA	CMIA[c] (automated)
AxSYM Anti-HCV	Abbott Laboratories Abbott Park, IL, USA	MEIA[d] (automated)
OraQuick HCV Rapid Antibody Test	OraSure Technologies, Inc. Bethlehem, PA, USA	Immunochromatographic (manual)
Ortho HCV Version 3.0 ELISA Test System	Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA	EIA[a] (manual)
VITROS Anti-HCV	Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA	CIA[b] (automated)

[a] EIA: enzyme immunoassay
[b] CIA: chemiluminescent immunoassay
[c] CMIA: chemiluminescent microparticle immunoassay
[d] MEIA: microparticle enzyme immunoassay
Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.

Figure 1. CDC-Recommended Testing Sequence for Identifying Current HCV Infection



[a] 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.
[b] 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 (CDC, 2013)

Persons who have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current HCV infection. Additional HCV testing is typically unnecessary. The HCV-RNA test can be repeated when there is a high index of suspicion for recent infection or in patients with ongoing HCV infection risk.

Clinicians (or patients) may seek additional testing to determine whether a positive HCV-antibody test represents a remote HCV infection that has resolved or a false positive. 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 HCV-antibody tests most commonly occur in populations with a low prevalence of HCV infection (Alter, 2003). If further testing is desired to distinguish between a true positive vs biologic false positivity for HCV antibody, repeat testing may be done with a different FDA-approved, HCV-antibody assay. A biologic false result should not occur with two different assays (Vermeersch, 2008); (CDC, 2013).

Prior to initiation of antiviral therapy, quantitative HCV-RNA testing may be used to determine the baseline level of viremia (ie, viral load), which may affect treatment duration with certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response (SVR) in the era of direct-acting antiviral (DAA) therapy compared to previous interferon-based treatment (see Pretreatment and On-Treatment Monitoring). Testing for HCV genotype helps guide selection of the most appropriate antiviral regimen.

Counseling Persons With Active HCV Infection

Recommendations for Counseling Persons With Active HCV Infection	
RECOMMENDED	RATING
Persons with current HCV infection should receive education and interventions aimed at reducing liver disease progression and preventing HCV transmission.	IIa, B
Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.	IIa, B
Evaluation for other conditions that may accelerate liver fibrosis, including hepatitis B and HIV infections, is recommended for all persons with active HCV infection.	IIb, B
Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy, and to determine the need for initiating additional measures for cirrhosis management (eg, hepatocellular carcinoma screening) (see Monitoring section).	I, A
Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.	IIa, C
Vaccination against pneumococcal infection is recommended for all patients with cirrhosis.	IIa, C
All persons with HCV infection should be provided education about how to avoid HCV transmission to others.	I, C

In addition to receiving antiviral therapy, HCV-infected persons should be educated about how to prevent further liver damage. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between excess alcohol use and the development or progression of liver fibrosis, and the development of hepatocellular carcinoma (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004).

Daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also has a deleterious effect on the liver; however, these data are controversial (Westin, 2002); (Younossi, 2013b); (Hagström, 2017). Excess alcohol intake may also cause steatohepatitis. Alcohol screening and brief interventions, such as those outlined by the National Institute on Alcohol Abuse and Alcoholism, have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily (Whitlock, 2004); (Dieperink, 2010); (Proeschold-Bell, 2012). Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

Hepatitis B virus (HBV) and HIV coinfection have been associated with a poorer HCV prognosis in cohort studies (Zarski, 1998); (Thein, 2008a); (Kruse, 2014); (Puoti, 2017b). Because of overlapping risk factors for these infections and benefits associated with their identification and treatment, HCV-infected persons should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard screening assays (Moyer, 2013); (CDC, 2008); (see USPSTF HIV screening recommendations and CDC hepatitis B screening recommendations). Patients should also be counseled about how to reduce their risk of acquiring these infections, including through HBV vaccination.

Patients with obesity and metabolic syndrome having underlying insulin resistance are at increased risk for nonalcoholic fatty liver disease, which is a risk factor for accelerated 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 of 25 to 29.9 kg/m^2, and ≥30 kg/m^2, respectively) should be counseled regarding strategies to reduce body weight and improve insulin resistance via diet, exercise, and medical therapies (Musso, 2010); (Shaw, 2006). HCV-infected patients with hyperlipidemia or cardiovascular comorbidities may also benefit from lipid-lowering drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease (Kamal, 2017); (Lewis, 2007). Therefore, these agents should not be withheld from HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease may have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit (Ghany, 2011). A liver biopsy can provide objective, semiquantitative information regarding the amount and pattern of collagen or scar tissue in the liver, which can help inform the development of treatment and monitoring plans. The Metavir fibrosis score (F0 to F4) and Ishak fibrosis score (0 to 6) are commonly used to quantify the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation and hepatic steatosis, and aid in excluding competing causes of liver injury (Kleiner, 2005). However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable (Regev, 2002).

Noninvasive methods frequently used to estimate liver disease severity include:

- Liver-directed physical exam (normal in most patients)
- Routine blood tests (eg, ALT, AST, albumin, bilirubin, international normalized ratio [INR], and CBC with platelet count)
- Serum fibrosis marker panels
- Liver imaging (eg, ultrasound, or CT scan)
- Transient elastography

Simple calculations derived from routine blood tests—such as the serum AST-to-platelet ratio index (APRI) (Wai, 2003) and fibrosis-4 (FIB-4) (Sterling, 2006)—as well as 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. The presence of portal hypertension is associated with a greater likelihood of developing future hepatic complications in untreated patients (Chou, 2013); (Rockey, 2006).

Liver elastography provides instant information regarding liver stiffness at the point of care and can reliably distinguish patients with a high versus low likelihood of cirrhosis (Castera, 2012); (Bonder, 2014). A more detailed discussion regarding fibrosis assessment is found in the When and In Whom to Initiate Therapy section.

Because persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require frequent follow-up. They should also avoid hepatotoxic drugs, such as excessive acetaminophen (>2 g/d) and certain herbal supplements. Nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, should also be avoided. Ongoing imaging surveillance for liver cancer and gastroesophageal varices is also recommended for these patients (Sangiovanni, 2006); (Fontana, 2010). Persons with cirrhosis are more susceptible to invasive pneumococcal infection (Marrie, 2011) and should receive pneumococcal vaccination (CDC, 2012).

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs given that HCV transmission in this population primarily results from sharing needles and other contaminated drug injection equipment. Epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described recently (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008). 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.

Table 2. Measures to Prevent HCV Transmission

HCV-infected persons 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. • Dispose of syringes and needles after 1 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.

Linkage to Care

Recommendation for Linkage to Care	
RECOMMENDED	RATING
All persons with active HCV infection should be linked to a clinician who is prepared to provide comprehensive management.	IIa, C

Improvement in identification of 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 clinician with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (Metavir stage ≥F3), including possible referral for consideration of liver transplantation.

In the United States, only an estimated 13% to 18% of HCV-infected persons had received treatment by 2013 (Holmberg, 2013). Lack of appropriate clinician assessment and delays in linkage to care can result in negative health outcomes. Furthermore, 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, 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 clinician-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 the cost of HCV treatment (Morrill, 2005); (Reilley, 2013); (McGowan, 2013).

Data are lacking to support exclusion of HCV-infected persons from considerations for hepatitis C therapy based on the amount of alcohol intake or use of illicit drugs. Based on data from interferon-based treatment, SVR rates among people who inject drugs are comparable to those among people who do not inject drugs (Aspinall, 2013). Some possible strategies to address barriers to HCV treatment are listed in Table 3.

Table 3. Common Barriers to HCV Treatment and Potential Strategies

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	• Conduct counseling and education • Refer for services (eg, psychiatry and opioid substitution therapy) • Optimize treatment with simpler, less toxic regimens
Competing priorities 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, better tolerated regimens • Conduct appropriate education and monitoring • Utilize directly observed therapy (tuberculosis model)
Lack of access to treatment (eg, high cost, lack of insurance, geographic distance, and/or 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 clinicians and specialists • Liaise with pharmaceutical patient assistance programs • Co-localize services (primary care, medical homes, drug treatment)
Lack of practitioner expertise	• Collaborate with specialists (eg, Project ECHO-like models and telemedicine) • Develop accessible, clear HCV treatment guidelines • Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)

One strategy that addresses several barriers is co-localization (integrated care) 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, needle exchange programs, substance abuse treatment centers, and methadone maintenance facilities) but this type of care is not uniformly available (Islam, 2012); (Stein, 2012); (Bruggmann, 2013). A study conducted by Ho and colleagues demonstrated that integrated care—consisting of multidisciplinary care coordination and patient case management—increased the proportion of patients with HCV infection and psychiatric illness or substance use who begin antiviral therapy and achieve a sustained virologic response, without serious adverse events (Ho, 2015).

A strategy that addresses lack of access to specialists—a primary barrier to hepatitis C care—is participation in models involving close collaboration between primary care practitioners and subspecialists (Arora, 2011); (Rossaro, 2013);

(Miller, 2012). Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists (Arora, 2011); (Rossaro, 2013). For example, Project ECHO (Extension for Community Healthcare Outcomes) 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 (gastroenterology, infectious disease, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV treatment in populations that might have otherwise remained untreated. The short duration of treatment and few serious adverse events associated with DAA therapy present an opportunity to expand the number of midlevel practitioners and primary care physicians engaged in the management and treatment of HCV infection.

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

Last update: May 24, 2018

When and in Whom to Initiate HCV Therapy

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure and, as such, is expected to benefit nearly all chronically infected persons. When the US Food and Drug Administration (FDA) approved the first interferon-sparing treatment for HCV infection, many patients who had previously been "warehoused" sought treatment. The infrastructure (ie, experienced practitioners, budgeted healthcare dollars, etc) did not yet exist to treat all patients immediately. Thus, the panel offered guidance for prioritizing treatment first for those with the greatest need.

Since that time, there have been opportunities to treat many of the highest-risk patients and accumulate real-world experience regarding the tolerability and safety of interferon-free HCV regimens. More importantly, from a medical standpoint, data continue to accumulate that demonstrate the many benefits, both intrahepatic and extrahepatic, that accompany HCV eradication. Therefore, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy. Accordingly, prioritization tables have been removed from this section.

Despite the strong recommendation for treatment of nearly all HCV-infected patients, pretreatment assessment of a patient's understanding of treatment goals and provision of education about adherence and follow-up are essential. A well-established therapeutic relationship between clinician and patient remains crucial for optimal outcomes with direct-acting antiviral (DAA) therapies. Additionally, in certain settings there remain factors that impact access to medications and the ability to deliver them to patients. In these settings, clinicians may still need to decide which patients should be treated first. The descriptions of unique populations discussed in this section may help physicians make more informed treatment decisions for these groups. For additional information, see unique patient populations: Patients With HIV/HCV Coinfection , Patients With Decompensated Cirrhosis, Patients Who Develop Recurrent HCV Infection Post Liver Transplantation, Patients With Renal Impairment, HCV in Children, and HCV Post Kidney Transplant.

Goal of Treatment

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

Recommendation for When and in Whom to Initiate Treatment

RECOMMENDED	RATING
Treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.	I, A

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA for 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 (Swain, 2010); (Manns, 2013). Patients in whom SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology (Marcellin, 1997); (Coppola, 2013); (Garcia-Bengoechea, 1999). Assessment of viral response, including documentation of SVR, requires use of an FDA-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of ≤25 IU/mL.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase levels (ie, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and a reduction in the rate of liver fibrosis progression (Poynard, 2002b). Among 3,010 treatment-naive patients from 4 randomized trials who had pretreatment and posttreatment liver biopsies (separated by a mean of 20 months) and were treated with 10 different interferon-based regimens, 39% to 73% of participants who achieved SVR had improvement in liver fibrosis and necrosis (Poynard, 2002b). Additionally, cirrhosis resolved in 49% 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 >70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]), and a 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan, 2013); (van der Meer, 2012); (Veldt, 2007).

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients (Fabrizi, 2013); (Landau, 2010); (Sise, 2016). HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection (Gisbert, 2005); (Takahashi, 2012); (Svoboda, 2005); (Mazzaro, 2002); (Hermine, 2002). These reductions in disease severity contribute to dramatic reductions in all-cause mortality (van der Meer, 2012); (Backus, 2011). Furthermore, patients who achieve SVR have a substantially improved quality of life, which spans their physical, emotional, and social health (Boscarino, 2015); (Neary, 1999); (Younossi, 2013); (Gerber, 2016). Because of the many benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving SVR, preferably early in the course of chronic HCV infection before the development of severe liver disease and other complications.

Benefits of Treatment at Early Fibrosis Stages (Metavir Stage Less Than F2)

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

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

A modeling study based on the Swiss HIV cohort study also demonstrated that waiting to treat HCV infection until Metavir fibrosis stages F3 and F4 resulted in 2- and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2 (Zahnd, 2015). A US Veterans Administration dataset analysis that used very limited end points of virologic response dating from the interferon-treatment era suggested that early initiation of therapy (at a fibrosis-4 [FIB-4] score of <3.25) increased the benefit attained with respect to likelihood of treatment success and mortality reduction, and ultimately decreased the number of patients needed to treat to preserve 1 life by almost 50% (McCombs, 2015).

Considerations in Specific Populations

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

Persons With Advanced Liver Disease

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

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

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

Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients within the first 6 months following liver transplantation (Neumann, 2004). By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis (Neumann, 2004); (Charlton, 1998). A small proportion of patients (4% to 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 is associated with decreased graft survival for recipients with HCV

infection compared to recipients who undergo liver transplantation for other indications (Forman, 2002).

Effective HCV therapy prior to transplantation resulting in 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 were wait-listed for liver transplantation (included patients with MELD scores up to 14 and CTP scores up to 8) found that treatment with sofosbuvir and weight-based ribavirin for up to 48 weeks was well tolerated and associated with an overall posttransplant SVR rate of 70% (Curry, 2015). Posttransplant SVR was nearly universal among patients who had undetectable HCV RNA for 28 days or longer prior to transplantation.

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

Persons at Increased Risk for Rapidly Progressive Fibrosis and Cirrhosis

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

HIV/HCV 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 count may mitigate this to some extent (Benhamou, 2001); (Bräu, 2006). However, antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfected patients with 435 paired biopsies were prospectively evaluated (Konerman, 2014). Thirty-four percent 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 lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for HCV treatment in this population regardless of current fibrosis stage (see Patients with HIV/HCV Coinfection) (Pineda, 2005); (Merchante, 2006); (Terrault, 2012).

HBV/HCV Coinfection

The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally (Tyson, 2013); (Chu, 2008). Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC. HBV/HCV-coinfected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus. Thus, when treating one or both viruses with antiviral drugs, periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. Treatment of HCV infection in

such cases utilizes the same genotype-specific regimens as are recommended for HCV monoinfection (see Initial Treatment of HCV Infection). HBV infections in such cases should be treated as recommended for HBV monoinfection (Lok, 2009).

Other Coexistent Liver Diseases

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

Persons With Extrahepatic Manifestations of Chronic HCV Infection

Cryoglobulinemia

Chronic hepatitis C is associated with a syndrome of cryoglobulinemia, an immune complex and lymphoproliferative disorder that leads to 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 (>50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. Interferon-based regimens can produce clinical remission; however, the adverse effects of interferon may mimic manifestations of cryoglobulinemia (Saadoun, 2014).

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli (Johnson, 1993). Successful treatment of HCV using interferon-based regimens can reverse proteinuria and nephrotic syndrome but usually does not fully ameliorate azotemia (Johnson, 1994). There is building new evidence of effective resolution of cryoglobulinemia upon clearance of HCV in most patients, making a strong case for HCV treatment in this clinical setting.

Diabetes

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 >3-fold greater risk in persons older than 40 years (Mehta, 2000). The positive correlation between quantity of plasma HCV RNA and established markers of insulin resistance confirms this relationship (Yoneda, 2007). Insulin resistance and type 2 diabetes are independent predictors of accelerated liver fibrosis progression (Petta, 2008). Patients with type 2 diabetes and insulin resistance are also at increased risk for HCC (Hung, 2010).

Successful antiviral treatment has been associated with improved markers of insulin resistance and a greatly reduced incidence of new-onset type 2 diabetes and insulin resistance in HCV-infected patients (Arase, 2009). Most recently, antiviral therapy for HCV infection has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence rates of end-stage renal disease, ischemic stroke, and acute coronary syndrome were greatly reduced in HCV-infected patients with diabetes who received antiviral therapy compared with untreated, matched controls (Hsu, 2014). Therefore, antiviral therapy may prevent progression to diabetes in HCV-infected patients with prediabetes, and may reduce renal and cardiovascular complications in HCV-infected patients with established diabetes.

Fatigue

Fatigue is the most frequently reported symptom in patients with chronic hepatitis C, and has a major effect on quality of life and activity level as evidenced by numerous measures of impaired quality of life (Foster, 1998). The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis (Poynard, 2002a). Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection (Bonkovsky, 2007). In the Virahep-C study, 401 patients with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and

severity of fatigue (Sarkar, 2012). At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving SVR was associated with a substantial decrease in the frequency and severity of fatigue.

A recent analysis of 413 patients from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and achieved SVR12 demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level (Younossi, 2014). After achieving SVR12, participants had marked improvements in fatigue over their pretreatment scores, measured by 3 separate validated questionnaires. Additional studies support and extend these findings beyond fatigue, with improvements in overall health-related quality of life and work productivity observed following successful HCV therapy (Gerber, 2016); (Younossi, 2015b); (Younossi, 2015c); (Younossi, 2015d); (Younossi, 2015e); (Younossi, 2016a).

Dermatologic Manifestations

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 interferon has frequently been described (Takikawa, 1995), there are currently insufficient data to determine whether treating HCV infection with DAAs and achievement of SVR results in porphyria cutanea tarda improvement.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. HCV antibodies are present in 10% to 40% of patients with lichen planus but a causal link with chronic HCV infection is not established. Resolution of lichen planus has been reported with interferon-based regimens, but there have also been reports of exacerbation with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with interferon-free regimens would appear to be a more advisable approach to addressing this disorder (Gumber, 1995); (Sayiner, 2017).

Benefit of Treatment to Reduce Transmission

Persons who have successfully achieved SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment of HCV infection benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence (Martin, 2013a); (Durier, 2012); (Martin, 2013b); (Hellard, 2012); (Harris, 2016). Models developed to estimate the impact of HCV testing and treatment on the burden of hepatitis C at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated (Wedemeyer, 2014).

There are also benefits to eradicating HCV infection between couples and among families, thus eliminating the perception that an individual might be contagious. In addition, mother-to-child transmission of HCV does not occur if the woman is not viremic, providing an additional benefit of curing a woman before she becomes pregnant (Thomas, 1998). However, the safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus have not yet been established; thus, treatment is not recommended for pregnant women.

The Society for Healthcare Epidemiology of America (SHEA) advises that healthcare workers who have substantial HCV viral replication ($\geq 10^4$ genome equivalents/mL) be restricted from performing procedures that are prone to exposure (Henderson, 2010) and that all healthcare workers with confirmed chronic HCV infection should be treated. For reasons already stated, the achievement of SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission (Henderson, 2010), the availability of effective, all-oral regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

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

effectiveness of the strategies when used in target populations.

Persons Who Inject Drugs

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

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

Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population (Murphy 2015); (Dore, 2016); (Mathei 2016); (Midgard 2016). Regardless of the treatment setting, recent or active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit treatment access in this patient population (Aspinall, 2013); (Hellard, 2014); (Grebely, 2011). Indeed, combining HCV treatment with needle exchange and opioid agonist therapy programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate high return on the modest investment of addressing this often-ignored segment of the HCV-infected population (Martin, 2013b). These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Scaling up HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the US and globally.

HIV-Infected Men Who Have Sex With Men

Since 2000, a dramatic increase in incident HCV infections among HIV-infected men who have sex with men (MSM) who did not report IDU as a risk factor has been demonstrated in several US cities (van de Laar, 2010); (Samandari, 2017). Recognition and treatment of HCV infection (including acute infection) in this population may represent an important step in preventing subsequent infections (Martin, 2016). As with persons who inject drugs, HIV/HCV-coinfected MSM who engage in ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education about risk-reduction strategies. In particular, safer-sex strategies should be emphasized given the high rate of reinfection after SVR, which may approach 30% over 2 years in HIV-infected MSM with acute HCV infection (Lambers, 2011).

Incarcerated Persons

Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% (Post, 2013) and the rate of acute infection is approximately 1% (Larney, 2013). Screening for HCV infection is relatively uncommon in state prison

systems. Treatment uptake has historically been limited, in part because of the toxic effects and long treatment duration of older interferon-based therapies as well as concerns about cost (Spaulding, 2006). In particular, truncation of HCV treatment owing to release from prison has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities (Post, 2013); (Chew, 2009). Shorter HCV treatment duration with DAAs reduces stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of DAA regimens diminishes concerns about toxic effects. Coordinated treatment efforts within prison systems would likely rapidly decrease the prevalence of HCV infection in this at-risk population (He, 2016), although research is needed in this area.

Persons on Hemodialysis

The prevalence rate of HCV infection is markedly elevated in persons on hemodialysis, ranging from 2.6% to 22.9% in a large multinational study (Fissell, 2004). Studies in the US found a similarly elevated prevalence rate of 7.8% to 8.9% (CDC, 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 risk 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 those who are uninfected (Fabrizi, 2002); (Fabrizi, 2007); (Fabrizi, 2009). HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival (Fabrizi, 2014). The increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments for HCV therapy as effective antiviral regimens that can be used in persons with advanced renal failure are now available (see Patients with Renal Impairment).

Patients Unlikely to Benefit From HCV Treatment

Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Chronic hepatitis C is associated with a wide range of comorbid conditions (Butt, 2011); (Louie, 2012). Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (<12 months) owing to nonliver-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).

Pretreatment Assessment

Recommendation for Pretreatment Assessment	
RECOMMENDED	RATING
Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate decision making regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care).	I, A

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

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to one-third of bilobar biopsies had a difference of at least 1 stage between the lobes (Bedossa, 2003). In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Although rare, serious complications such as bleeding 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 publication from the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis (Selph, 2014).

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

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

Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or fibrosis-4 (FIB-4) index score can prove helpful—although neither is sensitive enough to rule out substantial fibrosis (Sebastiani, 2009); (Castera, 2010); (Chou, 2013). Biopsy should be considered for 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

RECOMMENDED	RATING
Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.	I, C

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

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (Table 1); (Feld, 2006). Fibrosis may not progress linearly. Some individuals (often those aged >50 years) may progress slowly for many years followed by an acceleration of fibrosis progression. Others may never develop substantial liver fibrosis despite longstanding infection. The presence of existing fibrosis is a strong risk factor for future fibrosis progression. Fibrosis

results from chronic hepatic necroinflammation; thus, a higher activity grade on liver biopsy and higher serum transaminase values are associated with more rapid fibrosis progression (Ghany, 2003). However, even patients with normal ALT levels may develop substantial liver fibrosis over time (Pradat, 2002); (Nutt, 2000). The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

Host factors associated with more rapid fibrosis progression include male sex, longer duration of infection, and older age at the time of infection (Poynard, 2001). Many patients have concomitant nonalcoholic fatty liver disease. The presence of hepatic steatosis (with or without steatohepatitis) on liver biopsy, elevated body mass index, insulin resistance, and iron overload are associated with fibrosis progression (Konerman, 2014); (Everhart, 2009). Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression (Feld, 2006). A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression. For more counseling recommendations, see Testing and Linkage to Care.

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

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

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

Table. Factors Associated With Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable • 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 infection • Coinfection with hepatitis B virus or HIV

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Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens

The hepatitis C guidance describes diagnosis, linkage to care, and treatment for people with HCV infection (AASLD/IDSA, 2017). However, reduced access to treatment is a common challenge due to restrictions on drug reimbursement. This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and addresses the cost-effectiveness of HCV treatment access. Although these terms may sound similar, the following discussion seeks to clarify them with regard to HCV therapy. This section aims to be informational. As explained, actual costs are rarely known. Accordingly, the HCV guidance does not utilize cost-effectiveness analysis to guide recommendations at this time.

Drug Cost and Reimbursement

Many organizations are involved with hepatitis C drug distribution and each can impact costs as well as decisions about which regimens are reimbursed (US GAO, 2015); (US CBO, 2015). The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (analogous to a sticker price). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts to decrease the actual price paid.
- Pharmacy benefit managers (PBMs) act as intermediaries between pharmaceutical companies and health insurance companies. They negotiate contracts that may include restrictions on the types of providers or patients who can be reimbursed for treatment. They might also offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower negotiated prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets and use PBMs or directly negotiate drug pricing with pharmaceutical companies. Insurance companies determine formulary placement, which impacts the choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and have different formularies for each line of business.
- Medicaid is a heterogeneous consortium of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). For single-source drugs such as all-oral HCV treatments, Medicaid plans receive the lowest price offered to any other payer (outside of certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy (Barua, 2015); (Canary, 2015); (Lo Re, 2016). State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. As the price of HCV therapies has decreased, some states have loosened their Medicaid treatment restrictions with a growing number providing treatment to all infected persons. Most states, however, continue to restrict access to HCV treatment based on stage of liver fibrosis or history of recent drug use. Proposed rollbacks of Medicaid expansion implemented under the ACA threaten to reduce insurance coverage among HCV-infected people and could lead to new treatment restrictions.
- Medicare covers HCV drugs through part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may negotiate discounts or rebates with pharmaceutical companies.
- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule program, which sets drug prices for several government agencies (including the Department of Veterans Affairs, federal prisons, and the Department of Defense) and typically receives substantial discounts over average wholesale price (AWP).
- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating leverage of larger organizations and, therefore, may pay higher prices than most other organizations.

- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support and/or management of adverse effects, and outcome measurements, such as early discontinuation rates and sustained virologic response rates.
- Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs offered by pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

Except for mandated rebates, negotiated drug prices are considered confidential business contracts. Therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs (Saag, 2015). However, the average negotiated discount of 22% in 2014 increased to 46% less than the WAC in 2015, implying that many payers are paying well below the WAC for HCV medications (Committee on Finance US Senate, 2016).

Cost-Effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of 2 or more interventions. CEA explicitly recognizes budget limitations for healthcare spending and seeks to maximize public health benefits within those budgetary constraints. The core question that CEA addresses is whether to invest limited healthcare dollars in a new treatment/therapy, or use that money to invest in another healthcare intervention that would provide better outcomes for the same monetary investment. The focus of CEA is, therefore, not simply cost or saving money but health benefits. It assumes that all available resources will be spent and provides a framework for prioritizing among available treatment options by formally assessing the comparative costs and health benefits accrued from a new treatment relative to current treatment.

The cost-effectiveness of a treatment is typically expressed as an incremental cost-effectiveness ratio (ICER).

$$\frac{\text{cost new treatment - cost current treatment}}{\text{benefit new treatment - benefit current treatment}}$$

Estimating and interpreting the ICER requires that we answer three questions:

1. *How much more money will be spent with the new treatment versus the old treatment?*
   The additional cost of new treatment includes that of new medications as well as the costs that will be avoided by preventing disease complications. Prevention of long-term complications is especially important when considering the cost-effectiveness of HCV treatments because the costs of the therapy are immediate, while those avoided by preventing advanced liver disease and other complications of chronic infection often accrue years in the future.

2. *How much more benefit will occur with the new versus the old treatment?*
   Life expectancy is a valuable measure of benefit, but considering only mortality benefits fails to recognize the value of treatments that improve quality of life. The quality-adjusted life-year (QALY) provides a measure that integrates both longevity and quality of life and is the preferred outcomes for CEA.

3. *How is the ICER to be interpreted?*
   The ideal CEA would list every possible healthcare intervention, its lifetime medical cost, and QALYs lived. Such a list would allow for perfect theoretical prioritization of spending to maximize QALY across the population. In reality, CEA compares the ICER for a specific treatment to a threshold value and rejects treatments with an ICER exceeding a particular threshold as not being cost-effective. The threshold value is referred to as the societal willingness-to-pay threshold. It is not meant to be a valuation of how much society is willing to pay to save a life. Rather, it is meant to reflect the average return in QALY expected if the available budget was not used to provide a new treatment but instead invested into the current healthcare system. In the United States, the willingness-to-pay threshold is typically considered to be $50,000 or $100,000/QALY gained.

Affordability

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

1. *Perspective on cost*
   CEA seeks to inform decisions about how society should prioritize healthcare spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.

2. *Time horizon*
   CEA uses a lifetime time horizon, meaning it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have no impact on spending decisions today because they have little bearing on the solvency of the current budget.

3. *Weak association between willingness to pay and the real-world bottom line*
   Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little relationship to a payer's bottom line. Willingness to pay is meant to be an estimate of the opportunity cost of investing in a new therapy. In economics, opportunity cost refers to how else that money could have been spent and the benefits lost from not investing in that alternative. When payers make a decision about coverage, the calculation is more straightforward and relates to the short-term cost of medications and the budgetary impact. Given the rapid development of new technologies and therapies, funding all of them (even if they all fell below the societal willingness-to-pay threshold) would likely lead to uncontrolled growth in demand and exceed the limited healthcare budget.

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

Cost-Effectiveness of Current Direct-Acting Antiviral Regimens for Hepatitis C Treatment

Since the first direct-acting antivirals (DAAs) received US Food and Drug Administration approval in 2011, several cost-effectiveness investigations have compared DAA-based regimens to previous standard-of-care regimens to calculate ICERs. They have also investigated the cost-effectiveness of eliminating HCV treatment restrictions. Compared to interferon-based regimens, the ICER for DAAs has consistently been estimated at <$100,000/QALY for all genotypes and fibrosis stages.

Several studies have compared DAA regimens against one another. In general, when given a choice between recommended HCV DAA regimens, the less costly regimen is preferred as a more efficient use of resources (even if it requires multiple tablet dosing). Because of the similar efficacy of most DAA regimens, cost becomes the critical factor driving cost-effectiveness. Recent studies have also estimated the cost-effectiveness of HCV treatment in special populations, including patients awaiting liver transplantation, HIV/HCV coinfected patients, those with chronic kidney disease, and persons who inject drugs—all with favorable ICERs. At this time, it is reasonable to conclude that DAA regimens provide good value for the resources invested.

Cost vs Affordability for HCV Treatment

Despite a growing body of evidence that HCV treatment is cost-effective and may even be cost saving over the long term in some cases, many US payers—especially those offering Medicaid insurance products—continue to limit access to HCV treatment. Access has improved as cost has decreased but limitations remain. Proposed reductions in healthcare spending for Medicaid would likely exacerbate the problem as the value of the HCV medications would remain unchanged but the resources available to provide them would shrink.

Conclusions

Several recent studies have demonstrated the economic value of HCV treatment and made it clear that HCV therapy is cost-effective (Chahal, 2016); (Chatwal, 2015); (Chidi, 2016); (Linas, 2015); (Martin, 2016a); (Najafzadeh, 2015); (Rein, 2015); (Tice, 2015); (Younossi, 2015a). The high cost of these medications combined with the high prevalence of disease has led to limiting access for some patients. The issue is complex. Although the wholesale acquisition costs of HCV drugs often make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing and few actually pay this much-publicized price. Negotiated pricing and cost structure for pharmaceutical products in the US are not transparent, however. Thus, it is therefore difficult to estimate the true budgetary impact of providing HCV drugs. Competition and negotiated pricing have reduced prices but cost continues to limit the public health impact of new DAA therapies. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all persons in need of treatment are able to afford and readily access it.

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Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy

This section provides guidance on monitoring patients with chronic hepatitis C who are starting treatment, are on treatment, or have completed treatment. The section is divided into 3 parts: pretreatment and on-treatment monitoring; post-treatment follow-up for persons in whom treatment has failed to clear the virus; and post-treatment follow-up for those who achieved a sustained virologic response (SVR; virologic cure).

Pretreatment and On-Treatment Monitoring

Recommended Assessments Prior to Starting Antiviral Therapy	
RECOMMENDED	RATING
Staging of hepatic fibrosis is essential prior to HCV treatment (see Testing and Linkage to Care and see When and in Whom to Treat). Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy. • Patients should also be educated about the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment. **The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:** • Complete blood count (CBC) • International normalized ratio (INR) • Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels) • Calculated glomerular filtration rate (eGFR) **The following laboratory tests are recommended at any time prior to starting antiviral therapy:** • HCV genotype and subtype • Quantitative HCV RNA (HCV viral load)	I, C
Patients scheduled to receive an HCV NS3 protease inhibitor (ie, paritaprevir, simeprevir, grazoprevir, voxilaprevir, glecaprevir) should be assessed for a history of decompensated liver disease and for liver disease severity using the Child-Turcotte-Pugh (CTP) score (see third-party calculator). • Patients with current or prior history of decompensated liver disease or with a current CTP	I, A

Recommended Assessments Prior to Starting Antiviral Therapy

score ≥7 should **not** receive treatment with regimens that contain NS3 protease inhibitors due to increased blood levels and/or lack of safety data. • Similarly, patients with a CTP score of 5 or 6 who cannot be closely monitored for laboratory or clinical symptoms during treatment should **not** receive treatment with a regimen that contains paritaprevir/ritonavir.	
All patients initiating HCV direct-acting antiviral (DAA) therapy should be assessed for HBV coinfection with HBsAg testing, and for evidence of prior infection with anti-HBs and anti-HBc testing.	IIa, B
Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the Initial Treatment and the Retreatment sections.	IIb, B

Recommended Monitoring During Antiviral Therapy

RECOMMENDED	RATING
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.	I, B
Creatinine level, calculated glomerular filtration rate (eGFR), and a hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. More frequent assessment for drug-related adverse effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with a hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).	I, B
A 10-fold increase in alanine aminotransferase (ALT) activity at any time during treatment should prompt discontinuation of therapy. An increase in ALT <10-fold that is accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio (INR) should also prompt discontinuation of therapy. Asymptomatic increases in ALT <10-fold should be closely monitored with repeat testing at 2-week intervals. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.	I, B
Quantitative HCV viral load testing is recommended after 4 weeks of therapy and 12 weeks after completion of therapy. Antiviral drug therapy should **not** be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.	I, B

Recommended Monitoring During Antiviral Therapy	
Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.	I, B

For HBsAg-positive patients who are not already on HBV suppressive therapy, the following are recommended:
• For patients whose HBV DNA level meets AASLD criteria for treatment, antiviral therapy for HBV should be initiated.
• For patients whose baseline HBV DNA level does not meet criteria for treatment, one of two approaches may be taken:
  ◦ Initiate prophylactic antiviral therapy for those with low or undetectable HBV DNA levels. If this course is elected, pending further data, prophylaxis should be continued until 12 weeks after completion of DAA therapy.
  ◦ Monitor HBV DNA levels during and immediately after DAA therapy for HCV. Antiviral treatment for HBV should be given in the event of a rise in HBV DNA >10-fold above baseline or to >1000 IU/mL in those with a previously undetectable or unquantifiable HBV DNA level.
	IIa, B

Recommendations for Discontinuation of Treatment Because of Lack of Efficacy	
RECOMMENDED	RATING
If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by >10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), discontinuation of HCV treatment is recommended.	III, C
The significance of a positive HCV-RNA test result at week 4 that remains positive but lower at week 6 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.	III, C

Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin	
RECOMMENDED	RATING
Women of childbearing age should be counseled not to become pregnant while receiving a ribavirin-containing antiviral regimen, and for at least 6 months after stopping the regimen.	I, C
Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving a ribavirin-containing antiviral regimen, and for up to 6 months after stopping the regimen.	I, C
Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin.	I, C
Since the safety of DAA regimens that do not include ribavirin has not been established during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment.	I, C
Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment.	I, C

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

Prior to starting treatment, patients should be evaluated for potential drug-drug interactions with selected antiviral medications by consulting the prescribing information and using other resources (eg, http://www.hep-druginteractions.org). The table below lists known drug-drug interactions between HCV DAAs and selected medications.

Table. Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications
X = Assess potential drug interaction. Hover over column labels for complete treatment name.

Concomitant Medications	DCV	LDV	PrOD	SMV	SOF	EBV/GRZ	VEL
Acid-reducing agents[a]		X	X				X
Alfuzosin/tamsulosin			X				
Amiodarone	X	X	X	X	X		X
Anticonvulsants[a]	X	X	X	X	X	X	X
Antiretrovirals[a]	**See** HIV section						
Azole antifungals[a]	X[b]		X	X		X	
Buprenorphine/naloxone			X				
Calcineurin inhibitors[a]			X	X		X	
Calcium channel blockers[a]	X		X	X		X	
Cisapride			X	X		X	
Digoxin	X	X		X		X	
Ergot derivatives			X				
Ethinyl estradiol–containing products			X				
Furosemide			X				
Gemfibrozil			X				
Glucocorticoids[a]	X		X (inhaled, intranasal)	X		X	
Herbals St. John's wort Milk thistle	X	X	X	 X X	X	X X	X
HMG-CoA reductase inhibitors (statins)[a]	X	X	X	X		X	
Macrolide antimicrobials[a]	X[b]			X		X	
Other antiarrythmics[a]			X	X		X	
Phosphodiesterase inhibitors[a]			X	X		X	
Pimozide			X				
Rifamycin antimicrobials[a]	X	X	X	X	X	X	X
Salmeterol			X				
Sedatives[a]			X	X		X	

[a] Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
[b] Requires a daclatasvir dose modification

The education of patients and caregivers about potential adverse effects of therapy and their management is an integral component of treatment and is important for a successful outcome in all patient populations. During treatment, individuals should be followed at clinically appropriate intervals to ensure medication adherence, assess adverse events and potential

drug-drug interactions, and monitor blood test results necessary for patient safety. The frequency and type of contact (eg, clinic visit, phone call, etc) are variable but need to be sufficient to assess patient safety and response to treatment, as outlined above.

The assessment of HCV viral load at week 4 of therapy is useful to determine initial response to therapy and adherence. In phase 3 clinical trials, almost all patients who did not have cirrhosis had an undetectable HCV RNA level at week 4. Those with cirrhosis may require more than 4 weeks of treatment before the HCV RNA level is undetectable. There are minimal data on how to use the HCV RNA level during treatment to determine when to stop treatment for futility. The current recommendation to repeat quantitative HCV RNA testing at week 6 of treatment and to discontinue treatment if the quantitative HCV RNA level increases by >10-fold (>1 $\log_{10}$ IU/mL) is based on expert opinion. There are no data to support stopping treatment based on detectable HCV RNA at weeks 2, 3, or 4 of treatment, or that detectable HCV RNA at these time points signifies medication nonadherence.

Although HCV RNA testing is recommended at week 4 of treatment, failure to test for HCV RNA at week 4 is not a reason to discontinue therapy. HCV RNA assessment at the end of treatment allows for the differentiation of relapse from nonresponse/breakthrough for patients who fail to achieve SVR. Nevertheless, testing for HCV RNA at the end of treatment is optional. On the other hand, it is essential to test for HCV RNA 12 weeks (or longer) after treatment completion. Undetectable or unquantifiable HCV RNA 12 weeks or longer after treatment completion is defined as a sustained virologic response (SVR), which is consistent with cure of hepatitis C infection. Virologic relapse is rare 12 weeks or longer after treatment completion. Nevertheless, repeat quantitative HCV-RNA testing can be considered at 24 or more weeks after completing treatment for patients in whom ALT increases to above the upper limit of normal.

During clinical trials with elbasvir/grazoprevir, with or without ribavirin, 1% of subjects experienced ALT elevations from normal levels to >5 times the upper limit of normal, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing therapy or completion of therapy. Higher rates of late ALT elevations occurred in females, those of Asian descent, and patients aged ≥65 years. Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12 (Zepatier Package Insert, 2017).

Patients with compensated cirrhosis (Child's A) who are receiving a paritaprevir/ritonavir-based regimen should be followed closely. Patients with compensated cirrhosis who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy, or serum bilirubin >3 mg/dL) and for biochemical evidence of liver injury with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment. Paritaprevir/ritonavir-based regimens should be discontinued if a patient develops ascites, encephalopathy, or a significant increase in direct bilirubin, ALT, or AST. Please see the statement on the FDA warning regarding use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Patients being treated with amiodarone should not receive sofosbuvir-based regimens due to risk of life-threatening arrhythmias. Because of its long half-life, it is advised that persons should be off amiodarone for at least 6 months before initiating sofosbuvir. If the decision is made to start sofosbuvir in this setting, continued vigilance for bradycardia should be exercised.

Pregnancy

Ribavirin causes fetal death and fetal abnormalities in animals. Thus, it is imperative for persons of childbearing potential who receive ribavirin to use at least 2 reliable forms of effective contraception during treatment and for a period of 6 months thereafter. It is recommended that the healthcare practitioner document the discussion of the potential teratogenic effects of ribavirin in the patient's medical record. Ethinyl estradiol-containing contraceptives should be avoided in those receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir due to the risk of developing elevated transaminase levels.

No adequate human data are available to establish whether DAAs pose a risk to pregnancy outcomes. It is recommended that female patients have a thorough discussion of potential pregnancy-related drug effects prior to starting antiviral treatment. Given the relatively short duration of treatment and the potential to use ribavirin-free regimens in most patients, the potential risks and benefits of delaying pregnancy until HCV antiviral treatment is completed should be considered. For additional information on HCV and pregnancy, click here.

Reactivation of HBV

Cases of HBV reactivation, occasionally fulminant, during or after DAA therapy have been reported in HBV/HCV coinfected patients who were not receiving HBV suppressive therapy (Hayashi, 2016); (Takayama, 2016); (Ende, 2015); (Collins, 2015); (De Monte, 2016); (Sulkowski, 2016); (Wang, 2016); (Bersoff-Matcha, 2017). In light of these observations and consistent with general recommendations for the assessment of the HCV-infected patient, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg testing, and for prior infection with anti-HBs and anti-HBc testing. HBV vaccination is recommended for all susceptible individuals. A test for HBV DNA should be obtained prior to DAA therapy in patients who are HBsAg positive. HBsAg positivity does not represent a contraindication to HCV DAA therapy. Patients meeting criteria for treatment of active HBV infection should be started on therapy at the same time (or before) HCV DAA therapy is initiated (Terrault, 2015).

Patients with low or undetectable HBV DNA levels can either receive prophylactic treatment for HBV for the duration of the DAA treatment to SVR12 or be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV-DNA testing. If monitoring is elected, HBV treatment should be started if the HBV DNA level increases >10-fold or is >1000 IU/mL in a patient with undetectable or unquantifiable HBV DNA prior to DAA treatment. There are insufficient data to provide clear recommendations for the monitoring of HBV DNA among patients testing positive either for anti-HBc alone (isolated anti-HBc) or for anti-HBs and anti-HBc (immune recovery). However, the possibility of HBV reactivation should be considered in these patients in the event of an unexplained increase in liver enzymes during and/or after completion of DAA therapy.

Post-Treatment Follow-Up for Patients in Whom Treatment Failed

Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response

RECOMMENDED	RATING
Disease progression assessment every 6 to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended.	I, C
Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).	I, C
Endoscopic screening for esophageal varices is recommended if cirrhosis[a] is present.	I, A
Evaluation for retreatment is recommended as effective alternative treatments become available.	I, C

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

The Following Monitoring Is Not Recommended During or After Therapy

NOT RECOMMENDED	RATING
Monitoring for HCV drug resistance-associated substitutions during or after therapy is not recommended.	IIb, C

Patients who do not achieve SVR retain the possibility of continued liver injury and the potential to transmit HCV to others. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available (see Retreatment of Persons in Whom Prior Therapy Has Failed).

Given that persons in whom treatment failed remain at risk for ongoing liver injury and liver fibrosis progression (Dienstag, 2011), these patients should be monitored for signs and symptoms of cirrhosis. Patients in whom antiviral therapy failed may harbor viruses that are resistant to 1 or more of the antivirals at the time of virologic breakthrough (Lawitz, 2014a); (Schneider, 2014). However, there is no evidence to date that the presence of resistance-associated substitutions (RASs) results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. Additional information about RASs is available in the HCV Resistance Primer section. If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert in the treatment of HCV infection may be useful.

Information regarding retreatment of patients whose initial treatment regimen failed is available in the Retreatment section.

Post-Treatment Follow-Up for Patients Who Achieved a Sustained Virologic Response

Recommended Follow-Up for Patients Who Achieved a Sustained Virologic Response (SVR)	
RECOMMENDED	RATING
For patients who do not have advanced fibrosis (ie, those with Metavir stage F0, F1, or F2), recommended follow-up is the same as if they were never infected with HCV.	I, 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 test rather than an HCV-antibody test is recommended to assess for HCV recurrence or reinfection.	I, A
Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve SVR.	I, C
A baseline endoscopy is recommended to screen for varices if cirrhosis[a] is present. Patients in whom varices are found should be treated and followed as indicated.	I, C
Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving SVR.	I, C
[a] For decompensated cirrhosis, please refer to the appropriate section.	

Patients who have undetectable HCV RNA in the serum, as assessed by a sensitive polymerase chain reaction (PCR) assay, ≥12 weeks after treatment completion are deemed to have achieved SVR. In these patients, HCV-related liver injury stops, although they remain at risk for non-HCV–related liver disease, such as fatty liver disease or alcoholic liver disease. Patients with cirrhosis or advanced fibrosis remain at risk for developing hepatocellular carcinoma (HCC).

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving SVR among adherent, immunologically competent, treatment-naive patients with compensated liver disease generally exceeds 95%. Among patients who achieved SVR with peginterferon/ribavirin treatment, more than 99% have remained free of HCV infection when followed for 5 years after treatment completion (Manns, 2013). Thus, achieving SVR is considered a virologic cure of HCV infection.

SVR typically aborts progression of liver injury with regression of liver fibrosis in most, but not all, treated patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0, F1, or F2) who achieve 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 SVR, decompensated liver disease (with the exception of HCC) rarely develops during follow-up, and overall survival is prolonged (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Liver fibrosis and liver function test results improve in most patients who achieve SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Bleeding from esophageal varices is rare after 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; if varices are found, they should be treated or followed as indicated (Garcia-Tsao, 2007).

The risk of developing HCC among cirrhotic patients who receive DAA treatment is debated. Multiple studies of cirrhotic patients who achieved SVR with peginterferon/ribavirin reported a significant reduction in the risk of developing HCC (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). A recent report suggested a higher than expected frequency of HCC in patients with HCV-related cirrhosis treated successfully with DAAs (Reig, 2016). However, a meta-analysis evaluating the incidence of HCC among persons achieving SVR with DAAs found that the risk of HCC did not exceed that seen in patients who experienced SVR with interferon-based treatment after adjustment for baseline risk factors for HCC (Waziry, 2017).

Patients with cirrhosis who achieve SVR remain at risk for HCC. Thus, they should continue to undergo regular surveillance for HCC despite the lowered risk that results after viral eradication (Bruix, 2011). The risk of HCC 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 HCC and should be monitored at regular intervals for HCC. Alpha-fetoprotein (AFP) alone is considered an inadequate screening test for HCC (Bruix, 2011).

Patients in whom 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 fibrosis progression. It is recommended that such patients be educated about the risk of liver disease and monitored for liver disease progression with periodic physical examination, blood tests, and potentially, tests for liver fibrosis by a liver disease specialist.

Patients who achieve SVR can be reinfected with HCV if they are re-exposed to the virus. Annual testing for HCV reinfection among patients with ongoing risk for HCV infection (eg, injection drug use or high-risk sexual exposure) is recommended. A flare in liver enzyme levels should prompt immediate evaluation for HCV reinfection (see Management of Acute HCV Infection). HCV antibody (anti-HCV) remains positive in most patients following SVR. Thus, testing for HCV reinfection using an assay that detects HCV RNA (ie, a quantitative HCV-RNA test) is recommended.

Monitoring for HCV During Chemotherapy and Immunosuppression

NOT RECOMMENDED	RATING
Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc) is **not** routinely recommended.	III, C

Acute liver injury is common among patients receiving chemotherapy or immunosuppressive agents. Testing for hepatitis viruses should be included in the laboratory assessment of the cause of liver injury in these patients. Approximately 23% of patients with active HCV infection—especially those with a hematologic malignancy—have a flare in their HCV RNA level (>10-fold) during chemotherapy. An ALT level increase is less common and clinical symptoms of hepatitis are

uncommon (Torres, 2017). Among patients who have recovered from hepatitis C, either spontaneously or with DAA treatment, reactivation of HCV (ie, detectable HCV RNA) during chemotherapy is distinctly uncommon and is not anticipated to occur since there is no residual reservoir for the virus. Thus, in this latter group, routine testing for HCV RNA during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

Last update: May 24, 2018

HCV Resistance Primer

Introduction

Understanding principles of the emergence of drug-resistant viruses is critical when using targeted antiviral therapies. The best example of these principles can be gleaned from the study of HIV. Like HIV, HCV is an approximately 9.5 kilobase RNA virus that replicates very rapidly (billions of viruses daily). The production of each new virus is performed by an enzyme that results in 1 to 3 errors per replication cycle, on average. Many of these errors either have no effect on the progeny virus product or result in progeny viruses that are nonreplication competent (ie, dead viruses). For some newly produced viruses, however, the transcription errors result in changes in critical coding regions that may, by chance, change the susceptibility of the virus to 1 or more drugs used to treat the virus. The emergence of such drug-resistant viruses most often occurs when drug levels are subtherapeutic, thereby creating selective pressure for the resistant viruses to emerge as the dominant species. These newly formed resistant viruses have a selective growth advantage that allows them to replicate in the presence of antiviral drugs. In a subset of patients with chronic HCV infection, viral variants harboring substitutions associated with resistance to HCV directing-acting antivirals (DAAs) are detectable prior to antiviral therapy and, particularly in the case of NS5A inhibitor-containing regimens, may negatively impact treatment response. These substitutions often are referred to as baseline resistance-associated substitutions (RASs).

In the case of HCV DAAs, resistant viruses are also selected for and/or enriched in patients for whom a DAA regimen fails. These viruses contain substitutions that are designated as treatment-emergent (or treatment-selected) RASs. NS5A and NS3 RASs are frequently selected in patients with failure of NS5A or NS3 inhibitor-containing regimens, respectively. In contrast, NS5B nucleotide RASs are rarely detected (1% of failures) even after exposure to a failing DAA regimen containing a nucleotide inhibitor (Svarovskaia, 2014); (Wyles, 2017). This is likely due to the highly conserved catalytic site region that nucleotides bind, making substitutions in this region extremely rare—often referred to as a high barrier to resistance. Additionally, any such substitution would likely render the virus replication incompetent. Compounding the clinical impact of NS5A RASs is their ability to maintain high replication competence (aka, relative fitness) in the absence of continued drug pressure, allowing them to remain the dominant viral quasispecies for prolonged periods (years) relative to NS3 protease or NS5B nucleotide polymerase inhibitor RASs, which are typically less fit and tend to disappear over several months, being overcome by more fit wild-type virus species.

The magnitude of the negative impact of RASs, both baseline and selected, on treatment outcome varies according to regimen (coadministered drugs); patient factors that impact treatment response (cirrhosis); and the fold change decrease in potency conferred by the specific RAS(s). Given these considerations, RAS testing alone will not dictate optimal DAA regimen selection. In addition, a drug predicted to suffer a significant loss of potency in the presence of a RAS still may be used in specific clinical settings/regimens.

Terminology, Thresholds of Clinical Relevance, and Assays

Terminology

1. Naming Convention for Hepatitis C Proteins
   The hepatitis C genome codes for approximately 5 HCV-specific proteins, which are essential to: 1) form the viral structure (core and envelope proteins); 2) cut the HCV polyprotein; 3) provide enzymatic functions for replication and escape from the innate immune response (NS3/NS4A protease); 4) replicate the HCV RNA (NS5B RNA-dependent RNA polymerase); and 5) bind the HCV replication complex during replication and assembly (NS5A).

2. Polymorphism (Substitution)
   A reference (or consensus) nucleotide—and therefore amino acid sequence—has been defined for each HCV genotype. A polymorphism (or substitution) is a difference in an amino acid at a defined position of the HCV protein between a patient's HCV and the reference HCV protein. Substitution is the preferred terminology among most experts. However, the US Food and Drug Administration currently uses the term polymorphism.

To define a polymorphism, it is necessary to define: the HCV genotype (eg, genotype 1, 2, 3, etc) and subtype (eg, 1a vs 1b); the HCV protein (eg, NS5A); and the amino acid position (eg, 93). Polymorphisms are reported as letter-number-letter (eg, Y93H). The first letter refers to the amino acid typically expected for that position in the reference protein. The number refers to the amino acid position, and the final letter refers to the amino acid that is found in the patient's HCV isolate. Thus, NS5A Y93H refers to amino acid position 93 of the NS5A protein. The amino acid at this position in the reference strain is Y (ie, tyrosine) and the amino acid in the tested strain is H (ie, histidine). For some patients, multiple variants are present and several amino acids may be found at a given position. Thus, it is possible to have a virus with NS5A Y93H/M. Such a patient would have viruses with the amino acids histidine (H) or methionine (M) at position 93 of the NS5A protein.

3. Resistance-Associated Substitutions
   A resistance-associated substitution describes any amino acid change from the consensus sequence at a position that has been associated with reduced susceptibility of a virus to 1 or more antiviral drugs. A specific RAS may or may not confer a phenotypic loss of susceptibility to other/multiple antiviral agents.

4. Drug-Class RASs
   Drug-class RASs are amino acid substitutions that reduce the susceptibility of a virus to any (and at least 1) member of a drug class or, alternatively, the viral variants with reduced susceptibility that carry these substitutions. Class RASs may or may not confer resistance to a specific drug in that class.

5. Drug-Specific RASs
   Drug-specific RASs are amino acid substitutions that reduce the susceptibility of a virus to a specific drug. When assessing the potential clinical impact of RASs on a given regimen, drug-specific RASs should be used. In an HCV-infected population not previously exposed to a DAA drug or class, drug-specific RASs will be found less frequently than class RASs.

Thresholds of Clinical Relevance

HCV resistance to DAAs is a rapidly evolving field with demonstrated clinical impact in specific situations with currently available DAA regimens. Presently, the most clinically significant RASs are in the NS5A position for genotypes 1a and 3.

Data from clinical trials have demonstrated that RASs are commonly, but not always, found at the time of virologic failure. Viruses that are resistant to NS3/4A protease inhibitors seem to be less fit and may disappear from peripheral blood within a few weeks to months, whereas NS5A inhibitor-resistant viruses may persist for years, which could have implications for treatment and retreatment.

In general, drug-specific RASs need to be present in at least 15% of the viruses of a given patient to reduce the likelihood of achieving SVR (Pawlotsky, 2016). Drug-specific RASs that are found at a lower frequency may not convey sufficient resistance to reduce SVR with currently available DAA regimens.

Assays

Methods to detect RASs include population sequencing (aka, Sanger sequencing) and deep sequencing (aka, next generation sequencing [NGS]). Both methods depend on sequencing the HCV RNA, calculating the amino acid sequence, and then inferring the presence of RASs. The methods differ in their sensitivity for detecting RASs. For the purposes of clinical care and decisions regarding which DAA regimen to use, both methods can be considered equivalent if a ≥15% cut point is used for determination of RASs by NGS. Recent studies have shown that NGS at a 1% level of sensitivity often result in the identification of additional RASs that are not associated with clinical failure (Jacobson, 2015b); (Sarrazin, 2016); (Zeuzem, 2017).

1. Genotypic Analysis
    a. Population-Based Sequencing (Sanger)
    Population sequencing of the HCV coding region of interest may be performed using reverse transcription polymerase chain reaction (PCR) and standard Sanger sequencing of the bulk PCR product. The sensitivity for detection of resistance substitutions varies but is generally 15% to 25%. As a standard, substitutions are reported as differences compared with a genotype-specific, wild-type strain.

    b. Deep Sequencing Analysis
    NGS (deep sequencing approaches) can increase the sensitivity of detection for minor variants. After sequencing HCV coding regions using PCR, a software algorithm is used to process and align sequencing data via a multistep method to identify the substitutions present at a predetermined level. This level, or threshold, can vary but is often set as low as >1% for research purposes. To approximate results obtained by population sequencing, NGS thresholds are often set to ≥10%.

2. Phenotypic Analysis
    Phenotypic analysis involves laboratory techniques whereby the degree of drug resistance conferred by an amino acid change as well as the replicative capacity (fitness) of a particular RAS can be estimated in the presence of a wild-type or consensus strain. These research techniques are not routinely used for clinical practice. To assess the level of resistance, RASs are typically introduced as point mutations into the backbone of an existing standard HCV genome within an existing cell culture/replicon or enzyme-based assay. Isolates harboring these RASs are then challenged by appropriate antiviral agents at increasing concentrations and fold changes—based on EC_{50} or IC_{50} and EC_{90} or IC_{90} values—are determined for inhibition of replication or enzyme activity, respectively, in comparison to wild-type virus. Comparison of replication levels for variants and wild-type constructs in the absence of drug allows for estimation of fitness.

3. Assay Summary Points

- Either population sequencing or deep sequencing can be used to detect the presence of RASs in NS3, NS5A, and NS5B.
- For clinical decisions, population sequencing or deep sequencing with at least 15% prevalence of RASs as the cutoff is recommended. The presence of RASs with <15% prevalence should not be considered clinically significant.
- When assessing the potential clinical effect of RASs, it is important to determine the drug-specific RASs.

Resistance Testing in Clinical Practice

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice	
RECOMMENDED	RATING
Elbasvir/grazoprevir NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used. NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used.	I, A
Sofosbuvir/velpatasvir NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used.	I, A
Daclatasvir plus sofosbuvir NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added. NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used.	I, B
[a] Clinically important = greater than 100-fold resistance	

Regimen-Specific Clinical Practice Situations in Which RAS Testing Is Not Recommended	
NOT RECOMMENDED	RATING
Elbasvir/grazoprevir RAS testing is not recommended for any genotype 1b-infected patients being considered for elbasvir/grazoprevir therapy.	I, A
Glecaprevir/pibrentasvir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for glecaprevir/pibrentasvir for 8, 12, or 16 weeks.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing is not recommended for any genotype 1b-infected patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a-infected, treatment-naive patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a- or 1b-infected, treatment-naive patients without cirrhosis and with a viral load <6 million IU/mL being considered for an 8-week course of ledipasvir/sofosbuvir therapy.	I, A
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin RAS testing is not recommended for genotype 1- or 4-infected, treatment-naive or -experienced patients being considered for therapy with paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin, respectively.	I, A
Sofosbuvir/velpatasvir RAS testing is not recommended for patients with genotype 1, 2, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir therapy.	I, A
Sofosbuvir/velpatasvir/voxilaprevir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir/voxilaprevir therapy.	I, A

Resistance testing is most important in clinical practice when the results would modify treatment management by impacting the duration of therapy and/or inclusion of ribavirin, or result in selection of alternative therapy. Unfortunately, at this time, the utility of RAS testing varies by both patient characteristics and DAA regimen.

Approaches to Overcome Resistance

Data for currently approved DAAs provide limited insight on optimal retreatment approaches for patients with a previous DAA therapy failure and high fold change RASs, particularly those in NS5A. Until regimens combining multiple drugs predicted to be active (based on the available resistance profile) are available and adequate phase 2/3 studies in DAA

treatment failure populations are accomplished, other aspects of therapy must be optimized in treatment-experienced patients with RASs. In general, optimization involves appropriately characterizing the patient along with use of an extended duration of therapy and the addition of ribavirin (unless an absolute contraindication to ribavirin exists).

Characterizing Patients at Risk

The characteristics that increase the risk of DAA treatment failure are different for each oral regimen. Thus, understanding the population at risk is imperative. Generally, this requires accurate assessment of liver fibrosis and clarification of prior therapy.

Virus

Determination of HCV genotype, subtype, and baseline RASs may be necessary to fully characterize a patient's risk for therapeutic failure and optimize the treatment approach.

Treatment Duration

The duration of therapy should always be optimized to attain a cure. Although short-duration therapy has been associated with a higher chance of relapse, careful selection of patients for shortened therapy may minimize relapse risk and lead to significant cost savings. In contrast, extension of therapy (often to 24 weeks) in conjunction with the addition of ribavirin has been associated with reasonable SVR rates during retreatment of patients with past DAA therapy failure, even in the presence of significant drug-specific RASs prior to retreatment (Cooper, 2016); (Gane, 2016).

Ribavirin

The addition of ribavirin increases SVR in patient populations with an increased risk for treatment failure (eg, decompensated cirrhosis). It also improves SVR rates among patients with baseline NS5A RASs and prior DAA treatment failure.

Complementary Therapy

Although data are limited, patients with multiclass RASs can achieve SVR by combining triple or quadruple drug class regimens (see section on retreatment in prior DAA failure). This approach may become less necessary with the approval of standalone dual- or triple-drug regimens composed of second-generation protease and NS5A inhibitors with improved activity against common RASs.

Considerations With Current Antiviral Regimens

Daclatasvir + Sofosbuvir

Daclatasvir plus sofosbuvir is most commonly used for genotype 3-infected individuals. The phase 3 ALLY-3 study had an overall SVR rate of 89% in treatment-naive and -experienced, genotype 3-infected patients treated with 12 weeks of daclatasvir plus sofosbuvir without ribavirin. This study demonstrated that lower SVR rates were observed in patients with cirrhosis, irrespective of treatment experience (97% [73/75] SVR without cirrhosis vs 58% [11/19] SVR with cirrhosis). When RAS impact was assessed, the presence of baseline Y93H was associated with a lower SVR rate in those with cirrhosis. Thirteen patients had Y93H at baseline; 67% (6/9) without cirrhosis achieved SVR whereas only 25% (1/4) with cirrhosis achieved SVR (Nelson, 2015). The subsequent ALLY-3+ study evaluated 12 weeks or 16 weeks of daclatasvir plus sofosbuvir and ribavirin in treatment-naive or -experienced patients with genotype 3 infection and advanced fibrosis or compensated cirrhosis. The overall SVR rate was 90%. Again, virologic failure was higher in individuals with cirrhosis (86% SVR) compared to those with stage 3 fibrosis (100% SVR). Increased treatment duration did not appear to improve efficacy. Eight patients had a baseline RAS, including 2 with Y93H, 5 with A30K, and 1 with A30A/K. The only relapse occurred in a patient with the Y93H RAS (Leroy, 2016).

Elbasvir/Grazoprevir

Elbasvir/grazoprevir is indicated for treatment-naive and -experienced patients with genotype 1 or 4 infection. The presence of NS3 RASs has no significant impact on SVR12 in patients treated with elbasvir/grazoprevir. The presence of NS5A RASs has no significant impact in genotype 1b infection.

In treatment-naive, genotype 1a-infected patients (with or without cirrhosis) treated with 12 weeks of therapy, the

presence of NS3 RASs has no impact (Zeuzem, 2015). In treatment-naive or prior relapse patients treated for 12 weeks with elbasvir/grazoprevir without ribavirin, the presence of high fold change NS5A RASs (at amino acid positions 28, 30, 31, and 93) decreased SVR to 58% (14/24) compared to 98% SVR in those without NS5A RASs. The presence of NS5A RASs had a similar impact on treatment-experienced patients (with or without cirrhosis) who received 12 weeks of elbasvir/grazoprevir without ribavirin (SVR12 29% vs 97%, respectively) (Jacobson, 2015b).

Glecaprevir/Pibrentasvir

In a study of the resistance profiles of glecaprevir and pibrentasvir using cell cultures (Ng, 2017), selection of genotypes 1a, 1b, 2a, 3a, 4a, and 6a replicons for reduced susceptibility to glecaprevir resulted in the emergence of RASs at A156 or D/Q168. The A156 RAS resulted in the greatest reductions (>100-fold) in glecaprevir susceptibility. The D/Q168 RAS had varying effects on glecaprevir susceptibility depending on genotype/subtype and specific amino acid change; the greatest reductions (>30-fold) were observed in genotypes 1a (D168F/Y), 3a (Q168R), and 6a (D168A/G/H/V/Y). However, these RASs are rarely detected clinically. Pibrentasvir selected no viable colonies in genotype 1b, 2b, 4a, 5a, and 6a. Of the few RASs selected by pibrentasvir, Y93H/N conferred <7-fold resistance.

The presence of RAS at baseline had minimal impact on SVR rates with glecaprevir/pibrentasvir in registration trials, that predominantly enrolled non-cirrhotic subjects. In a pooled analysis of NS3/4A protease inhibitor- and NS5A inhibitor-naive patients who received glecaprevir/pibrentasvir in phase 2 and 3 studies (Forns, 2017); (Foster, 2017); (Asselah, 2018b); (Zeuzem, 2016); (Kwo, 2017b), baseline RASs in patients with genotype 1, 2, 4, 5, or 6 infection had no impact on SVR12 (Krishnan, 2018). Among treatment-naive genotype 3-infected patients without cirrhosis who received glecaprevir/pibrentasvir for 8 weeks, the A30K polymorphism was detected in 10%, of whom 78% achieved SVR12. There are insufficient data to characterize the impact of A30K in genotype 3-infected patients with cirrhosis or prior treatment experience. All genotype 3-infected patients with Y93H prior to treatment achieved SVR12.

Ledipasvir/Sofosbuvir

Several comprehensive analyses of genotype 1-infected patients treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies have helped clarify the impact of baseline RASs on SVR rates with this regimen (Sarrazin, 2016); (Zeuzem, 2017). In a pooled analysis of patients with genotype 1a or 1b infection who received ledipasvir/sofosbuvir, 93.5% (316/338) of those with baseline NS5A RASs achieved SVR12 compared to an SVR12 rate of 98.4% (1,741/1,770) in patients without baseline NS5A RASs (Sarrazin, 2016). In this analysis, the reduction in SVR rate was driven predominantly by patients with genotype 1a NS5A RASs. The SVR12 rates for genotype 1a-infected patients with and without NS5A RASs were 92.3% and 98.3%, respectively. A slightly lower SVR12 rate of 90% was observed for genotype 1a-infected patients with NS5A RASs using a 15% deep sequencing cutoff value.

Notably, other factors further delineated populations at risk for relapse in this analysis, including high-level baseline NS5A RASs (>100-fold resistance with Q30H/R, L31M/V, and Y93C/H/N in genotype 1a) and a shorter duration therapy (8 weeks or 12 weeks vs 24 weeks). SVR12 rates were 97.4% to 100% in treatment-experienced patients without NS5A RASs or with RASs with <100-fold resistance treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks. However, when RASs with >100-fold resistance were present, SVR12 rates dropped to 64.7% (11/17) with 12 weeks of therapy compared to 100% (6/6) with 24 weeks of therapy. In this small subset of patients, the addition of ribavirin did not appear to offer the same benefit as extension of therapy to 24 weeks in this pooled analysis. SVR12 rate was 81.8% in those with >100-fold NS5A resistance who received 12 weeks of ledipasvir/sofosbuvir with ribavirin. In contrast, in the SIRIUS trial, all 8 treatment-experienced cirrhotic patients with >100-fold resistance treated for 12 weeks with ledipasvir/sofosbuvir plus ribavirin achieved SVR12.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir ± Ribavirin

Paritaprevir/ritonavir/ombitasvir plus dasabuvir is currently indicated for genotype 1-infected patients. Paritaprevir/ritonavir/ombitasvir is indicated for genotype 4-infected patients, including those with prior peginterferon/ribavirin therapy failure. Patients with genotype 1a or 4 infection receive the addition of ribavirin whereas genotype 1b-infected patients do not. RAS testing has not been demonstrated to impact SVR rates, partially due to the addition of ribavirin in those patients at higher risk for treatment failure in the setting of RASs. Use of paritaprevir/ritonavir/ombitasvir plus dasabuvir alone in patients with a history of prior DAA treatment failure is not recommended.

Sofosbuvir/Velpatasvir
Sofosbuvir/velpatasvir is a pangenotypic therapy indicated for treatment-naive and -experienced patients with or without cirrhosis. The presence of NS5A RASs had no impact on SVR12 for patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir/velpatasvir for 12 weeks in the ASTRAL studies (Hézode, 2018). The presence of Y93H in genotype 3-infected patients decreased the SVR12 rate to 84% (21/25 patients) compared to 97% (242/249) in those without this RAS (Foster, 2015a). This appeared to be more impactful in patients with cirrhosis and/or prior treatment experience with an interferon-based regimen. Ribavirin was not used in these trials and thus, an evidence-based strategy to improve efficacy in those with genotype 3 infection and the NS5A Y93H RAS is not known.

Sofosbuvir/Velpatasvir/Voxilaprevir
Sofosbuvir/velpatasvir/voxilaprevir fills an important role as a pangenotypic regimen for patients who have experienced treatment failure with DAA therapy. The presence of NS3, NS5A, or NS5B RASs prior to treatment did not influence the likelihood of SVR12, and 12 weeks of treatment produced high SVR12 rates (96%) in DAA-experienced patients. RAS testing has not been demonstrated to impact SVR rates with sofosbuvir/velpatasvir/voxilaprevir therapy (Bourlière, 2017).

Table 1. Most Common, Clinically Important RASs by DAA, Genotype, and Fold Change

DAA	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N
Ledipasvir	20x	>100x	>100x / >100x	>1000x / >10,000	>100x/ >50x	>100x / --
Ombitasvir	>1000x	>100x	<3x / >100x	>10,000x / >10,000x	<10x	20x / 50x
Daclatasvir	>100x	>1000x	>100x / >1000x	>1000x / >10,000x	<10x	20x / 50x
Elbasvir	20x	>100x	>10x / >100x	>1000x / >1000x	<10x	>100x / --
Velpatasvir	<10x	<3x	20x / 50x	>100x/ >1000x	<3x	<3x / --

Color Key: light green = <3-fold change; dark green = <10-fold change; orange = >10- to 100-fold change; pink = >100-fold change

Table 2. Clinically Important RASs by DAA Regimen and Genotype

DAA Regimen	Genotype		
	1a	1b	3
Ledipasvir/sofosbuvir	Q30H/R L31M/V Y93C/H/N	L31V ?Y93H	n/a
Elbasvir/grazoprevir	M28A/T Q30H/R L31M/V Y93C/H/N	Y93H	n/a
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin	n/a	n/a	n/a
Sofosbuvir/velpatasvir	n/a	n/a	Y93H

Table 3. NS5A RAS Testing Recommendations Prior to Initiation of DAA Treatment Among Genotype 1 Patients by DAA Regimen, Virus Subtype, Prior Treatment Experience, and Cirrhosis Status

DAA Regimen	1b TN[a] or TE[b]	1a TN	1a TE No Cirrhosis	1a TE Cirrhosis
Ledipasvir/sofosbuvir	No	No	Yes	Yes
Elbasvir/grazoprevir	No	Yes	Yes	Yes
Sofosbuvir/velpatasvir	No	No	No	No
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin	No	No	No	No

[a] TN = treatment naive
[b] TE = treatment experienced

Last update: May 24, 2018

Initial Treatment of HCV Infection

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

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

Simplification of the treatment regimen may expand the number of healthcare professionals who prescribe antiviral therapy and increase the number of persons treated. This would align with the National Academies of Science, Engineering, and Medicine strategy to reduce cases of chronic HCV infection by 90% by 2030 (NASEM, 2017).

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

The following pages include guidance for management of treatment-naive patients.

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6

Mixed Genotypes

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

Last update: September 21, 2017

Treatment-Naive Genotype 1

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

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

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs are found by population sequencing in roughly 5% to 10% of patients and relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic response with certain regimens in those with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations (Zeuzem, 2015c). For further guidance, please see the HCV Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with an increased risk of drug-drug interactions with concomitant medications. Thus, attention to drug interactions is an important treatment consideration (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all the regimens discussed.

The following pages include guidance for management of treatment-naive patients with genotype 1 infection.

- Treatment-Naive Genotype 1a Without Cirrhosis
- Treatment-Naive Genotype 1b Without Cirrhosis
- Treatment-Naive Genotype 1a With Compensated Cirrhosis
- Treatment-Naive Genotype 1b With Compensated Cirrhosis

Last update: September 21, 2017

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For genotype 1a-infected, treatment-naive patients without cirrhosis, there are 4 recommended regimens with comparable efficacy. Four regimens are classified as alternative because, compared to the recommended regimens, they require a longer duration of treatment, involve greater prescribing complexity, are potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2015f). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) in treatment-naive patients with genotype 1a infection and 99% (129/131) in genotype 1b patients. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive, noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin (Sulkowski, 2015b). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of elbasvir/grazoprevir in genotype 1a-infected patients (Zeuzem, 2017). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir (Zeuzem, 2017). Among treatment-naive patients, the presence of baseline NS5A RASs with greater than 5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

Recommendations for prolonging treatment duration to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a-infected patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017). Subsequent integrated analysis of the elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir plus ribavirin for 16 or 18 weeks (Jacobson, 2015b); (Thompson, 2015).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. Based on favorable data for 8 weeks of treatment among noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) (Kwo, 2017b), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 or 12 weeks of glecaprevir/pibrentasvir (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either study arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse

occurred in a genotype 1a patient; SVR for genotype 1a was 98% (47/48) (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on a pair of registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 was 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without ribavirin) (Kowdley, 2014). SVR12 rates were 93% to 95% across all study arms with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2/123; 2%). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2/131; 2%). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8-week and 12-week courses of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis (Backus, 2016); (Ingiliz, 2016); (Ioannou, 2016); (Kowdley, 2016); (Terrault, 2016). However, only about half of patients eligible for 8 weeks of treatment received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see HIV/HCV Coinfection section) and black patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014); (Ioannou, 2016). For others, it should be done at the discretion of the practitioner with consideration of other potential negative prognostic factors.

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2018). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotypes 1, 2, 3, 4, 5, or 6—with or without compensated cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with

genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir and Ribavirin

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based ribavirin was approved by the FDA for the treatment of genotype 1a infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a infection without cirrhosis); PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis); and TURQUOISE-II (261 treatment-naive and -experienced patients with genotype 1a and cirrhosis).

The SAPPHIRE-I trial reported a 95.3% SVR12 rate with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir and ribavirin (Feld, 2014). Overall, virologic failure was higher for patients with genotype 1a (7/8 failures) than genotype 1b (1/8 failures). PEARL-IV was specifically designed to determine the role of paritaprevir/ritonavir/ombitasvir + dasabuvir—with or without weight-based ribavirin—for treatment-naive, genotype 1a-infected patients without cirrhosis (Ferenci, 2014).

SVR12 was lower in the ribavirin-free arm than in the ribavirin-containing arm (90% vs 97%, respectively) due to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based ribavirin for patients with genotype 1a. An extended-release formulation of paritaprevir/ritonavir/ombitasvir + dasabuvir was approved in 2016, allowing once-daily dosing; ribavirin, when needed, remains at twice-daily dosing (AbbVie Inc, 2017).

Simeprevir + Sofosbuvir

The OPTIMIST-1 trial investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in patients with genotype 1 without cirrhosis. In this study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 or 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). Overall SVR12 rates were 97% (150/155) for the 12-week arm and 83% (128/155) for the 8-week arm, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm, there was no difference in SVR12 based on past treatment experience; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or the presence of the baseline Q80K resistance substitution.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for the treatment of genotype 1 infection is recommended based on data from the phase 3 ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotype 1, 2, 3, or 4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with genotype 1. Eighty-three (54%) of these patients were treatment naive. The SVR rate was 96% in treatment-naive patients with genotype 1a infection (n=71) receiving 12 weeks of therapy. Similarly, in a phase 2b study of daclatasvir plus sofosbuvir among 88 treatment-naive patients with genotype 1a infection—21 treated for 24 weeks (11 with ribavirin) and 67 treated for 12 weeks (33 with ribavirin)—there were no virologic relapses (Sulkowski, 2014a).

Last update: September 21, 2017

Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease (Zeuzem, 2015f). SVR12 was 97% in this subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients (Lawitz, 2015c). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Lawitz, 2015c); (Zeuzem, 2017).

Presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients (Zeuzem, 2017). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to 99% (133/135) in patients without these RASs (Zeuzem, 2017). Among treatment-naive patients, the

presence of baseline NS5A RASs with a greater than 5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

Recommendations for prolonging duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017). Subsequent integrated analysis of elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6 patients) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir for 16 or 18 weeks plus ribavirin (Jacobson, 2015b); (Thompson, 2015).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated the use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse occurred in a genotype 1a patient; SVR among these patients was 98% (47/48) (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference in SVR observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2018). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6—19% with cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Last update: September 21, 2017

Treatment-Naive Genotype 1b Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Patients Genotype 1b Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	I, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For genotype 1b-infected, treatment-naive patients without cirrhosis, there are 4 regimens of comparable efficacy. Three additional regimens are classified as alternative because, compared to the recommended regimens, they require a longer duration of treatment, involve greater prescribing complexity, are potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2015f). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The SVR12 was

92% (144/157) in treatment-naive patients with genotype 1a and 99% (129/131) in those with genotype 1b. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin (Sulkowski, 2015b). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs.

Glecaprevir/Pibrentasvir

Based on favorable data for 8 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) (Kwo, 2017b), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. All genotype 1b patients achieved SVR (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected persons with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on a pair of registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening ledipasvir/sofosbuvir therapy from 12 weeks to 8 weeks (with or without ribavirin) (Kowdley, 2014). SVR12 rates were 93% to 95% across all study arms, with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2/123; 2%). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2/131; 2%). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8 and 12 weeks of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis (Backus, 2016); (Ingiliz, 2016); (Ioannou, 2016); (Kowdley, 2016); (Terrault,

2016). However, only about half of patients eligible for 8 weeks received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV-infected patients (see HIV/HCV Coinfection section) and black patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014); (Ioannou, 2016). For others, it should be done at the discretion of the practitioner with consideration of other potential negative prognostic factors.

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2018). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotypes 1, 2, 3, 4, 5, or 6—with or without compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed in each subtype.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) was approved by the FDA for the treatment of genotype 1b infection in treatment-naive patients based on 3 registration trials; 2 focused specifically on those without cirrhosis. SAPPHIRE-I, which included 151 treatment-naive, genotype 1b-infected patients without cirrhosis, reported an SVR12 rate of 98% with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir in these patients (Feld, 2014).

Given the high SVR12 rates seen in SAPPHIRE-I, PEARL-III was specifically designed to determine the role of weight-based ribavirin with paritaprevir/ritonavir/ombitasvir + dasabuvir in treatment-naive, genotype 1b-infected patients without cirrhosis (Ferenci, 2014). The SVR12 rate among the 419 study participants was 99% in both treatment arms, confirming there is no added benefit from use of weight-based ribavirin for patients without cirrhosis who have genotype 1b infection.

GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week course of paritaprevir/ritonavir/ombitasvir + dasabuvir. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage 0 to 2, 93% had HCV RNA levels <6 million IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage 3 experienced virologic relapse, suggesting that if used, an 8-week strategy should be reserved for those with early-stage fibrosis (Welzel, 2016b).

Simeprevir + Sofosbuvir

The OPTIMIST-1 trial investigated the safety and efficacy of simeprevir (150 mg) plus sofosbuvir (400 mg) in patients with genotype 1 without cirrhosis. In this study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 weeks or 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). Overall SVR12 rates were 97% (150/155) in the 12-week arm and 83% (128/155) in the 8-week arm, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm, there was no difference in SVR12 based on past treatment experience; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or the presence of the baseline Q80K resistance substitution.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for the treatment of genotype 1 infection is recommended based on data from the phase 3 ALLY-2 trial, which assessed the efficacy and safety of daclatasvir/sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotype 1, 2, 3, or 4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with genotype 1. Eighty-three (54%) of these patients were treatment naive. Only 12 had genotype 1b and all achieved SVR12 (Wyles, 2015). Furthermore, in the ALLY-1 study, all 11 genotype 1b-infected patients with advanced cirrhosis achieved SVR12. Due to the limited numbers of genotype 1b patients represented in the phase 3 trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

Last update: September 21, 2017

Treatment-Naive Genotype 1b With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1b Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)[c]	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

For genotype 1b-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease (Zeuzem, 2015f). SVR12 was 97% in the subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients (Lawitz, 2015c). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Lawitz, 2015c); (Zeuzem, 2017).

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in DAA-naive (75%) or -experienced (interferon or

peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12; all genotype 1b patients achieved SVR (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference in SVR observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). Baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2018). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotypes 1, 2, 3, 4, 5, or 6—19% with compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) was approved by the FDA for the treatment of genotype 1b infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (151 treatment-naive patients with genotype 1b without cirrhosis); PEARL-III (419 treatment-naive patients with genotype 1b without cirrhosis); and TURQUOISE-II (119 treatment-naive and -experienced patients with genotype 1b and cirrhosis). TURQUOISE-II enrolled treatment-naive and -experienced patients with Child-Turcotte-Pugh class A cirrhosis to receive either 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir and ribavirin. Overall SVR12 rates were 98.5% in the 12-week arm and 100% in the 24-week arm (Poordad, 2014).

To address the need for ribavirin with this regimen in patients with genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of paritaprevir/ritonavir/ombitasvir + dasabuvir without ribavirin for 12 weeks in patients

with genotype 1b infection and compensated cirrhosis. Sixty patients (62% men; 55% treatment-experienced; 83% with the IL28B non-CC genotype; 22% with platelet counts <90 x 10^9/L; 17% with albumin <3.5 g/dL) were enrolled. All patients completed treatment and all achieved SVR12. Based on this study, treating patients with genotype 1b with paritaprevir/ritonavir/ombitasvir + dasabuvir without ribavirin is recommended, regardless of prior treatment experience or the presence of compensated cirrhosis (Feld, 2016).

Last update: September 21, 2017

Treatment-Naive Genotype 2

The following pages include guidance for management of treatment-naive patients with genotype 2 infection.

- Treatment-Naive Genotype 2 Without Cirrhosis
- Treatment-Naive Genotype 2 With Compensated Cirrhosis

Last update: September 21, 2017

Treatment-Naive Genotype 2 Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 2 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-2 was a randomized, double-blind, placebo-controlled trial of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks among 302 genotype 2-infected treatment-naive or -experienced participants. Treatment-experienced patients included those previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon. Patients randomized to placebo later received open-label treatment with glecaprevir/pibrentasvir for 12 weeks. Among 202 patients randomized to active treatment, 70% (141/202) were treatment naive and none had cirrhosis. The SVR12 rates were 99% and 100% by intention-to-treat and modified intention-to-treat analysis, respectively. There were no virologic failures. One participant who achieved SVR4 was lost to follow-up before the SVR12 evaluation. There was no effect of baseline RASs on SVR12 rate. Overall, therapy was well tolerated and the adverse event profile was not different compared to placebo (Asselah, 2018b).

A shorter duration of glecaprevir/pibrentasvir for 8 weeks was evaluated in the SURVEYOR-II, part 4 study. This was a single-arm, phase 2 study that evaluated glecaprevir/pibrentasvir for 8 weeks among 203 treatment-naive or -experienced patients (previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 2, 4, 5, or 6 infection without cirrhosis. Of the 142 genotype 2-infected patients, 137 (96%) were treatment naive. Among the treatment-naive, genotype 2-infected participants, 135/137 (99%) achieved SVR12. The presence of baseline RASs had minimal effect on SVR12 rates. Fifty-three of 126 (42%) treatment-naive and -experienced participants with genotype 2 had the L31M RAS within the NS5A gene at baseline. Fifty-one of 53 (96%) of these participants achieved SVR12 (Asselah, 2018b).

While not a head-to-head comparison, the results of ENDURANCE-2 and SURVEYOR-II, part 4 indicate that glecaprevir/pibrentasvir administered for 8 or 12 weeks is highly efficacious among genotype 2-infected, treatment-naive patients without cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir (SVR12 99% vs 94%); (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced participants without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in participants with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure (Asselah, 2018).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (Jacobson, 2017).

Alternative Regimen

Daclatasvir + Sofosbuvir

A 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir plus sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir plus sofosbuvir for 12 weeks is reasonable.

Last update: September 21, 2017

Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	16 to 24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir compared to sofosbuvir plus ribavirin (SVR12 99% vs 94%); (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in those with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure (Asselah, 2018).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (Jacobson, 2017).

Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1, 2, 4, 5, or 6

infection and compensated cirrhosis. Participants were treated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 (Forns, 2017). EXPEDITION-1 included 31 treatment-naive and -experienced persons with genotype 2 infection and compensated cirrhosis; all achieved SVR12. Baseline NS5A RASs were detected (by next-generation sequencing using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced patients with genotype 2 infection.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir with sofosbuvir for 12 weeks is reasonable.

Last update: September 21, 2017

Treatment-Naive Genotype 3

The following pages include guidance for management of treatment-naive patients with genotype 3 infection.

- Treatment-Naive Genotype 3 Without Cirrhosis
- Treatment-Naive Genotype 3 With Compensated Cirrhosis

Last update: September 21, 2017

Treatment-Naive Genotype 3 Without Cirrhosis

Recommended and alternative regimens listed alphabetically for:

Treatment-Naive Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	I, A

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (222/233 participants receiving the 12-week regimen; 149/157 participants receiving the 8-week regimen) (Foster, 2017). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8- and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared to the standard of care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. While the baseline presence of the Y93H substitution did not affect SVR rates (10/10 with Y93H achieved SVR with an 8 week duration vs 165/171 without Y93H), the presence of the A30K substitution was associated with a lower SVR rate (14/18 with A30K achieved SVR with an 8 week duration vs 161/163 without A30K) (Krishnan, 2018). Of the 14 treatment-naive patients with genotype 3 without cirrhosis with baseline A30K who received a 12 week duration of glecaprevir/pibrentavir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence to recommend testing for RASs or extension of therapy in the setting of A30K at this time, but the effect of the A30K mutation should continue to be explored in real world cohorts. These data support an 8-week regimen of glecaprevir/pibrentasvir for the treatment of genotype 3-infected patients who are treatment-naive without cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for

the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis (Foster, 2015a). Among treatment-naive, noncirrhotic patients, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared to 90% (141/156) for sofosbuvir plus ribavirin. Among patients with compensated cirrhosis, SVR12 was 93% (40/43) for sofosbuvir/velpatasvir compared to 73% (33/45) for sofosbuvir plus ribavirin. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline RASs. Eighty-four percent (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with cirrhosis.

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in genotype 3-infected, noncirrhotic patients who were either treatment-naive or interferon-experienced. Eighty-nine genotype 3 patients received the sofosbuvir/velpatasvir regimen and 97% achieved SVR12 (86/89) (Jacobson, 2017). There were no virologic failures. This confirms the efficacy of sofosbuvir/velpatasvir in genotype 3-infected patients without cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. Among treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12; in treatment-naive patients with compensated cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests that patients with genotype 3 infection and compensated cirrhosis are likely to benefit from an extension of therapy.

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% (149/162) in those without it (Nelson, 2015). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with compensated cirrhosis had lower SVR12 rates (1/5); (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

ENDURANCE-3 was a randomized (2:1) trial comparing 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to 12 weeks of daclatasvir/sofosbuvir among 348 treatment-naive participants with genotype 3 infection without cirrhosis. In the 115 patients randomized to daclatasvir/sofosbuvir, 97% achieved SVR12, and 20 of 21 participants (95%) with baseline NS5A RAS achieved SVR (Foster, 2017).

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Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)[c]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present	12 weeks	IIa, B
Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg) with or without weight-based ribavirin[c]	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] RAS testing for Y93H is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered.
[d] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

SURVEYOR-II—a partially randomized, open-label, multicenter, 4-part, phase 2 trial—compared 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to glecaprevir/pibrentasvir plus ribavirin among 48 treatment-naive, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 (Kwo, 2016b). The presence of baseline NS3 and/or NS5A RASs had no impact on SVR12 rate regardless of inclusion of ribavirin in the treatment regimen; however the analysis was limited because few patients had NS5A RASs. These data indicate that 12 weeks of glecaprevir/pibrentasvir yields high SVR12 rates among treatment-naive, genotype 3-infected patients with compensated cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 randomized

552 treatment-naive and -experienced patients (without cirrhosis or with compensated cirrhosis) to 12 weeks of sofosbuvir/velpatasvir or 24 weeks sofosbuvir plus ribavirin (Foster, 2015a). Among those with compensated cirrhosis, the SVR12 was 93% (40/43) in the sofosbuvir/velpatasvir arm compared to 73% (33/45) among those in the sofosbuvir plus ribavirin arm. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline substitutions. Eighty-four percent (21/25) of those with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with compensated cirrhosis.

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). The SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR. Four participants in the sofosbuvir/velpatasvir arm had the Y93H substitution; all achieved SVR12.

Alternative Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). Thirty-one percent of participants were interferon treatment experienced. The SVR12 rate was 96% in both arms, 106/110 of patients randomized to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir. There were 2 virologic failures in each arm (2 relapses in the sofosbuvir/velpatasvir/voxilaprevir arm; 1 virologic breakthrough and 1 relapse in the sofosbuvir/velpatasvir arm). Baseline RASs had no effect on treatment response. Among the 6 participants with Y93H in the sofosbuvir/velpatasvir/voxilaprevir arm and 4 in the sofosbuvir/velpatasvir arm, all achieved SVR12. Additionally, no patients receiving sofosbuvir/velpatasvir/voxilaprevir with virologic failure developed RASs. Although an 8-week regimen was studied in POLARIS-3, a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir was approved by the FDA for the indication of retreatment of DAA-experienced patients and could be considered as an alternative regimen for patients with cirrhosis and Y93H.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of daclatasvir/sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, compared to 58% SVR12 in treatment-naive patients with cirrhosis (Metavir F4) (Nelson, 2015).

The results of the ALLY-3 study suggest that patients with genotype 3 infection and cirrhosis are likely to benefit from an extension of therapy. This has been confirmed in cohort studies, including the European compassionate-use program, which reported SVR12 rates of 70% vs 86% when daclatasvir/sofosbuvir was used for 12 weeks and 24 weeks in genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified as only 4 patients received daclatasvir/sofosbuvir plus ribavirin for 12 weeks, all of which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without ribavirin; 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85% to 90%) compared to 70.6% in Child-Pugh B/C. Again, the addition of ribavirin did not increase SVR12 rates in the 24-week treatment arms (Hézode, 2017). Seventy-three percent of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91% to 100%) compared to treatment-experienced (81% to 82%). SVR12 rates were similar in patients who received ribavirin (88%, 29/33) and those who did not (86%, 42/49) (Hézode, 2017).

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% in those without it (149/162). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI, 2016).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI, 2016). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

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Treatment-Naive Genotype 4

The following pages include guidance for management of treatment-naive patients with genotype 4 infection.

- Treatment-Naive Genotype 4 Without Cirrhosis
- Treatment-Naive Genotype 4 With Compensated Cirrhosis

Last update: September 21, 2017

Treatment-Naive Genotype 4 Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin	12 weeks	I, A

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in part 4 of the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Asselah, 2018b). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week versus 12-week course of glecaprevir/pibrentasvir for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 43/46 with genotype 4, 2/2 with genotype 5, and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

EXPEDITION-1 investigated use of glecaprevir/pibrentasvir in treatment-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 16/16 (100%) with genotype 4, 2/2 (100%) with genotype 5, and 7/7 (100%) with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for treatment of genotype 4-infected, DAA-naive, noncirrhotic patients for a duration of 8 weeks.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) versus 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse (Jacobson, 2017).

Elbasvir/Grazoprevir

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and genotype subtype did not appear to impact SVR12 rates (Asselah, 2018c).

Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was a randomized, open-label, phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients (Esmat, 2015).

Last update: September 21, 2017

Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 4 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin[c]	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive patients (19% with compensated cirrhosis, overall) to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse (Jacobson, 2017).

Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Patients received the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 (Forns, 2017). EXPEDITION-1 included 16 treatment-naive and -experienced genotype 4-infected participants with compensated cirrhosis. All 16 patients achieved SVR12. Baseline NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested

participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced participants with genotype 4. Based on this study, a 12-week course of glecaprevir/pibrentasvir is recommended for genotype 4-infected, treatment-naive patients with compensated cirrhosis.

Elbasvir/Grazoprevir

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and subtype did not appear to impact SVR12 rates (Asselah, 2018c).

Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was a randomized, open-label phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. Additionally, AGATE-II randomized 60 treatment-naive and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR rate from the 12-week arm was 97%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015).

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Treatment-Naive Genotype 5 or 6

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	8 weeks (no cirrhosis)	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	12 weeks (cirrhosis)	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg pills (Asselah, 2018b). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week vs 12-week course for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Asselah, 2018b). In the intention-to-treat analysis, 2/2 with genotype 5 and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

In addition, EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 2/2 with genotype 5 and 7/7 with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (noncirrhotic) and 12-week course (cirrhotic) of treatment for people with genotype 5 or genotype 6 infection.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naive participants with and without cirrhosis, 23 (96%) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12 (100%). An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

Ledipasvir/Sofosbuvir

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

Ledipasvir has in vitro activity against most genotype 6 subtypes, except for 6e (Wong, 2013); (Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with genotype 6 infection. Twenty-five patients (92% were treatment-naive) who were primarily Asian (88%) had infection from 7 different subtypes (32% 6a; 24% 6e; 12% 6l; 8% 6m; 12% 6p; 8% 6q; 4% 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

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Retreatment of Persons in Whom Prior Therapy Failed

This section provides guidance on the retreatment of persons with chronic HCV infection in whom prior therapy failed. The level of the evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different viral genotypes). Recommended regimens are those that are favored for most patients in that group, based on optimal efficacy, favorable tolerability and toxicity profiles, complexity, and duration.

Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data. In certain situations, an alternative regimen may be optimal for a specific patient.

Not recommended regimens are clearly inferior compared to recommended and alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer treatment duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection.

Specific considerations for pediatric patients and persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh [CTP] class B or C), HCV infection post liver transplantation, and severe renal impairment, end-stage renal disease (ESRD), or HCV infection post kidney transplantation are addressed in other sections of the guidance.

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

Mixed Genotypes

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

The following pages include guidance for management of treatment-experienced patients.

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6

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Treatment-Experienced Genotype 1

Multiple highly potent, DAA combination regimens are recommended for patients with genotype 1 infection. There are differences in the recommended regimens based on viral subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), the presence or absence of compensated cirrhosis, and the type of prior failed regimen(s). Genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs are found by population sequencing in roughly 5% to 10% of patients; relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic outcome with certain regimens in genotype 1a-infected patients, testing for these RASs prior to deciding on a therapeutic course is recommended in selected situations (Zeuzem, 2015c). For further guidance please see the Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with an increased risk of drug interactions with concomitant medications. With combinations of DAAs in the various treatment regimens, attention to drug-drug interactions is that much more important (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be consulted regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all regimens discussed.

The following pages include guidance for management of treatment-experienced patients with genotype 1 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis
- NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis
- NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis
- Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis
- Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis
- NS5A Inhibitor DAA-Experienced Genotype 1 Patients

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), and weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR12 rate of 93.8% (90/96), which was nearly identical to the rate seen in those treated for 12 weeks with ribavirin (94.4%, 84/89) (Kwo, 2017). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1 infection without cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a infection, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR in the ledipasvir/sofosbuvir plus ribavirin study arm (Afdhal, 2014b). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir + Ribavirin

In the SAPPHIRE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed (Zeuzem, 2014). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin (Andreone, 2014). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naive or -experienced without cirrhosis (Kwo, 2016). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure (Foster, 2015); (Pol, 2017); (Foster, 2016). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and

sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).

Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

Last update: May 24, 2018

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir	16 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. Baseline testing for these RASs is recommended for patients receiving elbasvir/grazoprevir-based regimens.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) (Kwo, 2017). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR with cirrhosis 95% [19/20]; SVR without cirrhosis 94.9% [37/39]).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR compared to 96% (52/54) among those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype1-infected patients. The single treatment failure occurred in a patient with genotype 1a infection who relapsed at post-treatment week 8 (Forns, 2017). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected patients with compensated

cirrhosis who did not achieve SVR with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) (Bourliere, 2015).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1-infected patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Reddy, 2015). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several factors, including virus (genotype subtype, specific RAS); regimen (companion drugs, use of ribavirin); and patient factors (treatment experience, presence of cirrhosis). In an analysis of more than 350 genotype 1-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC_{50}) detected at a 1% level resulted in a lower SVR12 rate compared to those without baseline RASs (Zeuzem, 2017). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a-infected, treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10^9/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 (Feld, 2016). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a warning in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

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

Last update: May 24, 2018

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	I, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR12 rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) (Kwo, 2017). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1 infection without cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a infection, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR in the ledipasvir/sofosbuvir plus ribavirin study arm (Afdhal, 2014b). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among

patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

In the SAPPHIRE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed (Zeuzem, 2014). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin (Andreone, 2014). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naive or -experienced without cirrhosis (Kwo, 2016). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure (Foster, 2015); (Pol, 2017); (Foster, 2016). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).

Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)[c]	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) (Kwo, 2017). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR with cirrhosis 95% [19/20]; SVR without cirrhosis 94.9% [37/39]).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week

elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR compared to 96% (52/54) among those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype1-infected patients. The single treatment failure occurred in a patient with genotype 1a infection who relapsed at post-treatment week 8 (Forns, 2017). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected patients with compensated cirrhosis who did not achieve SVR with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized

to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) (Bourliere, 2015).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1-infected patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Reddy, 2015). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several factors, including virus (genotype subtype, specific RAS); regimen (companion drugs, use of ribavirin); and patient factors (treatment experience, presence of cirrhosis). In an analysis of more than 350 genotype 1-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC_{50}) detected at a 1% level resulted in a lower SVR12 rate compared to those without baseline RASs (Zeuzem, 2017). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a-infected, treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10^9/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 (Feld, 2016). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a warning in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

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

Last update: September 21, 2017

NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RASs[b] for elbasvir	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RASs[b] for elbasvir	16 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Recommended Regimens

Ledipasvir/Sofosbuvir

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1-infected patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed (Afdhal, 2014b). SVR12 rates with the 12-week and 24-week ledipasvir/sofosbuvir regimens were 94% and 98%, respectively. Relapse rates were numerically higher with the 12-week regimen versus the 24-week regimen. The presence of cirrhosis and/or baseline NS5A RASs were the major reasons for the higher relapse rate in the 12-week study arm. Thus, genotype 1-infected patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed can receive a 12-week course of ledipasvir/sofosbuvir.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). In this study, 100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 (Feld, 2015). These data are supported by similarly high SVR rates seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy (Pianko, 2015).

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1-infected patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with protease inhibitor-based therapy (which includes simeprevir, boceprevir or telaprevir without NS5A inhibitor exposure) who were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR, neither experienced virologic failure (Poordad, 2017); (Poordad, 2017b).

Alternative Regimens

Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor resistant substitutions (Summa, 2012); (Howe, 2014). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced prior treatment failure with interferon-based therapy plus a protease inhibitor (Forns, 2015a). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including in 93% (28/30) of genotype 1a-infected patients and 94% (32/34) in those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 rate of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.

Consistent with recommendations for other populations, a 12-week course of elbasvir/grazoprevir is a recommended regimen for patients with genotype 1a infection and no baseline NS5A RASs. Extension of therapy to 16 weeks plus weight-based ribavirin is an alternative treatment option for genotype 1a-infected patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency.

Last update: September 21, 2017

NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin Treatment-Experienced, Genotype 1 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RASs[c] for elbasvir	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RASs[c] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99.1% (109/110), with 100% (78/78) in patients with genotype 1a infection and 96.9% (31/32) among those with genotype 1b infection. In this study,

100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 (Feld, 2015). These data are supported by similarly high SVR rates seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy (Pianko, 2015).

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1-infected patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with NS3/4A protease inhibitor-based therapy (which includes simeprevir, boceprevir or telaprevir without NS5A inhibitor exposure) who were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR, neither experienced virologic failure (Poordad, 2017); (Poordad, 2017b).

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1-infected patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed (Afdhal, 2014b). SVR12 with 12 weeks of therapy was 94%. Relapse rates were numerically higher in the 12-week treatment arms than in the 24-week arms. The pretreatment presence of cirrhosis and/or NS5A RASs were the major reasons for the higher relapse rate in the 12-week arm. Thus, genotype 1-infected patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed should receive ledipasvir/sofosbuvir plus weight-based ribavirin for 12 weeks to optimize treatment response (Bourliere, 2015). Due to the need for ribavirin, this is recommended as an alternative regimen.

Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor RASs (Summa, 2012); (Howe, 2014). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced a prior treatment failure with interferon-based therapy plus a protease inhibitor (Forns, 2015a). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including 93% (28/30) of genotype 1a-infected patients and 94% (32/34) of those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 rate of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.

Consistent with recommendations for other populations, extension of therapy to 16 weeks with ribavirin is recommended for patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency. Due to the need for ribavirin, both the 12-week and 16-week course of therapy are recommended as alternative regimens.

Last update: September 21, 2017

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) for genotype 1a patients	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a], regardless of subtype	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin, except in simeprevir failures	12 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of daily fixed-dose sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 infection were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. There was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure using a non-NS5A inhibitor sofosbuvir-containing DAA regimen.

Glecaprevir/Pibrentasvir

There are limited data to guide recommendations for the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for patients with genotype 1a or 1b infection and a prior treatment failure with a sofosbuvir-containing DAA regimen. In the phase 3, open-label ENDURANCE-1 study, 351 and 352 patients received 8 weeks or 12 weeks of glecaprevir/pibrentasvir, respectively (Zeuzem, 2016). All patients had genotype 1 infection and were noncirrhotic; 38% of patients in each study arm were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). However, only 1 patient in the 8-week arm and 2 patients in the 12-week arm had a history of treatment failure with a sofosbuvir-containing regimen.

In the EXPEDITION-1 study, 146 patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis were treated with 12 weeks of glecaprevir/pibrentasvir. Twenty-five of these patients were treatment experienced; only 11 had a previous treatment failure with a sofosbuvir-containing regimen (Forns, 2017). None of these patients had a prior simeprevir plus sofosbuvir regimen failure. However, 12 weeks of glecaprevir/pibrentasvir was evaluated in prior NS3/4A treatment failures in the MAGELLAN-1 trial, which included patients with prior simeprevir plus sofosbuvir treatment failure (Poordad, 2017); (Poordad, 2017b).

With the limited clinical trial experience with glecaprevir/pibrentasvir in patients with a history of sofosbuvir-containing regimen treatment failure coming primarily from a 12-week duration of therapy, we recommend 12 weeks of therapy in this patient population until there are further clinical trial or real-world data to support a shorter treatment duration.

Sofosbuvir/Velpatasvir

As described in the discussion of sofosbuvir/velpatasvir/voxilaprevir, the POLARIS-4 trial included a 12-week arm of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor-DAA experienced patients (Bourliere, 2017). While only sofosbuvir/velpatasvir/voxilaprevir met the overall prespecified efficacy (SVR12) threshold of 85%, this was primarily driven by treatment failure in patients with genotype 1a or 3 infection. Forty-four patients with genotype 1a infection, 22 with genotype 1b infection, 33 with genotype 2 infection, and 52 with genotype 3 infection were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a-infected patients and 8 were in those with genotype 3 infection. One genotype 1b-infected patient and a single genotype 2-infected patient also experienced treatment failure. Although this study was not powered to assess differences in efficacy by genotype/subtype, the SVR12 rates in genotype 1b-infected patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b-infected patients who experienced a previous treatment failure specifically with a non-NS5A inhibitor sofosbuvir-containing regimen (n=12), and no virologic failures.

Alternative Regimen

Ledipasvir/Sofosbuvir + Ribavirin

Retreatment with the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in patients with genotype 1 infection, with or without cirrhosis, in whom a sofosbuvir-containing (excluding simeprevir) regimen failed was evaluated in 2 small pilot studies utilizing ledipasvir/sofosbuvir for 12 weeks. Among patients with a prior treatment failure with 24 weeks of sofosbuvir plus ribavirin, high SVR rates were noted when patients were retreated with ledipasvir/sofosbuvir for 12 weeks (Osinusi, 2014). Ledipasvir/sofosbuvir plus ribavirin has also been evaluated in patients in whom prior treatment with sofosbuvir plus peginterferon/ribavirin or sofosbuvir and ribavirin failed. In a study of 51 patients, retreatment with ledipasvir/sofosbuvir plus ribavirin for 12 weeks led to SVR12 in 100% of 50 patients with genotype 1 infection. One virologic failure was observed in a patient determined to have genotype 3 infection prior to retreatment (Wyles, 2015b).

Last update: September 21, 2017

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for genotype 1a patients	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b], regardless of subtype	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 infection were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. The vast majority of patients had experienced prior treatment failure with a sofosbuvir plus simeprevir regimen. Overall, there was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure with a sofosbuvir-containing DAA regimen, regardless of the presence of cirrhosis.

Glecaprevir/Pibrentasvir

In the EXPEDITION-1 study, 146 patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis were treated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks (Forns, 2017). Of these patients, 25 patients were previously treated with interferon or peginterferon ± ribavirin and 11 were previously treated with sofosbuvir and ribavirin ± peginterferon. Overall, 99% (145/146) of patients achieved SVR 12. The single patient who did not respond to therapy had genotype 1a infection and relapsed at post-treatment week 8. None of the patients enrolled in the EXPEDITION-1 trial were previously treated with simeprevir plus sofosbuvir. However, 12 weeks of glecaprevir/pibrentasvir was evaluated in patients with NS3/4A treatment failure in the MAGELLAN-1 trial, which included simeprevir plus sofosbuvir treatment failures (Poordad, 2017); (Poordad, 2017b).

Sofosbuvir/Velpatasvir

As described in the discussion of sofosbuvir/velpatasvir/voxilaprevir, the POLARIS-4 trial included a 12-week arm of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). While only sofosbuvir/velpatasvir/voxilaprevir met the overall prespecified efficacy (SVR12) threshold of 85%, this was primarily driven by treatment failure in patients with genotype 1a or 3 infection. Forty-four patients with genotype 1a infection, 22 with genotype 1b infection, 33 with genotype 2 infection, and 52 with genotype 3 infection were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a-infected patients and 8 were in those with genotype 3 infection, and most of these patients had cirrhosis. One genotype 1b-infected patient and a single genotype 2-infected patient also experienced treatment failure. Although this study was not powered to assess differences in efficacy by genotype/subtype, the SVR12 rates in genotype 1b-infected patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b-infected patients who had specifically experienced a prior non-NS5A inhibitor sofosbuvir-containing regimen failure (n=12), and no virologic failures.

Last update: September 21, 2017

NS5A Inhibitor DAA-Experienced Genotype 1 Patients

Recommended and alternative regimens for:

NS5A Inhibitor DAA-Experienced, Genotype 1 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] except NS3/4 protease inhibitor inclusive DAA combination regimens	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

The placebo-controlled, phase 3 POLARIS-1 trial evaluated a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) in patients with a prior NS5A inhibitor-containing DAA regimen. The majority (61%) experienced a failure with a combination regimen of an NS5B inhibitor plus an NS5A inhibitor, such as sofosbuvir/ledipasvir (Bourliere, 2017). The overall SVR12 rate was 97% (146/150) in genotype 1-infected patients. SVR12 rates were 96% (97/101) for participants with genotype 1a infection and 100% (45/45) for those with genotype 1b infection. A single genotype 1-infected patient experienced relapse; this individual had subtype 1a infection and cirrhosis. Baseline RASs and the presence of cirrhosis were not significant predictors of virologic failure in genotype 1 infection. Serious adverse events were similar between the placebo and treatment arms; only 1 patient discontinued therapy due to an adverse event. Headache, diarrhea, and nausea were more common in those patients receiving sofosbuvir/velpatasvir/voxilaprevir compared to placebo.

Alternative Regimen

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1-infected patients had previously been treated with either an NS5A inhibitor or an NS3/4A protease inhibitor (Poordad, 2017); (Poordad, 2017b). Twenty-four percent of these patients had cirrhosis and 79% were genotype 1a infected. Patients who were previously treated with an NS5A inhibitor (ledipasvir or daclatasvir) and not concomitantly treated with a NS3/4A protease inhibitor were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination

pills for 16 weeks. Among these patients, 94% (16/17) achieved SVR 12. The single patient who did not respond to therapy had an on-treatment virologic failure. Due to the 16-week duration of therapy and limited supporting data, this is recommended as an alternative regimen.

Last update: September 21, 2017

Treatment-Experienced Genotype 2

The following pages include guidance for management of treatment-experienced patients with genotype 2 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis
- DAA-Experienced (Including NS5A Inhibitors), Genotype 2 Patients With or Without Compensated Cirrhosis

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 4 trial was a single-arm study of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 8 weeks in patients with genotype 2, 4, 5, or 6 infection without cirrhosis who were treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) (Asselah, 2018b). One hundred forty-five genotype 2-infected patients were enrolled with a 98% SVR12. Two patients experienced relapse; both were treatment experienced.

Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2-infected patients were treated with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) or sofosbuvir plus ribavirin (Foster, 2015a). Of the 266 participants, a minority (15%) had a history of previous peginterferon/ribavirin treatment failure and a similar proportion (14%) had compensated cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate of 99% vs 94% for sofosbuvir plus ribavirin. The only treatment failure in the sofosbuvir/velpatasvir arm was a patient who withdrew from the study after a single day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study randomized patients to 8 weeks of the fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2-infected patients were in the sofosbuvir/velpatasvir arm and all achieved SVR (100%, 53/53) (Jacobson, 2017). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

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

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	16 to 24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2-infected patients were treated with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) or sofosbuvir plus ribavirin (Foster, 2015a). Of the 266 participants, a minority (15%) had a history of previous peginterferon/ribavirin treatment failure and a similar proportion (14%) had compensated cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate of 99% vs 94% for sofosbuvir plus ribavirin. The only treatment failure in the sofosbuvir/velpatasvir arm was a patient who withdrew from the study after a single day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study randomized patients to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir or 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2-infected patients were included in the sofosbuvir/velpatasvir arm and all achieved SVR (100%, 53/53) (Jacobson, 2017). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

Considering the high SVR12 rate and fewer side effects with sofosbuvir/velpatasvir, regimens with peginterferon and/or

ribavirin are no longer recommended for genotype 2 infection.

Glecaprevir/Pibrentasvir

The phase 3, single arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis (Forns, 2017). Treatment-naive and -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) were included in the trial. Overall, only 25% (n=36) of patients were treatment experienced. The SVR12 in the genotype 2-infected patients was 100% (31/31). Overall, 91% percent (133/146) of patients had a Child-Pugh score of 5, and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. This is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

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

Last update: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 2 Patients With or Without Compensated Cirrhosis

Recommended regimens listed by evidence level for:

Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIb, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimen for:

Sofosbuvir + NS5A-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, B

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

Recommended Regimens

Sofosbuvir/Velpatasvir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. Among patients with genotype 2 infection, 97% (32/33) who received 12 weeks of sofosbuvir/velpatasvir achieved SVR12. Overall for the study, the sofosbuvir/velpatasvir arm did not meet the prespecified performance goal of > 85% efficacy (prespecified p value 0.025). However, this was primarily driven by treatment failure in patients with genotype 3 or 1a infection. The single genotype 2-infected patient who experienced virologic failure in the sofosbuvir/velpatasvir arm had virologic breakthrough rather than relapse and was the only patient with an NS5B RAS at any time point. The S292T substitution emerged at the time of virologic failure. Diarrhea and nausea were more commonly

reported in the sofosbuvir/velpatasvir/voxilaprevir group.

Glecaprevir/Pibrentasvir

The phase 3, randomized, double-blind, placebo-controlled ENDURANCE-2 study enrolled treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) genotype 2-infected patients without cirrhosis. Participants were treated with 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills or placebo (Asselah, 2018b). Among 202 patients in the glecaprevir/pibrentasvir arm, 30% (61/202) were treatment experienced, of whom 6 had previously received sofosbuvir plus ribavirin ± peginterferon. The overall SVR12 in the intention-to-treat analysis was 99%, and SVR12 was achieved in all 6 patients with a prior sofosbuvir-based treatment failure. The most common adverse events in the glecaprevir/pibrentasvir arm were headache and fatigue.

The phase 3, single arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of glecaprevir/pibrentasvir in patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Treatment-naive and -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) were included in the trial. Overall, only 25% (n=36) of patients were treatment experienced, 11 of which had a history of sofosbuvir failure (although it is unclear how many of these patients had genotype 2 infection). The SVR12 in the genotype 2-infected patients was 100% (31/31) (Forns, 2017).

No sofosbuvir treatment failures were included in the SURVEYOR study, which investigated 8 weeks of therapy in patients with genotype 2 infection without cirrhosis. Thus, this regimen cannot be recommended in this patient population until supported by clinical data (Poordad, 2017).

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-1 evaluated 12 weeks of sofosbuvir/velpatasvir/voxilaprevir compared to placebo among patients with all genotypes who were previously treated with an NS5A inhibitor-containing regimen (including daclatasvir and velpatasvir but not glecaprevir). There were 5 genotype 2 patients and all achieved SVR12 (Bourliere, 2017).

Last update: May 24, 2018

Treatment-Experienced Genotype 3

The following pages include guidance for management of treatment-experienced patients with genotype 3 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis
- DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)[a]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)[a]	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present	12 weeks	IIb, B

[a] Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimen

Sofosbuvir/Velpatasvir

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin (Pianko, 2015).

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir versus 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in patients (any genotype) who were either treatment naive or had a previous peginterferon/ribavirin treatment failure. Eighty-nine genotype 3-infected patients (all without cirrhosis) received the sofosbuvir/velpatasvir regimen and 97% (86/89) achieved SVR12 (Jacobson, 2017). There were no virologic failures. These findings confirm the efficacy of this 12-week regimen in genotype 3-infected patients without cirrhosis.

Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of participants (Nelson, 2015). SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom sofosbuvir/velpatasvir is being considered. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

Alternative Regimens

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-3 study evaluated a 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) in treatment-naive or -experienced (interferon-based therapy or sofosbuvir plus ribavirin), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Treatment-experienced, genotype 3-infected patients without cirrhosis did well with an SVR12 rate of 94% (32/34) (Nelson, 2015).

Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of patients (Nelson, 2015). The SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom daclatasvir plus sofosbuvir is being considered. If the Y93H substitution is identified, a different recommended regimen should be used, or weight-based ribavirin should be added as an alternative option.

Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naive or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Among the 44 treatment-experienced patients without cirrhosis, the SVR rates were 91% (20/22) and 96% (21/22) for 12 weeks and 16 weeks, respectively. All patients who experienced treatment failure had baseline RAS mutations. One patient in the 12-week study arm had an A30K RAS at baseline and a treatment-emergent Y93H RAS at failure resulting in the A30K+Y93H double RAS, which confers 69-fold resistance to glecaprevir/pibrentasvir. This was also true in the single relapse in the 16-week study arm. The second patient with relapse in the 12-week arm had a baseline Y93H RAS, which persisted at the time of failure. The Y93H substitution does not confer high-fold resistance to this regimen (Wyles, 2018).

Based on these data, the appropriate length of therapy is unclear for genotype 3-infected, peginterferon/ribavirin-experienced patients. Until further data are available, a 16-week duration of treatment is recommended as an alternative option, especially if a baseline A30K substitution is present.

Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 infection is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naive patients and 12 weeks in DAA-experienced patients. The 8-week

regimen achieved noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis (Jacobson, 2017). Thus, this regimen is recommended as an alternative option for patients with genotype 3 infection who have evidence of the Y93H RAS at baseline.

In the ASTRAL-3 study, which investigated 12 weeks of sofosbuvir/velpatasvir, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a). Due to the low number of patients with the Y93H mutation in the POLARIS-3 study and the difficult-to-treat nature of treatment-experienced, genotype 3-infected patients, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIb, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Elbasvir/Grazoprevir + Sofosbuvir

The C-ISLE study evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir, with or without ribavirin, for 8 weeks to 16 weeks for treatment-naive or -experienced, genotype 3-infected patients with compensated cirrhosis. One hundred patients were enrolled, including 53 with a history peginterferon/ribavirin failure. Treatment-experienced participants were randomized to 12 weeks of elbasvir/grazoprevir plus sofosbuvir, 12 weeks of elbasvir/grazoprevir plus sofosbuvir and weight-based ribavirin, or 16 weeks of elbasvir/grazoprevir plus sofosbuvir (Foster, 2016b). All 3 arms had 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was high regardless of the presence of baseline RASs, including 3 patients with the Y93H substitution.

Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 infection is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naive patients and 12 weeks in DAA-experienced patients. The 8-week regimen achieved noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis (Jacobson, 2017). Thus, this regimen

is recommended in patients with genotype 3 infection and cirrhosis.

In the ASTRAL-3 study, which investigated 12 weeks of sofosbuvir/velpatasvir, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a). Patients with genotype 3 infection, prior non-DAA treatment failure, and cirrhosis are among the most difficult to treat. For this reason, ribavirin is recommended for all patients receiving sofosbuvir/velpatasvir, making this an alternative regimen. Due to the low number of patients with the Y93H mutation in the POLARIS-3 study, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Alternative Regimens

Sofosbuvir/Velpatasvir + Ribavirin

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. Among those with both compensated cirrhosis and prior treatment, the SVR12 rate was 89% (33/37). The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin (Pianko, 2015).

In the POLARIS-3 study noted previously, the SVR12 rate in the 32 patients with prior peginterferon/ribavirin treatment failure and cirrhosis was 91% (29/32). Although the 2 virologic failures did not have Y93H at baseline, both developed treatment-emergent Y93H mutations (Jacobson, 2017). Based on this finding and analogous to the similar ALLY-3 study, the addition of weight-based ribavirin (if not contraindicated) is recommended for all treatment-experienced, genotype 3-infected patients with compensated cirrhosis when using sofosbuvir/velpatasvir pending additional data. Due to the need for ribavirin, this is recommended as an alternative regimen.

Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naive or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Among the 47 treatment-experienced participants with compensated cirrhosis who were treated for 16 weeks, the SVR rate was 96% (45/47). One of the virologic failures was a relapse and the other was viral breakthrough. The patient with viral breakthrough had low serum DAA levels at week 4 of the study, suggesting poor adherence. The patient with relapse did not have baseline NS3 or NS5A RASs but did have dual NS5A RASs emerge at the time of failure (Wyles, 2018).

Last update: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis

Recommended regimen for:

DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg)	12 weeks	I, A
For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.	12 weeks	IIa, C

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

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir ± Ribavirin

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 3 infection, without cirrhosis or with compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The POLARIS-4 study included treatment-experienced patients who had previously received a DAA regimen but not an NS5A inhibitor. Participants were randomized to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) (54 with genotype 3 infection) or 12 weeks of sofosbuvir/velpatasvir (52 with genotype 3 infection). SVR rates for the genotype 3-infected patients were 96% (52/54) and 85% (44/52), respectively. The 8 patients who experienced a relapse in the sofosbuvir/velpatasvir arm were primarily white males with compensated cirrhosis (7/8) and a high BMI (>25). Although none had baseline Y93H variants, all had emergence of Y93H variants at the time of relapse (Bourliere, 2017).

The POLARIS-1 study included patients who had previously received a regimen containing an NS5A inhibitor. Participants were randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (78 with genotype 3 infection) versus placebo. The SVR12 rate was 95% (74/78) for the genotype 3-infected patients. All 4 patients who experienced a relapse had cirrhosis (Bourliere, 2017). These data support the use of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in all DAA-experienced patients. However, in NS5A inhibitor-experienced genotype 3-infected patients with cirrhosis, the relapse rate is higher and adding weight-based ribavirin is recommended to minimize relapse risk.

Last update: September 21, 2017

Treatment-Experienced Genotype 4

The following pages include guidance for management of treatment-experienced patients with genotype 4 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis
- DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients With or Without Compensated Cirrhosis

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin	16 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). The study included 116 patients with genotype 4 infection. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients (Feld, 2015).

Glecaprevir/Pibrentasvir

The phase 2, open-label, single arm SURVEYOR-II, part 4 study investigated the efficacy of 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose

combination pills in patients with genotype 2, 4, 5, or 6 infection without cirrhosis. Patients were treatment naive or experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Forty-six genotype 4-infected patients accounted for 23% of the study population; only 27 of these patients (13% of the study population) were treatment experienced. The SVR12 was 93%; 3 patients had nonvirologic outcomes, including missed follow-up and study discontinuation. There were no virologic failures but the number of treatment-experienced patients is small (Asselah, 2018b).

Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 infection (Asselah, 2018c). The overall SVR12 rate among treatment-experienced, genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. However, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

Ledipasvir/Sofosbuvir

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study (Kohli, 2015). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 rate of 94% (32/34) in treatment-experienced patients with genotype 4 infection (Asselah, 2018b).

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was an open-label, phase 2b study that included a cohort of 49 noncirrhotic, treatment-experienced patients (peginterferon/ribavirin) with genotype 4 infection who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. Based on intention-to-treat analysis, SVR12 was achieved in 100% of these patients. The regimen was well tolerated with no serious adverse events reported (Hézode, 2015).

The phase 3, open-label, partly randomized AGATE-II trial enrolled genotype 4-infected, treatment-naive or -experienced (interferon-based therapy) patients, without cirrhosis or with compensated cirrhosis. The 100 noncirrhotic participants were treated with 12 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 in this group of patients was 94% (94/100) (Esmat, 2015a).

These data support the use of paritaprevir/ritonavir/ombitasvir plus ribavirin for 12 weeks in treatment-experienced, genotype 4-infected patients. Due to the need for ribavirin resulting in a greater pill burden and adverse events profile, this regimen is an alternative recommendation.

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy	12 weeks	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin[c]	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin	16 weeks	IIa, B
Daily ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). The study included 116 patients with genotype 4 infection. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients and 27 with compensated cirrhosis (Feld, 2015).

Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 infection (Asselah, 2018c). The overall SVR12 rate among treatment-experienced, genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. However, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the nonribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach and is an alternative recommendation.

Glecaprevir/Pibrentasvir

The phase 3, single-arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis (Forns, 2017). Overall, 25% of patients were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). All 16 patients with genotype 4 infection (unknown number with prior treatment experience) achieved SVR.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

The AGATE-I trial randomized 120 treatment-naive or -experienced patients (interferon-based regimens) with genotype 4 infection and compensated cirrhosis to 12 weeks or 16 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a).

The phase 3, open-label, partly randomized AGATE-II trial included a cohort of 60 treatment-naive or -experienced (interferon-based regimens), genotype 4-infected patients with compensated cirrhosis. These participants were randomized to 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rate from the 12-week arm was 97%.

These data support the use of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks in treatment-experienced genotype 4 patients, including those with compensated cirrhosis (Esmat, 2015a). Due to the number of treatment options that exist, including those that do not use ribavirin, this is an alternative rather than a recommended option.

Ledipasvir/Sofosbuvir + Ribavirin

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study (Kohli, 2015). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 rate of 94% (32/34) in treatment-experienced patients with genotype 4

infection (Asselah, 2018b). Due to the small number of patients overall and with cirrhosis, the addition of ribavirin to the 12-week regimen is recommended in patients with cirrhosis (Kohli, 2015). This is an alternative regimen due to the need for ribavirin.

Last update: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients, With or Without Compensated Cirrhosis

Recommended regimen for:

DAA-Experienced (Including NS5A Inhibitors), Genotype 4 Patients, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A

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

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 4 infection, with or without compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The trials included 22 genotype 4-infected patients with a prior treatment failure with an NS5A inhibitor-containing DAA regimen, and 19 genotype 4-infected patients with a prior treatment failure with a DAA regimen not containing an NS5A inhibitor. The study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for 12 weeks in these patients. Overall, 46% of patients in these clinical trials had compensated cirrhosis, although the number of genotype 4-infected patients with cirrhosis was not provided. Among the 22 patients who had a prior treatment failure with an NS5A inhibitor-containing regimen, 91% (20/22) achieved SVR; 1 patient relapsed and another experienced treatment failure for nonvirologic reasons. All patients with a history of treatment failure with a DAA regimen not containing an NS5A inhibitor achieved SVR (19/19, 100%) (Bourliere, 2017).

Last update: September 21, 2017

Treatment-Experienced Genotype 5 or 6

The following pages include guidance for management of treatment-experienced patients with genotype 5 or 6 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis
- DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 5 or 6 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] for patients without cirrhosis	8 weeks	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] for patients with compensated cirrhosis	12 weeks	I, B
Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

A combined analysis of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 8 weeks or 12 weeks among 1,904 patients participating in phase 2 and phase 3 clinical trials included 30 patients with genotype 5 infection and 41 with genotype 6 infection (Puoti, 2017). Approximately 21% to 26% of patients in the overall study had a prior interferon-based treatment failure (DAA failure was excluded); no patients had cirrhosis. SVR among treatment-naive or -experienced, genotype 5-infected participants was 100% (2/2) for those receiving 8 weeks of glecaprevir/pibrentasvir and 100% (28/28) for those receiving 12 weeks of glecaprevir/pibrentasvir. SVR rates among treatment-naive or -experienced, genotype 6-infected participants were 90% (9/10) for those receiving 8 weeks of glecaprevir/pibrentasvir and 100% (31/31) among those receiving 12 weeks of glecaprevir/pibrentasvir. The single treatment failure in the 8-week group was a nonvirologic failure.

Ledipasvir/Sofosbuvir

Ledipasvir has in vitro activity against most genotype 6 subtypes, except 6e (Wong, 2013); (Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in treatment-naive or -experienced patients with genotype 6

infection. Twenty-five patients (92% treatment naive) who were primarily of Asian descent (88%) were infected with different genotype 6 subtypes (n=8 6a; n=6 6e; n=3 6l; n=2 6m; n=3 6p; n=2 6q; n=1 6r). Two patients (8%) had compensated cirrhosis. The SVR12 rate was 96% (24/25). The single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

Similarly, 41 patients with genotype 5 infection were treated with 12 weeks of ledipasvir/sofosbuvir. The group included both treatment-naive and -experienced patients, with and without cirrhosis. The SVR was 93% (38/41) (Abergel, 2016).

Sofosbuvir/Velpatasvir

Velpatasvir has in vitro activity against genotypes 5 and 6. The ASTRAL-1 study included 35 patients with genotype 5 infection and 41 patients with genotype 6 infection. Among those participants, only 11 and 3, respectively, were treatment experienced (Feld, 2015). All genotype 5 and 6, treatment-experienced patients treated with 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) achieved SVR12.

Last update: September 21, 2017

DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis

Recommended regimen for:

DAA-Experienced (Including NS5A Inhibitors), Genotype 5 or 6 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIa, B

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

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

Minimal data are available from phase 3 clinical trials regarding the efficacy of a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) among patients with genotype 5 or 6 infection with a history of treatment failure with a DAA-containing regimen. All 7 patients with genotype 5 or 6 infection (1 genotype 5; 6 genotype 6) participating in the phase 3 POLARIS-1 trial achieved SVR. All participants enrolled in the study had a prior treatment failure with an NS5A inhibitor-containing regimen. Forty-six percent had compensated cirrhosis, although the percentage of patients with genotype 5 or 6 infection with cirrhosis was not provided (Bourliere, 2017).

Last update: September 21, 2017

Management of Unique & Key Populations With HCV Infection

The following pages include guidance for management of patients with HCV in unique and key populations.

- Patients With HIV/HCV Coinfection
- Patients With Decompensated Cirrhosis
- Patients Who Develop Recurrent HCV Infection Post Liver Transplantation
- Patients With Renal Impairment
- Kidney Transplant Patients
- Management of Acute HCV Infection
- HCV in Pregnancy
- HCV in Children

- Key Populations:
  - Identification and Management of HCV in People Who Inject Drugs
  - HCV in Key Populations: Men Who Have Sex With Men
  - HCV Testing and Treatment in Correctional Settings

Last update: May 24, 2018

Patients With HIV/HCV Coinfection

This section provides guidance on the treatment of chronic HCV infection in HIV/HCV-coinfected patients. For individuals with acute HCV infection, please refer to the Acute HCV section. HIV/HCV-coinfected patients suffer from more liver-related morbidity and mortality, nonhepatic organ dysfunction, and overall mortality than HCV-monoinfected patients (Lo Re, 2014); (Chen, 2009). Even in the potent HIV antiretroviral therapy era, HIV infection remains independently associated with advanced liver fibrosis and cirrhosis in patients with HIV/HCV coinfection (Thein, 2008a); (de Ledinghen, 2008); (Fierer, 2013); (Kirk, 2013). As such, treatment of HCV in HIV-infected patients should be a priority for providers, payers, and patients. However, if HCV treatment is delayed for any reason, liver disease progression should be monitored at routine intervals as recommended in the guidance (see When and in Whom to Initiate Therapy, recommendation for repeat liver disease assessment).

Similar to HCV-monoinfected patients, HIV/HCV-coinfected patients cured with peginterferon/ribavirin have lower rates of hepatic decompensation, hepatocellular carcinoma, and liver-related mortality (Berenguer, 2009); (Limketkai, 2012); (Mira, 2013). Uptake of HCV therapy was lower in the HIV/HCV-coinfected population owing to historically lower response rates, patient comorbidities, patient and practitioner perceptions, and adverse events associated with interferon-based therapy (Mehta, 2006a); (Thomas, 2008).

With the availability of HCV direct-acting antivirals (DAAs), efficacy and adverse event rates among those with HIV/HCV coinfection are similar to those observed with HCV monoinfection (Bhattacharya, 2017); (Naggie, 2015); (Sulkowski, 2015); (Wyles, 2015); (Wyles, 2017b) and many prior barriers have diminished. However, treatment of HIV/HCV-coinfected patients requires continued awareness and attention to the complex drug-drug interactions that can occur between DAAs and antiretroviral medications. Drug interactions with DAAs and antiretroviral agents are summarized in the text and tables of this section as well as in the US Department of Health and Human Services HIV treatment guidelines (https://aidsinfo.nih.gov/guidelines). Another resource for screening for drug-drug interactions with DAAs is the University of Liverpool website (www.hep-druginteractions.org).

Risk for Hepatitis B Virus Reactivation

Due to shared modes of transmission, HIV/HCV-coinfected patients are also at risk for hepatitis B virus (HBV) infection. Reactivation of HBV has been reported in patients starting DAA HCV therapy who are not on active HBV agents. Consistent with general recommendations for the assessment of both HIV- and HCV-infected patients, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc testing. HIV-infected patients who have evidence of HBV infection should be on antiretroviral agents with activity against HBV, preferably tenofovir disoproxil fumarate or tenofovir alafenamide. For patients who are only anti-HBc positive and not on tenofovir-based antiretroviral therapy, subsequent monitoring for HBV reactivation should be as detailed in the Monitoring section of the guidance.

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications

RECOMMENDED	RATING
Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.	I, A
Daclatasvir when used in combination with other antivirals Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (decrease to 30 mg/d), cobicistat-boosted atazanavir (decrease to 30 mg/d), elvitegravir/cobicistat (decrease to 30 mg/d), and efavirenz or etravirine (increase to 90 mg/d).	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.	IIa, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a] Glecaprevir/pibrentasvir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir. Given the limited data on the safety of elvitegravir/cobicistat with glecaprevir/pibrentasvir, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients.	IIa, B
Simeprevir used in combination with other antivirals Simeprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, dolutegravir, rilpivirine, and tenofovir.	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) Sofosbuvir/velpatasvir can be used with most antiretrovirals, but not efavirenz, etravirine, or nevirapine. Because velpatasvir has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. Due to limited experience with this drug combination, renal monitoring is recommended during the dosing period. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) Ledipasvir/sofosbuvir can be used with most antiretrovirals. Because this therapy increases tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min.	IIa, C

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications	
The absolute tenofovir levels are highest, and may exceed exposures for which there are established renal safety data, when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens. Due to lack of sufficient safety data with this drug combination, consideration should be given to changing the antiretroviral regimen. If the combination is used, renal monitoring is recommended during the dosing period. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	
For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.	IIa, C
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which they do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir. The dose of ritonavir used for boosting atazanavir should be held when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. Atazanavir (300 mg) should be administered at the same time as the fixed-dose HCV combination.	IIa, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) Sofosbuvir/velpatasvir/voxilaprevir should be used with antiretroviral drugs with which they do not have substantial interactions: dolutegravir, emtricitabine, enfuvirtide, lamivudine, rilpivirine, and raltegravir. Given increases in voxilaprevir AUC with darunavir/ritonavir or elvitegravir/cobicistat coadministration and lack of clinical safety data, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Because this therapy has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. In patients receiving sofosbuvir/velpatasvir/voxilaprevir and tenofovir disoproxil fumarate concomitantly, renal monitoring is recommended during the dosing period.	IIa, B
[a] This is a 3 tablet coformulation. Please refer to the prescribing information.	

Regimens Not Recommended for Patients with HIV/HCV Coinfection	
NOT RECOMMENDED	RATING
Antiretroviral treatment interruption to allow HCV therapy is **not** recommended.	III, A
Elbasvir/grazoprevir should **not** be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B
Glecaprevir/pibrentasvir should **not** be used with atazanavir, ritonavir-containing antiretroviral regimens, efavirenz, or etravirine.	III, B
Sofosbuvir/velpatasvir should **not** be used with efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir/velpatasvir/voxilaprevir should **not** be used with ritonavir-boosted atazanavir, efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir-based regimens should **not** be used with tipranavir.	III, B
Paritaprevir/ritonavir/ombitasvir plus dasabuvir should **not** be used with darunavir, efavirenz, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, etravirine, nevirapine, cobicistat, or rilpivirine.	III, B
Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should **not** be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.	III, B
Ribavirin should **not** be used with didanosine, stavudine, or zidovudine.	III, B
Simeprevir should **not** be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B

Clinical Trial, Pharmacokinetic, and Drug Interaction Data

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

Antiretroviral drug switches may be performed to allow compatibility with DAAs with the goal of maintaining HIV suppression without compromising future options. Considerations include prior treatment history, responses to antiretroviral therapy, resistance profiles, and drug tolerance (Gunthard, 2014); (DHHS, 2017). Treatment interruption in HIV/HCV-coinfected individuals is not recommended as it is associated with increased cardiovascular events (SMART, 2006) and increased rates of fibrosis progression and liver-related events (Tedaldi, 2008); (Thorpe, 2011). The availability of multiple effective HCV DAA and HIV antiretroviral regimens makes it possible for all HIV/HCV-coinfected patients to safely and successfully receive HCV treatment. Switching an optimized antiretroviral regimen carries risks, including adverse effects and HIV viral breakthrough (Eron, 2010). HIV viral breakthrough is a particular concern for those with substantial antiretroviral experience or known resistance to antiretroviral drugs. If necessary, antiretroviral therapy switches should be done in close collaboration with the treating HIV provider prior to HCV treatment initiation.

Although fewer HIV/HCV-coinfected patients than HCV-monoinfected patients have been treated in DAA trials, efficacy rates to date have been remarkably similar between the groups (Sulkowski, 2013); (Sulkowski, 2014); (Dieterich, 2014b); (Rodriguez-Torres, 2015); (Osinusi, 2015); (Sulkowski, 2015); (Dieterich, 2015); (Naggie, 2015); (Wyles, 2015). Thus, results from HCV monoinfection studies largely justify the recommendations for HIV/HCV coinfection (discussed in the Initial Treatment and Retreatment sections). Discussion specific to studies of HIV/HCV coinfection is included here.

Daclatasvir + Sofosbuvir

The phase 3 ALLY-2 study evaluated the 12-week regimen of daclatasvir plus sofosbuvir in patients with HIV/HCV coinfection with genotype 1, 2, 3, or 4 (Wyles, 2015). This open-label clinical trial enrolled both treatment-naive (n=151) and -experienced (n=52) HIV/HCV-coinfected patients. Treatment-naive patients were randomly assigned (2:1), with stratification by cirrhosis status and genotype, to receive 12 weeks or 8 weeks of once-daily daclatasvir (60 mg dose adjusted based on antiretroviral regimen) and sofosbuvir (400 mg). Treatment-experienced patients received daclatasvir and sofosbuvir for 12 weeks. Genotype distribution was 83%, 9%, 6%, and 2% of patients, respectively, for genotype 1, 2, 3, and 4 HCV infection; 14% of all participants had compensated cirrhosis. Antiretroviral drugs allowed were ritonavir-boosted darunavir, atazanavir, or lopinavir, efavirenz, nevirapine, rilpivirine, raltegravir, and dolutegravir.

The combination of daclatasvir and sofosbuvir once daily for 12 weeks achieved SVR12 in 97% of HIV/HCV-coinfected patients with genotype 1, 2, 3, or 4 infection, and was safe and well tolerated. Ninety-seven percent of treatment-naive patients and 98% of treatment-experienced patients achieved SVR. However, among patients who received 8 weeks of therapy, only 76% of patients achieved SVR. Factors associated with relapse in this patient group included high baseline HCV RNA level (>2 million IU/mL; 69%), concomitant use of a boosted darunavir-based antiretroviral regimen with 30 mg of daclatasvir (67%), and the presence of compensated cirrhosis (60%).

Pharmacology and Drug Interaction Data

Daclatasvir is metabolized by cytochrome P450 (CYP) 3A4 and is therefore susceptible to drug interactions with potent inducers and inhibitors of this enzyme (Eley, 2014). The dose of daclatasvir should be increased from 60 mg to 90 mg when used with efavirenz, etravirine, or nevirapine (Bifano, 2013). The dose of daclatasvir should be decreased from 60 mg to 30 mg when used with ritonavir-boosted atazanavir, cobicistat-boosted atazanavir, or elvitegravir/cobicistat (Smolders, 2017). A daclatasvir dose of 60 mg should be used with ritonavir-boosted darunavir and ritonavir-boosted lopinavir (Gandhi, 2015).

Elbasvir/Grazoprevir

The safety, tolerability, and efficacy of the second-generation NS3/4A serine protease inhibitor grazoprevir (MK-5172) plus the NS5A inhibitor elbasvir (MK-8742) were assessed in patients with HIV/HCV coinfection in the C-EDGE COINFECTION study. C-EDGE COINFECTION was a phase 3, nonrandomized, open-label, single-arm study in which treatment-naive patients with genotype 1, 4, or 6 infection and HIV coinfection, with or without compensated cirrhosis, were enrolled in Europe, the US, and Australia (Rockstroh, 2015). All patients were either naive to treatment with any antiretroviral therapy (ART) with a CD4 cell count >500/mm^3 (n=7), or stable on current ART for at least 8 weeks with a CD4 cell count >200/mm^3 (n=211) and undetectable HIV RNA. All 218 enrolled patients received the once-daily fixed-dose combination of elbasvir (50 mg) plus grazoprevir (100 mg) for 12 weeks. All 218 patients completed follow-up at week 12. The median baseline CD4 cell count was 568 (424-626)/mm^3. Limited antiretrovirals were allowed, specifically a nucleoside/nucleotide backbone of abacavir (21.6%) versus tenofovir (75.2%), in combination with raltegravir (52%), dolutegravir (27%), or rilpivirine (17%).

SVR12 was achieved by 96% (210/218) of patients (95% CI, 92.9-98.4). One patient did not achieve SVR12 for a nonvirologic reason and 7 patients without cirrhosis relapsed (2 subsequently confirmed as reinfections, highlighting the requirement of continued harm-reduction strategies after SVR). Thirty-five patients with compensated cirrhosis achieved SVR12. The most common adverse events were fatigue (13%; 29), headache (12%; 27), and nausea (9%; 20). No patient discontinued treatment because of an adverse event. Three out of 6 patients who relapsed before SVR12 had NS3 and/or NS5A resistance-associated substitutions (RASs) while the others had wild type virus at the time of relapse. Two patients receiving ART had transient HIV viremia but subsequently returned to undetectable levels without a change in ART. No significant changes were observed with CD4 cell counts or new opportunistic infections. Elbasvir/grazoprevir without ribavirin seems to be effective and well tolerated among patients coinfected with HIV, with or without compensated cirrhosis. These data are consistent with previous trials of this regimen in the monoinfected population (Zeuzem, 2017).

Pharmacology and Drug Interaction Data

Elbasvir is a substrate for CYP3A4 and the efflux transporter P-glycoprotein (P-gp). Grazoprevir is a substrate for CYP3A4, P-gp, and the liver uptake transporter OATP1B1. Moderate and strong CYP3A and P-gp inducers (including efavirenz) are not recommended for coadministration with elbasvir/grazoprevir. OATP1B1 inhibitors are also not recommended with grazoprevir.

Elbasvir/grazoprevir is not compatible with any ritonavir- or cobicistat-boosted HIV protease inhibitor, elvitegravir/cobicistat, efavirenz, or etravirine (Feng, 2016).

Glecaprevir/Pibrentasvir

The safety and efficacy of glecaprevir (ABT-493), a pangenotypic NS3/4A protease inhibitor, coformulated with pibrentasvir (ABT-530), a pangenotypic NS5A inhibitor, were evaluated in the phase 3, multicenter EXPEDITION-2 study (Rockstroh, 2017). This study evaluated 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in 137 HIV/HCV-coinfected adults without cirrhosis and 12 weeks of glecaprevir/pibrentasvir in 16 HIV/HCV-coinfected patients with compensated cirrhosis. Treatment-naive and -experienced patients with genotype 1, 2, 3, 4, or 6 infection were enrolled. Patients were either antiretroviral naive with a CD4 cell count ≥500/mm^3, or on a stable ART regimen for at least 8 weeks with a CD4 cell count ≥200/mm^3. ART drugs included raltegravir, dolutegravir, rilpivirine, tenofovir disoproxil fumarate, tenofovir alafenamide, abacavir, emtricitabine, and lamivudine. One patient received elvitegravir/cobicistat. Overall SVR12 was 98% (136/136 among those without cirrhosis on the 8-week regimen, and 14/15 in those with compensated cirrhosis on the 12-week regimen). Four serious adverse events were reported, none of which were DAA related. One of these led to treatment discontinuation.

Pharmacology and Drug Interaction Data

Glecaprevir and pibrentasvir area under the curve (AUC) are increased roughly 3-fold and 1.57-fold, respectively, with tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat (Kosloski, 2017). Only 1 patient received this combination in the EXPEDITION-2 study. Although the increases in AUC of glecaprevir and pibrentasvir when coadministered with elvitegravir/cobicistat are not considered clinically relevant by the manufacturer or the US Food and Drug Administration (FDA), due to lack of sufficient clinical safety data, close monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Consider liver enzyme testing every 4 weeks. Ritonavir-boosted protease inhibitors are not recommended with glecaprevir/pibrentasvir.

Glecaprevir and pibrentasvir AUCs are reduced 25% and 27%, respectively, with abacavir/lamivudine/dolutegravir. These reductions are unlikely to have clinical relevance. Raltegravir and rilpivirine AUCs are increased 47% and 84%, respectively, with glecaprevir/pibrentasvir (Oberoi, 2016). These interactions do not require dose adjustment. Forty-five and 32 individuals received raltegravir or rilpivirine, respectively, in the EXPEDITION-2 study.

Glecaprevir absorption is pH dependent and glecaprevir exposures are reduced approximately 50% with 40 mg of omeprazole daily.

Ledipasvir/Sofosbuvir

The safety and efficacy of 12 weeks of ledipasvir/sofosbuvir were evaluated in the phase 2, single-center, open-label ERADICATE trial, which included 50 HIV/HCV-coinfected patients with genotype 1 infection who were treatment naive without cirrhosis (Osinusi, 2015). Thirteen patients were not receiving antiretroviral therapy and 37 patients were on protocol-allowed medications (tenofovir, emtricitabine, rilpivirine, raltegravir, and efavirenz). Although the inclusion criteria for patients receiving antiretroviral therapy allowed CD4 cell counts >100/mm^3, the median CD4 cell count was 576/mm^3. Overall, 98% achieved SVR12 (13/13 in the treatment-naive arm and 36/37 in the treatment-experienced arm). There were no deaths, discontinuations, or clinically significant, serious adverse events. Renal function was monitored frequently

during this trial and after administration of study drugs using a battery of tests (serum creatinine, eGFR, urinary beta-2 microglobulin, and urine protein and glucose). No clinically significant changes in these parameters or renal toxicity were observed.

A larger study, ION-4, reported similar outcomes with ledipasvir/sofosbuvir (Naggie, 2015). A total of 335 HCV treatment-naive and -experienced HIV/HCV-coinfected patients were enrolled in the study and received ledipasvir/sofosbuvir once daily for 12 weeks. Patients received tenofovir disoproxil fumarate and emtricitabine with raltegravir (44%), efavirenz (48%), or rilpivirine (9%). Genotypes included were 1a (75%), 1b (23%), and 4 (2%). Twenty percent of patients had compensated cirrhosis, 34% were black, and 55% had not responded to prior HCV treatment. The overall SVR12 rate was 96% (321/335). Two patients had on-treatment virologic failure judged to be a result of nonadherence, 10 had virologic relapse after discontinuing treatment, 1 died from endocarditis associated with injection drug use, and 1 was lost to follow-up. SVR12 rates were 94% (63/67) among patients with compensated cirrhosis and 97% (179/185) among treatment-experienced patients. No patients discontinued the study drugs because of an adverse event. Although all patients had an eGFR >60 mL/min at study entry, drug interaction studies suggested that patients receiving tenofovir disoproxil fumarate could have increased tenofovir levels. There were 4 patients in whom serum creatinine level rose to ≥0.4 mg/dL. Two remained on tenofovir disoproxil fumarate, 1 had the tenofovir disoproxil fumarate dose reduced, and the other stopped taking tenofovir disoproxil fumarate.

Neither the ERADICATE nor the ION-4 study investigators reported clinically significant changes in CD4 cell counts or HIV RNA levels in the study participants. Thus, these data suggest that 12 weeks of ledipasvir/sofosbuvir is a safe and effective regimen for HIV/HCV-coinfected patients with genotype 1 infection taking selected antiretroviral therapy (Osinusi, 2015); (Naggie, 2015). There are limited data regarding an 8-week course of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients (Ingiliz, 2016). Additionally, clinical trial data of daclatasvir (an NS5A inhibitor similar to ledipasvir) plus sofosbuvir in HIV/HCV-coinfected patients demonstrated a lower SVR rate (76%) with 8 weeks of treatment compared to 12 weeks of therapy (97%). Therefore, a shortened treatment course for HIV/HCV-coinfected persons cannot be recommended at this time.

Pharmacology and Drug Interaction Data

Drug interaction studies of ledipasvir (with or without sofosbuvir) with antiretroviral drugs in uninfected persons did not identify clinically significant interactions with abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, or rilpivirine (German, 2014); (Garrison, 2015). Interactions with maraviroc and enfuvirtide are not expected based on their pharmacologic profiles. Ledipasvir AUC is decreased by 34% when coadministered with efavirenz-containing regimens and increased by 96% when coadministered with ritonavir-boosted atazanavir (German, 2014). No dose adjustments of ledipasvir are recommended to account for these interactions.

Ledipasvir absorption is pH dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Ledipasvir/sofosbuvir increases tenofovir levels when given as tenofovir disoproxil fumarate, which may increase the risk of tenofovir-associated renal toxicity. This combination should be avoided in patients with an eGFR <60 mL/min. With the addition of ledipasvir/sofosbuvir, tenofovir levels (when given as tenofovir disoproxil fumarate) are increased with efavirenz, rilpivirine (German, 2014), dolutegravir, ritonavir-boosted atazanavir, and ritonavir-boosted darunavir (German, 2015). The absolute tenofovir levels are highest, and may exceed exposures for which there are established renal safety data, when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens. Due to lack of sufficient safety data with this drug combination, consideration should be given to changing the antiretroviral regimen. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.

In patients with an eGFR <60 mL/min who are taking tenofovir disoproxil fumarate with ledipasvir/sofosbuvir, renal parameters should be checked at baseline and at the end of treatment. Baseline parameters should include measuring creatinine level, electrolytes (including phosphorus), and urinary protein and glucose, according to recent guidelines for the management of chronic kidney disease in those with HIV, which include indications for nephrology consultation (Lucas, 2014). Changing antiretroviral therapy may be considered for those at high risk for renal toxicity—especially those with an eGFR between 30 mL/min and 60 mL/min or who have preexisting evidence of Fanconi syndrome, and particularly

those taking tenofovir disoproxil fumarate and a ritonavir- or cobicistat-containing regimen. Tenofovir disoproxil fumarate should also be properly dosed and adjusted for eGFR at baseline and while on therapy (Lucas, 2014).

Although there is an absence of data at this time on the renal safety of tenofovir when given as tenofovir alafenamide with ledipasvir/sofosbuvir, a study of tenofovir pharmacokinetics in healthy volunteers receiving the combination of tenofovir alafenamide, emtricitabine, and cobicistat-boosted elvitegravir with ledipasvir/sofosbuvir found that tenofovir levels were only 20% of the typical tenofovir exposures seen with tenofovir disoproxil fumarate (Garrison, 2015). Based on these pharmacokinetic data in healthy volunteers, tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients on ritonavir- or cobicistat-containing regimens.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

Paritaprevir/ritonavir/ombitasvir plus dasabuvir was approved by the FDA for use in genotype 1a and 1b infection because of its efficacy and safety in treatment-naive patients and peginterferon/ribavirin treatment-experienced patients, with or without compensated cirrhosis. Available information about response rates with this regimen in HIV/HCV-coinfected patients comes from the first part of the phase 2 TURQUOISE-1 study. In this study, treatment-naive (n=42) and -experienced (n=21) patients were randomly assigned to 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and weight-based ribavirin (100 mg [<75 kg] to 1200 mg [≥75 kg]). Of the 63 study participants, 12 had compensated cirrhosis, 56 had genotype 1a infection, and 7 had genotype 1b infection. Two study-permitted antiretroviral regimens were chosen based on pharmacokinetic data from uninfected volunteers; 35 patients entered taking tenofovir disoproxil fumarate and emtricitabine with raltegravir, and 28 patients entered taking tenofovir disoproxil fumarate and emtricitabine with ritonavir-boosted atazanavir (with the ritonavir coming from the HCV regimen during the time of coadministration). Of the 31 patients who received 12 weeks of paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin, 93.5% (29/31) achieved SVR12, 1 relapsed, and 1 withdrew consent from study participation. Among the 32 patients in the 24-week arm, 90.6% (29/32) achieved SVR12, 1 experienced viral breakthrough, and 2 had apparent HCV reinfection. No treatment-related serious adverse events occurred, and no patients discontinued treatment because of medication intolerance (Sulkowski, 2015).

Pharmacology and Drug Interaction Data

Paritaprevir is an inhibitor of the hepatic uptake transporter OATP1B1. Ritonavir is coformulated with paritaprevir and ombitasvir to improve the pharmacokinetics of paritaprevir. As ritonavir has anti-HIV activity, HIV/HCV-coinfected patients should have achieved HIV RNA suppression with an ART regimen prior to initiation of this DAA therapy. Those not taking antiretroviral therapy should not receive this fixed-dose combination due to the potential for low-dose ritonavir to select for HIV protease-inhibitor resistance.

Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir are metabolized by and inhibitors of CYP enzymes (3A4 and 2C8), P-gp, BCRP, and OATP1B1. Studies of uninfected volunteers did not reveal notable pharmacologic interactions with paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) plus dasabuvir (250 mg), or tenofovir disoproxil fumarate and emtricitabine (when tested separately from other fixed-dose combinations), raltegravir (Menon, 2015), abacavir, lamivudine, or dolutegravir (Khatri, 2015). In uninfected volunteers, when paritaprevir/ritonavir/ombitasvir plus dasabuvir was combined with efavirenz, emtricitabine, and tenofovir disoproxil fumarate, clinically significant gastrointestinal and neurologic adverse events occurred, coincident with elevations of alanine aminotransferase levels. When paritaprevir/ritonavir/ombitasvir plus dasabuvir was combined with rilpivirine, exposures to rilpivirine were substantially increased. Therefore, rilpivirine and efavirenz should not be used with paritaprevir/ritonavir/ombitasvir plus dasabuvir.

Because ritonavir is a component of the fixed-dose combination of paritaprevir and ombitasvir, the total daily dose of ritonavir must be carefully considered when using paritaprevir/ritonavir/ombitasvir plus dasabuvir with ritonavir-boosted HIV protease inhibitors. Coadministration with ritonavir-boosted lopinavir would result in a 300 mg daily dose of ritonavir, a dose associated with substantial gastrointestinal adverse effects; this combination is not recommended. In uninfected individuals, darunavir troughs are reduced with paritaprevir/ritonavir/ombitasvir plus dasabuvir. Thus, paritaprevir/ritonavir/ombitasvir plus dasabuvir should not be used with ritonavir-boosted darunavir.

Paritaprevir/ritonavir/ombitasvir plus dasabuvir can be given with atazanavir but the separate ritonavir-boosting tablet should be held during paritaprevir/ritonavir/ombitasvir plus dasabuvir therapy, and atazanavir (300 mg) should be administered at the same time as the fixed-dose combination of ritonavir-boosted paritaprevir and ombitasvir. Paritaprevir levels are increased 1.5- to 3-fold with atazanavir but no dose adjustment of paritaprevir is recommended (Khatri, 2016). Inhibition of OATP1B1 by paritaprevir/ritonavir/ombitasvir plus dasabuvir increases indirect bilirubin concentrations and this effect may be attenuated in individuals taking atazanavir (Eron, 2014).

Simeprevir + Sofosbuvir

The combination of simeprevir plus sofosbuvir, with or without ribavirin, has been studied in the phase 2 COSMOS trial in patients with HCV monoinfection (Lawitz, 2014b). This study is the main basis for the recommendation supporting use of this combination for genotype 1a or 1b monoinfection. Simeprevir plus sofosbuvir has been used anecdotally in patients with HIV/HCV coinfection, with a recent report of achieving SVR in 92% (11/12) of patients (Del Bello, 2016). Despite the dearth of study data, this regimen may be considered for the treatment of genotype 1 infection in patients with HIV/HCV coinfection who are receiving an antiretroviral therapy regimen that may be coadministered with simeprevir plus sofosbuvir.

Similarly, few data exist for the combination of sofosbuvir plus simeprevir for the retreatment of HCV infection in HIV/HCV-coinfected patients. However, preliminary results obtained for HCV-monoinfected patients, including those with prior treatment failure and advanced fibrosis, support the expectation that this regimen will be highly effective in HIV/HCV-coinfected patients receiving compatible antiretroviral therapy (see Retreatment section) (Lawitz, 2014b).

Pharmacology and Drug Interaction Data

Simeprevir is metabolized primarily by CYP3A4 and is therefore susceptible to drug interactions with inhibitors and inducers of this enzyme. Simeprevir is also an inhibitor of OATP1B1 and P-gp. Drug interaction studies with antiretroviral drugs in HIV-uninfected volunteers suggest no substantial interactions with tenofovir, rilpivirine, dolutegravir, or raltegravir. However, simeprevir concentrations were substantially decreased when dosed with efavirenz, and substantially increased when dosed with ritonavir-boosted darunavir (MacBrayne, 2017). Use with efavirenz, etravirine, cobicistat, or boosted HIV protease inhibitors is not recommended (Ouwerkerk-Mahadevan, 2016).

Sofosbuvir/Velpatasvir

The safety and efficacy of 12 weeks of sofosbuvir/velpatasvir were evaluated in a phase 3 study among 106 antiretroviral-controlled, HIV/HCV-coinfected patients (Wyles, 2016). Patients with genotype 1, 2, 3, or 4 infection were included; 18% (19/106) had compensated cirrhosis. HIV was controlled on ART including non-nucleoside reverse-transcriptase inhibitor- (rilpivirine), integrase inhibitor- (raltegravir or elvitegravir/cobicistat), or ritonavir-boosted protease inhibitor- (atazanavir, lopinavir, or darunavir) based regimens with either tenofovir/emtricitabine or abacavir/lamivudine. Fifty-three percent (56/106) of participants were on tenofovir disoproxil fumarate with a pharmacologic boosting agent (either ritonavir or cobicistat). Neither efavirenz nor etravirine were allowed in this study as concomitant dosing with sofosbuvir/velpatasvir in healthy volunteers resulted in clinically significant decreases in velpatasvir exposure. SVR12 was 95% with 2 relapses, both occurring in genotype 1a-infected patients. Similar results were noted in patients with compensated cirrhosis and in those with baseline NS5A RASs (n=12 at 15% threshold; SVR12=100%). There were no clinically significant changes in serum creatinine or eGFR, and no patients required a change in their antiretroviral therapy during the study period.

In general, few HIV/HCV-coinfected patients with compensated cirrhosis have been included in clinical trials of DAAs, and no data are available regarding HIV/HCV-coinfected patients with renal insufficiency or who have undergone solid organ transplantation. Despite a lack of data, it is highly likely that response rates are similar to those of HCV-monoinfected patients, as no study to date in the DAA era has showed a lower efficacy for HIV/HCV-coinfected patients. Therefore, the respective guidance from these sections should be followed if treatment is otherwise warranted, with consideration of drug interactions.

Pharmacology and Drug Interaction Data

Velpatasvir is available only in a fixed-dose combination tablet with sofosbuvir. Velpatasvir is metabolized by CYP3A4, CYP2C8, and CYP2B6. It does not appear to inhibit or induce any CYP enzymes. Velpatasvir is a substrate for P-gp and BCRP, and inhibits P-gp, BCRP, and OATP1B1/1B3 but does not induce any transporters.

Velpatasvir absorption is pH dependent. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Drug interaction studies with sofosbuvir/velpatasvir have been performed in HIV and HCV seronegative volunteers. As with ledipasvir/sofosbuvir, tenofovir exposures are increased, which may be problematic for individuals with an eGFR <60 mL/min or in those receiving ritonavir- or cobicistat-containing antiretroviral therapy with tenofovir disoproxil fumarate. Fifty-six HIV/HCV-coinfected individuals receiving the combination of tenofovir disoproxil fumarate with ritonavir- or cobicistat-containing antiretroviral therapy were treated with sofosbuvir/velpatasvir in the ASTRAL-5 study with no difference in median creatinine clearance before and after sofosbuvir/velpatasvir treatment (but poor renal function was an exclusion for this study) (Wyles, 2017b). In individuals with an eGFR <60 mL/min, consider use of tenofovir alafenamide in place of tenofovir disoproxil fumarate in those requiring ritonavir- or cobicistat-containing antiretroviral therapy. If the combination of tenofovir disoproxil fumarate with a ritonavir- or cobicistat-containing antiretroviral therapy is required in patients with an eGFR <60 mL/min, renal parameters should be checked at baseline and regularly thereafter while on sofosbuvir/velpatasvir.

Velpatasvir exposures are significantly reduced with efavirenz and this combination is not recommended. Etravirine has not been studied with sofosbuvir/velpatasvir and is also not recommended. Indirect bilirubin level increases have been reported when sofosbuvir/velpatasvir was used in patients on atazanavir/ritonavir. These changes are not considered clinically significant.

Based on data from healthy volunteers, tenofovir pharmacokinetics are lower with tenofovir alafenamide relative to tenofovir disoproxil fumarate. Thus, tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy. However, there are no safety data for this combination in HIV/HCV-coinfected patients.

Sofosbuvir/Velpatasvir/Voxilaprevir

The data supporting use of sofosbuvir/velpatasvir/voxilaprevir are described in the Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections of the guidance. This regimen has not been studied in HIV/HCV-coinfected patients. Despite a lack of data, it is highly likely that response rates in HIV/HCV-coinfected patients will be similar to those of HCV-monoinfected patients, as no study to date in the DAA era has shown a lower efficacy for HIV/HCV-coinfected patients. Therefore, the respective guidance from the aforementioned treatment and retreatment sections of the guidance should be followed, with consideration of drug-drug interactions.

Pharmacology and Drug Interaction Data

Voxilaprevir is a substrate for P-gp, OATP, BCRP, CYP3A, CYP1A2, and CYP2C8. Voxilaprevir inhibits OATP, P-gp, and BCRP. Voxilaprevir AUC is increased 331% with ritonavir-boosted atazanavir and this combination is not recommended (Garrison, 2017). Voxilaprevir AUC is increased 171% with tenofovir alafenamide/emtricitabine/elvitegravir/cobicistat, and 143% with tenofovir disoproxil fumarate/emtricitabine and ritonavir-boosted darunavir. Although these increases in voxilaprevir AUC were not deemed clinically relevant by the manufacturer or the FDA, due to lack of clinical safety data, close monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Consider liver enzyme testing every 4 weeks.

Tenofovir concentrations are increased with sofosbuvir/velpatasvir/voxilaprevir when given as tenofovir disoproxil fumarate (Garrison, 2017). In individuals with an eGFR <60 mL/min, consider use of tenofovir alafenamide in place of

tenofovir disoproxil fumarate in those requiring ritonavir- or cobicistat-containing antiretroviral therapy. No substantial interactions were observed with dolutegravir, emtricitabine, raltegravir, or rilpivirine.

Velpatasvir absorption is pH dependent. Velpatasvir AUC is reduced approximately 50% when given with omeprazole 20 mg daily as part of the fixed-dose sofosbuvir/velpatasvir/voxilaprevir combination. Refer to product labeling for guidance on temporal separation and dosing of gastric acid modifying agents.

Table 1.
Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Recommended Regimens
Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and pink indicates the combination should be avoided.

	Ledipasvir/ Sofosbuvir (LDV/SOF)	**Sofosbuvir/ Velpatasvir (SOF/VEL)**	**Elbasvir/ Grazoprevir (ELB/GRZ)**	**Glecaprevir/ Pibrentasvir (GLE/PIB)**	**Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)**
Ritonavir-boosted atazanavir (ATZ)	▲ LDV ▲ ATZ[a]	▲ VEL ▲ ATZ[a]	▲ ELB ▲ GRZ ▲ ATZ	▲ GLE ▲ PIB ▲ ATZ	▲ VOX ▲ ATZ
Ritonavir-boosted darunavir (DRV)	▲ LDV ◀▶ DRV[a]	◀▶ VEL ◀▶ DRV[a]	▲ ELB ▲ GRZ ◀▶ DRV	▲ GLE ◀▶ PIB ▲ DRV	▲ VOX ▼ DRV
Ritonavir-boosted lopinavir (LPV)	ND[a]	◀▶ VEL ◀▶ LPV[a]	▲ ELB ▲ GRZ ◀▶ LPV	▲ GLE ▲ PIB ▲ LPV	ND
Ritonavir-boosted tipranavir (TPV/r)	ND	ND	ND	ND	ND
Efavirenz (EFV)	▼ LDV ▼ EFV[a]	▼ VEL ▼ EFV	▼ ELB ▼ GRZ ▼ EFV	ND	ND
Rilpivirine (RPV)	◀▶ LDV ◀▶ RPV	◀▶ VEL ◀▶ RPV	◀▶ ELB ◀▶ GRZ ◀▶ RPV	◀▶ GLE ◀▶ PIB ▲ RPV	◀▶ VOX ▼ RPV
Etravirine (ETV)	ND	ND	ND	ND	ND
Raltegravir (RAL)	◀▶ LDV ◀▶ RAL	◀▶ VEL ◀▶ RAL	◀▶ ELB ◀▶ GRZ ▲ RAL	◀▶ GLE ◀▶ PIB ▲ RAL	ND
Cobicistat-boosted elvitegravir (COB)	▲ LDV ▲ COB[a]	▲ VEL ▲ COB[a]	▲ ELB ▲ GRZ ▲ COB	▲ GLE ▲ PIB ▲ COB	▲ VOX ▲ COB[a]
Dolutegravir (DTG)	◀▶ LDV ◀▶ DTG	◀▶ VEL ◀▶ DTG	◀▶ ELB ◀▶ GRZ ▲ DTG	▼ GLE ▼ PIB ▲ DTG	ND
Tenofovir	▼ LDV	ND	ND	ND	◀▶ VOX

	Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Alafenamide (TAF)/ Emtricitabine (FTC)/ Bictegravir (BIC)	◀▶ BIC				▲ BIC
Maraviroc (MVC)	ND	ND	ND	ND	ND
Tenofovir (TFV) disoproxil fumarate	◀▶ LDV ▲ TFV[c]	◀▶ VEL ▲ TFV[b]	◀▶ ELB ◀▶ GRZ ▲ TFV	▲ TFV	▲ TFV[b]
Tenofovir (TFV) alafenamide	◀▶ LDV ▲ TFV[d]	◀▶ VEL ▲ TFV[d]	ND	◀▶ TFV	▲ TFV[b]

ND, No data
[a] Caution only with tenofovir disoproxil fumarate
[b] Increase in tenofovir depends on which additional concomitant antiretroviral agents are administered.
[c] Avoid tenofovir disoproxil fumarate in patients with an eGFR <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens.
[d] Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

Table 2.
Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Alternative Regimens
Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and pink indicates the combination should be avoided.

	Simeprevir/ Sofosbuvir (SMV/SOF)	Daclatasvir/ Sofosbuvir (DCV/SOF)	Paritaprevir/ Ritonavir/ Ombitasvir + Dasabuvir (PrOD)	Paritaprevir/ Ritonavir/ Ombitasvir (PrO)
Ritonavir-boosted atazanavir (ATZ)	ND	▲ DCV[a]	▲ PRV ▲ ATZ	▲ PRV ◀▶ ATZ
Ritonavir-boosted darunavir (DRV)	▲ SMV ◀▶ DRV	▲ DCV ◀▶ DRV	▼▲ PRV ▼ DRV	▲ PRV ◀▶ DRV
Ritonavir-boosted lopinavir (LPV)	ND	▲ DCV ◀▶ LPV	▲ PRV ◀▶ LPV	▲ PRV ◀▶ LPV
Ritonavir-boosted tipranavir (TPV/r)	ND	ND	ND	ND
Efavirenz (EFV)	▼ SMV ◀▶ EFV	▼ DCV[b]	NPD[c]	ND
Rilpivirine (RPV)	◀▶ SMV ◀▶ RPV	ND	▲ PRV ▲ RPV	ND

	Simeprevir/ Sofosbuvir (SMV/SOF)	**Daclatasvir/ Sofosbuvir (DCV/SOF)**	**Paritaprevir/ Ritonavir/ Ombitasvir + Dasabuvir (PrOD)**	**Paritaprevir/ Ritonavir/ Ombitasvir (PrO)**
Etravirine (ETV)	ND	▼ DCV[b]	ND	ND
Raltegravir (RAL)	◀▶ SMV ◀▶ RAL	ND	◀▶ PrOD ▲ RAL	◀▶ PrO ▲ RAL
Cobicistat-boosted elvitegravir (COB)	ND	▲ DCV[a]	ND	ND
Dolutegravir (DTG)	◀▶ SMV ◀▶ DTG	◀▶ DCV ▲ DTG	▼ PRV ▲ DTG	ND
Tenofovir Alafenamide (TAF)/ Emtricitabine (FTC)/ Bictegravir (BIC)	ND	ND	ND	ND
Maraviroc (MVC)	ND	ND	ND	ND
Tenofovir (TFV) disoproxil fumarate	◀▶ SMV ◀▶ TFV	◀▶ DCV ◀▶ TFV	◀▶ PrOD ◀▶ TFV	◀▶ PrO ◀▶ TFV
Tenofovir (TFV) alafenamide	ND	ND	ND	ND

ND, No data
[a] Daclatasvir dose should be reduced to 30 mg.
[b] Daclatasvir dose should be increased to 90 mg.

Ribavirin

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

Treatment Recommendations for Patients With HIV/HCV Coinfection	
RECOMMENDED	RATING
HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed).	I, B
Daily daclatasvir (refer to information above for dose) plus sofosbuvir (400 mg), with or without ribavirin, is a recommended regimen when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals. Refer to Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections for treatment duration.	I, B

Regimens Not Recommended for Patients With HIV/HCV Coinfection	
NOT RECOMMENDED	RATING
Ledipasvir/sofosbuvir for 8 weeks is **not** recommended, regardless of baseline HCV RNA level.	IIb, C

Mixed Genotypes

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

Last update: May 24, 2018

Patients With Decompensated Cirrhosis

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis

RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and post-treatment week 12, including patients with CTP class C cirrhosis (Manns, 2016); (Curry, 2015); (Charlton, 2015); (Welzel, 2016). However, improvements may be insufficient to avoid liver-related death or the need for liver transplantation (Belli, 2016), highlighting that not everyone benefits from DAA therapy (Fernandez-Carrillo, 2016). Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease. The predictors of improvement or decline have not been clearly identified, though patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than treatment (Terrault, 2017); (Belli, 2016).

Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotics without HCC (Prenner, 2017); (Beste, 2017). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (with and without ribavirin), overall SVR rates were 91% in patients without HCC vs 74% in those with HCC (Beste, 2017). After adjusting for confounders, the presence of HCC was associated with a lower likelihood of SVR (AOR=0.38). Whether this lower rate of SVR can be overcome with an extended duration of therapy is unknown.

Decompensated Cirrhosis Genotype 1, 4, 5, or 6 Infection

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	12 weeks	I, A[d]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[e] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[c] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
[d] Only available data for genotype 6 are in patients with compensated cirrhosis.
[e] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[c]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg)	24 weeks	II, C

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[c] Only available data for genotype 6 are in patients with compensated cirrhosis.
[d] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] and Genotype 1, 4, 5, or 6 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

RECOMMENDED	DURATION	RATING
Prior sofosbuvir-based treatment failure only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated)	24 weeks	II, C[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	24 weeks	II, C[d]

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotype 6 are in patients with compensated cirrhosis.
[c] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis.
[d] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.

Ledipasvir/Sofosbuvir

The US-based, multicenter, randomized, open-label, phase 2 SOLAR-1 trial included 108 patients with genotype 1 or 4 infection and decompensated cirrhosis; 59 were categorized as CTP class B (score 7 to 9) and 49 were categorized as CTP class C (score 10 to 12). Participants were randomly assigned to 12 weeks or 24 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated) (Charlton, 2015b). After excluding the 7 patients who underwent liver transplantation during the study, the SVR rate was 87% in CTP class B patients who received 12 weeks of treatment and 89% in those who received 24 weeks of treatment. Similarly, the SVR rates were 86% and 87%, respectively, with 12 weeks and 24 weeks of antiviral therapy in the CTP class C patients. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively.

In the majority of participants with CTP class B or C disease, the MELD and CTP scores decreased between baseline and post-treatment week 4. As expected, the frequency of serious adverse events increased with treatment duration in both the CTP class B group (10% week 12; 34% week 24) and the CTP class C group (26% week 12; 42% week 24). Most of the serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the patients with decompensated cirrhosis was 600 mg. Therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients in the 24-week treatment arm.

The multicenter (Europe, Canada, Australia, and New Zealand), randomized, open-label, phase 2 SOLAR-2 study included 160 genotype 1- or 4-infected patients with decompensated cirrhosis (CTP class B or C). Study participants, who were treatment-naive or -experienced, were randomly assigned to 12 weeks or 24 weeks of daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated). All participants had a hemoglobin level >10 g/dL and an estimated glomerular filtration rate (eGFR) >40 mL/min (Manns, 2016). Among the 150 patients with decompensated cirrhosis who completed therapy and had evaluable efficacy results, SVR12 was achieved in 85% (61/72) of those in the 12-week study arm (90% [43/48] CTP class B; 75% [18/24] CTP class C). SVR 12 was achieved by 90% (70/78) of patients with decompensated cirrhosis in the 24-week study (98% [47/48] CTP class B ; 77% [23/30] CTP class C). Post-therapy virologic relapse occurred in 6% (9/150) of the patients with decompensated cirrhosis who completed therapy (7 in 12-week arm; 2 in 24-week arm).

Baseline CTP and MELD scores improved in the majority of the treated patients, but some participants experienced

worsening hepatic function. Among nontransplanted patients whose MELD score was ≥15 at baseline, 80% (20/25) had a MELD score <15 at SVR12. Among those with a MELD score <15 at baseline, 4% (2/56) had a MELD score ≥15 at SVR12. During the study, 8% (13/160) of the enrolled patients with decompensated cirrhosis (2 CTP class B, 11 CTP class C) died from various causes but none of the deaths were attributed to antiviral therapy. Serious adverse events occurred in approximately 28% of patients with decompensated cirrhosis with no significant difference between the 12-week and 24-week treatment arms.

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared to daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks (with a 12-week placebo phase). Study participants included 154 patients with compensated cirrhosis and genotype 1 infection in whom prior peginterferon/ribavirin treatment failed (for most patients, treatment with peginterferon/ribavirin plus a protease inhibitor also failed) (Bourliere, 2015). The mean MELD score was 7 (range, 6 to 16), 26% of patients had varices, and 13% had low serum albumin levels. The SVR12 rate was 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache, and pruritus; the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks in patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed.

Collectively, these results indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis and genotype 1 or 4 infection. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients received a ribavirin dose of 600 mg/d. Of 17 patients (16 genotype 1; 1 genotype 4) in the SOLAR-1 and SOLAR-2 trials (6 CPT class B; 11 CPT class C) who received ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks prior to or up to the time of liver transplant, all had HCV RNA <15 IU/mL at the time of transplantation. Sixteen of the 17 patients achieved post-transplant SVR12; 1 patient died at post-op day 15, but the HCV RNA was <15 IU/mL on day 14 (Yoshida, 2017).

Real-world cohort studies have reported SVR rates in patients with decompensated cirrhosis. Foster and colleagues reported on the use of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg)/sofosbuvir (400 mg), with or without ribavirin, for 12 weeks in 235 genotype 1-infected patients from the United Kingdom (Foster, 2016). The SVR rates were similar in the 235 genotype participants receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% and 81%, respectively). In this observational cohort study, 91% of the patients received ribavirin; only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the patients had a serious adverse event; none were treatment related.

The multicenter, prospective, observational HCV-TARGET study examined the real-world efficacy of ledipasvir/sofosbuvir (with or without ribavirin) for various treatment durations. The SVR12 rate among genotype 1 patients with a history of clinically decompensated cirrhosis was 90% (263/293) among evaluable patients (Terrault, 2016). In this cohort, 29% of patients with decompensated cirrhosis were treated with ribavirin and 48% received 24 weeks treatment.

A phase 2a, open-label study of 14 patients with compensated cirrhosis and genotype 1 infection in whom prior sofosbuvir-based therapy failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate (Osinusi, 2014). In addition, results of an open-label, phase 2 study of 51 genotype 1-infected patients in whom prior sofosbuvir-based therapy failed demonstrated that a 12-week course of ledipasvir/sofosbuvir plus weight-based ribavirin (1000 mg/d to 1200 mg/d) led to an overall SVR12 rate of 98%, including 100% (14/14) among those patients with compensated cirrhosis (Wyles, 2015b).

Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Notably, 10% of patients were CTP class A or class C at treatment baseline. Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight <75 kg; 1200 mg/d, weight ≥75 kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype. All participants had a hemoglobin level >10 g/dL

and an eGFR ≥50 mL/min (Curry, 2015b). The genotype/subtype distribution of the participants was 60% (159/267) genotype 1a; 18% (48/267) genotype 1b; 4% (12/267) genotype 2; 15% (39/267) genotype 3; 3% (8/267) genotype 4; and <1% (1/267) genotype 6. Ninety-five percent of patients had a baseline MELD score ≤15.

The SVR rates were 83% among those in the 12-week sofosbuvir/velpatasvir study arm, 94% in the 12-week sofosbuvir/velpatasvir plus ribavirin arm, and 86% in the 24-week sofosbuvir/velpatasvir arm. Among patients with genotype 1 infection, the SVR rates were 88%, 96%, and 92%, respectively. Twenty-two participants had virologic failure, including 20 patients with relapse and 2 patients (genotype 3) with on-treatment virologic breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virologic relapse.

At post-treatment week 12, 47% of patients had an improvement in CTP score, 42% had no change, and 11% had an increased CTP score. Nine patients (3%) died due to various causes during the study; no deaths were judged to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia (ie, hemoglobin <10 g/dL) was reported in 23% of the group receiving ribavirin, and 8% and 9% in those who received 12 weeks and 24 weeks of sofosbuvir/velpatasvir without ribavirin, respectively.

A phase 2, open-label, single-arm study conducted by Gane and colleagues evaluated a 24-week course of sofosbuvir/velpatasvir plus weight-based ribavirin among 65 patients with a history of treatment failure with an NS5A-containing regimen (Gane, 2016). Twenty-six percent of enrolled patients had compensated cirrhosis. The overall SVR12 rate was 91% (59/65), including 97% (33/34) among genotype 1-infected patients, 91% (13/14) in those with genotype 2 infection, and 76% (13/17) in patients with genotype 3. To date, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

The phase 3, multicenter ASTRAL-1 trial evaluated the efficacy and safety of a 12-week course of daily fixed-dose sofosbuvir/velpatasvir among treatment-naive and-experienced patients with genotype 1, 2, 4, 5, or 6 infection. The study included 35 patients with genotype 5 infection and 41 patients with genotype 6 infection (Feld, 2015). The overall SVR12 rates were 97% (34/35) in genotype 5-infected patients and 100% (41/41) in those with genotype 6 infection. Of note, 100% SVR12 was achieved in the small number of genotype 5 patients (n=5) and genotype 6 patients (n=6) with compensated cirrhosis enrolled in ASTRAL-1.

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-1 trial evaluated the efficacy and safety of 12 weeks of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin (600 mg with possible escalation to 1000 mg as tolerated) among patients with cirrhosis (CTP class A, B, or C; n=60) or HCV recurrence after liver transplantation (n=53). Treatment-naive and -experienced patients were enrolled. More than 75% of participants had genotype 1 infection, although patients with genotype 2, 3, or 4 infection were also represented in the cirrhosis cohort. The CTP breakdown was 20% (12/60) class A, 53% (32/60) class B, and 26% (16/60) class C.

The SVR12 rates were 83% (50/60) among those in the cirrhosis group and 94% (50/53) among those with recurrent HCV infection post liver transplant. In the population with cirrhosis, SVR12 rates by genotype were: 82% (37/45) genotype 1; 80% (4/5) genotype 2; 83% (5/6) genotype 3; and 100% (4/4) genotype 4. Response rates differed based on severity of cirrhosis; SVR12 rates were 92% (11/12) among those with CTP class A cirrhosis, 94% (30/32) among those with class B, and 56% (9/16) in patients with class C cirrhosis (Poordad, 2016).

An observational cohort study from the United Kingdom conducted by Foster and colleagues examined various combinations of DAA agents in patients with decompensated cirrhosis (CTP score ≥7), recurrent HCV after liver transplantation, or a severe extrahepatic manifestation of HCV disease. The study treatment regimens included a 12-week course of daclatasvir plus sofosbuvir, with or without ribavirin. Among the 200 genotype 1-infected patients with decompensated cirrhosis enrolled in the study, the SVR12 for 12 weeks of daclatasvir/sofosbuvir plus ribavirin was 88% (30/34). SVR12 for daclatasvir/sofosbuvir without ribavirin was 50%, but only 4 patients received this regimen (Foster, 2016).

Overall SVR12 rates were similar in the genotype 1-infected participants receiving ledipasvir/sofosbuvir plus ribavirin or

ledipasvir/sofosbuvir (86% and 81%, respectively) and those receiving daclatasvir/sofosbuvir with ribavirin or daclatasvir/sofosbuvir therapy (82% and 60%, respectively). In this real-world study, 91% of the patients received ribavirin; only 6% discontinued ribavirin but 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the participants had a serious adverse event; none were treatment related. These data highlight the lower efficacy and increased safety concerns when treating patients with more advanced liver failure.

Protease-Inhibitor Containing Regimens

To date, the fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) has not been rigorously studied in patients with decompensated cirrhosis. A phase 2, nonrandomized, open-label study of elbasvir/grazoprevir for 12 weeks was completed in 30 genotype 1-infected patients with CTP class B cirrhosis (Jacobson, 2015). The SVR12 rate was 90% (27/30); 1 patient died of liver failure at post-treatment week 4 and 2 patients relapsed. MELD scores improved in 15 treated patients, were unchanged in 9, and increased in 6. However, there are no safety or efficacy data regarding the US Food and Drug Administration (FDA)-approved elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Recent data reported by the FDA have demonstrated that some patients with compensated cirrhosis treated with paritaprevir/ritonavir/ombitasvir ± dasabuvir may develop rapid-onset direct hyperbilirubinemia without ALT elevation within 1 to 4 weeks of starting treatment, which can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received paritaprevir/ritonavir/ombitasvir plus dasabuvir developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in all patients with decompensated cirrhosis due to concerns about hepatotoxicity. In addition, all patients with compensated cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks while on therapy.

The daily fixed dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has not been studied in patients with decompensated cirrhosis and, pending additional safety data, is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) has not been studied in patients with hepatic decompensation. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CTP class B or C) until further data are available.

Decompensated Cirrhosis Genotype 2 or 3 Infection

Recommended Regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 2 or 3 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, B

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 2 or 3 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	24 weeks	II, C

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information for daclatasvir.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] and Genotype 2 or 3 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[b]	24 weeks	II, C

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C.

Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight <75 kg; 1200 mg/d, weight ≥75 kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype.

The SVR rates among the 12 patients with CTP class B cirrhosis and genotype 2 infection were 100% (8/8) with sofosbuvir/velpatasvir for 12 weeks (with or without ribavirin), and 75% (3/4) with sofosbuvir/velpatasvir for 24 weeks. Among 39 patients with CTP class B cirrhosis with genotype 3 infection, the SVR rates were 50% (7/14) for 12 weeks of sofosbuvir/velpatasvir without ribavirin, 85% (11/13) for 12 weeks of sofosbuvir/velpatasvir plus ribavirin, and 50% (6/12) for 24 weeks of sofosbuvir/velpatasvir. Therefore, genotype 3-infected patients in particular appear to benefit from the addition of ribavirin to the regimen (Curry, 2015b). For patients with decompensated cirrhosis who are ribavirin ineligible, sofosbuvir/velpatasvir for 24 weeks is currently recommended, but additional studies involving larger numbers of patients are needed to define the optimal duration of therapy.

Sofosbuvir/velpatasvir has not been studied in CTP class C patients. There are no data on the outcomes of patients with decompensated cirrhosis and a history of prior sofosbuvir plus NS5A failure. However, among 69 patients (28% with compensated cirrhosis) with prior NS5A failure treated with sofosbuvir/velpatasvir plus ribavirin for 24 weeks, the SVR rates were 97% for genotype 1 (83% with compensated cirrhosis), 93% (13/14) for genotype 2 (no patients with cirrhosis), and 78% (75% with compensated cirrhosis) for genotype 3 (Gane, 2017).

Daclatasvir + Sofosbuvir

Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without and with cirrhosis. Although daclatasvir/sofosbuvir was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In clinical trials, daclatasvir/sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment to 24 weeks. For patients with genotype 2 infection who require treatment but cannot tolerate ribavirin, an alternative regimen of daclatasvir/sofosbuvir for 12 weeks is

recommended with consideration of extending treatment to 24 weeks for patients with poor baseline characteristics (ie, decompensated cirrhosis).

Relevant data from the ALLY-1 study support use of daclatasvir/sofosbuvir plus ribavirin in patients with genotype 2 or 3 infection who have decompensated cirrhosis. Sixty patients with predominantly (80%) decompensated cirrhosis (CPT class B/C) were treated with daclatasvir/sofosbuvir plus ribavirin (600 mg/d, increased to tolerability). SVR rates were 80% (4/5) for genotype 2 patients and 83% (5/6) for genotype 3 patients with advanced cirrhosis (Poordad, 2016).

Broader experiences with treatment of genotype 3-infected patients with decompensated cirrhosis have been reported from real-world cohort studies. In a cohort from the United Kingdom, 110 patients with decompensated cirrhosis and genotype 3 infection treated with daclatasvir/sofosbuvir with or without ribavirin (600 mg/d, increased to tolerability) demonstrated SVR12 rates of 71% (75/105) and 60% (3/5), respectively (Foster, 2016). In comparison, among 62 patients with decompensated cirrhosis and genotype 3 infection treated with ledipasvir/sofosbuvir with or without ribavirin, the SVR12 rates were 65% (37/57) and 40% (2/5), respectively. In a multicenter Spanish study of daclatasvir/sofosbuvir with or without ribavirin in 123 genotype 3-infected patients (71% receiving 24 weeks), SVR12 was 94% in both CPT class A and CPT class B/C patients (Alonso, 2017). However, compared to CPT class A patients, the CPT class B/C patients had more frequent serious adverse events (16.7% vs 3.6%) and episodes of hepatic decompensation (5.2% vs 2.3%).

Protease-Inhibitor Containing Regimens

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has activity against genotypes 2 and 3 but has not been studied in patients with decompensated cirrhosis. Pending additional safety data, this regimen is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) is effective in patients with genotypes 2 and 3 but this drug combination has not been studied in patients with decompensated cirrhosis. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CPT class B or C) until further data are available.

Mixed Genotypes

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

Regimens not recommended for:

Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C)

NOT RECOMMENDED	RATING
Paritaprevir-based regimens	III, B
Simeprevir-based regimens	III, B
Elbasvir/grazoprevir-based regimens	III, C
Glecaprevir/pibrentasvir	III, C
Sofosbuvir/velpatasvir/voxilaprevir	III, C

Interferon 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. Limited data exist for the use of simeprevir in patients with CPT class B cirrhosis (Modi, 2016); (Lawitz, 2017). In a study of 40 patients (19 CPT class A, 21 CPT class B) with genotype 1 or 4 infection treated with simeprevir, sofosbuvir and daclatasvir for 12 weeks, the mean pharmacokinetic exposure to simeprevir at week 8 of therapy was 2.2-fold higher in patients with CPT class B versus CPT class A cirrhosis. (Lawitz, 2017). All patients achieved SVR12 but grade 3 or 4 bilirubin elevations were seen in 18% and 5% of patients, respectively, though none were associated with an ALT increase or the need for drug discontinuation. No data are available for use of the currently approved doses of elbasvir/grazoprevir, glecaprevir/pibrentasvir, or sofosbuvir/velpatasvir/voxilaprevir in patients with decompensated cirrhosis.

Recent data reported by the FDA have demonstrated that some patients with compensated cirrhosis treated with paritaprevir/ritonavir/ombitasvir ± dasabuvir may develop rapid-onset direct hyperbilirubinemia without ALT elevation within 1 to 4 weeks of starting treatment, which can lead to rapidly progressive liver failure and death. A multicenter cohort study from Israel reported 7 patients who received paritaprevir/ritonavir/ombitasvir plus dasabuvir developed decompensation within 1 to 8 weeks of starting therapy, including 1 patient who died (Zuckerman, 2016). Therefore, paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in all patients with decompensated cirrhosis due to concerns about hepatotoxicity. In addition, all patients with compensated cirrhosis receiving this regimen should be monitored for clinical signs and symptoms of hepatic decompensation and undergo hepatic laboratory testing at baseline and at least every 4 weeks while on therapy.

Last update: September 21, 2017

Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

Post Liver Transplantation: Genotype 1, 4, 5, or 6 Infection

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	I, A

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimen for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks	12 weeks	I, A

Alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft, With or Without Compensated Cirrhosis

ALTERNATIVE	DURATION	RATING
Daily daclatasvir (60 mg)[a] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B
Genotype 1 or 4 infection only: Daily simeprevir (150 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIa, C

[a] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimen for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft and Decompensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

[a] Includes CTP class B and class C patients.

Post Liver Transplantation: Genotype 2 or 3 Infection

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg)[a] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	II, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C

[a] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft and Decompensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C

[a] Includes CTP class B and class C patients.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Glecaprevir/Pibrentasvir

The MAGELLAN-2 trial was an open-label, multicenter, single-arm, phase 3 study that evaluated a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in 80 liver transplant recipients and 20 kidney transplant recipients without cirrhosis. All genotypes were represented except genotype 5; 57% of participants had genotype 1 infection and 24% had genotype 3. Except for genotype 3-infected patients (all of whom were treatment naive), treatment-experienced patients were included (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Eighty percent of patients had Metavir stage F0 or F1 fibrosis, 6% had F2, and 14% had F3. Any stable immunosuppressive regimen was allowed, except cyclosporine >100 mg/d and prednisone >10 mg/d. SVR was achieved in 98% (98/100) of patients with no virologic breakthroughs on treatment and 1 post-treatment relapse (Reau, 2017). There were no treatment discontinuations due to drug-associated adverse effects. One episode of mild rejection occurred that was assessed to be unrelated to drug interactions. This regimen offers a ribavirin-free option for noncirrhotic liver or kidney transplant recipients. Although glecaprevir/pibrentasvir has not been studied in transplant recipients with compensated cirrhosis, this regimen may be considered in patients who are ribavirin ineligible.

Ledipasvir/Sofosbuvir

The SOLAR-1 study was a large, US-based, multicenter, open-label, phase 2 trial that included 223 liver transplant recipients with genotype 1 or 4 infection whose baseline characteristics encompassed a broad spectrum of histologic and clinical severity of HCV recurrence. One hundred and eleven patients were Metavir stage F0 to F3, 51 had compensated CTP class A cirrhosis, and 61 had decompensated CTP class B or class C cirrhosis. Study participants were randomly assigned to 12 weeks or 24 weeks of a fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin. The ribavirin dose was weight based for patients without cirrhosis or with compensated cirrhosis (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]). For patients with CTP class B or class C cirrhosis, ribavirin was initiated at 600 mg/d followed by dose escalation as tolerated. Only 4% of enrolled participants discontinued treatment prematurely because of adverse events related to the study drugs (Charlton, 2015b).

On an intention-to-treat basis, SVR was achieved in 96% (53/55) and 98% (55/56) of liver transplant patients without cirrhosis in the 12- and 24-week treatment arms, respectively. Among those with compensated cirrhosis, SVR was 96% in both the 12- and 24-week treatment arms. Efficacy was lower in patients with CTP class B or class C cirrhosis post liver transplantation. Among those with CTP class B cirrhosis, SVR rates were 86% and 88% in the 12- and 24-week treatment

arms, respectively. Among patients with CTP class C cirrhosis, SVR rates were 60% and 75% in the 12- and 24-week treatment arms, respectively. Mortality rate during the study was 10% among patients with CTP class B or class C cirrhosis (Charlton, 2015b).

Similar results were achieved using an identical study design in the SOLAR-2 study, which was conducted in Europe, Australia, Canada, and New Zealand. The study included 168 liver transplant recipients with genotype 1 or 4 infection. Among the post-transplantation patients, 101 had no cirrhosis (Metavir stage F0 to F3), 67 had CTP class A compensated cirrhosis, 45 had CTP class B cirrhosis, and 8 had CTP class C decompensation. SVR rates in post-transplantation, noncirrhotic patients were 94% (49/52) and 100% (49/49) for 12 weeks and 24 weeks of treatment, respectively. Among patients with compensated cirrhosis after transplantation, SVR was 97% (33/34; 32/33) in both the 12- and 24-week treatment arms. For patients with CTP class B cirrhosis, comparable SVR rates were 95% (21/22) and 100% (23/23), respectively. Among those with CTP class C cirrhosis, SVR rates were 33% (1/3) and 80% (4/5), respectively. Considering both pre- and post-transplantation patients with CTP class B or class C cirrhosis, SVR rates were 85% (61/72) and 90% (70/78) for 12 weeks and 24 weeks of treatment, respectively.

As the relative importance of ribavirin cannot be ascertained from the SOLAR studies (all patients received ribavirin), the safest presumption is that ribavirin may contribute to the high SVR rates observed.

Most clinical trials to date have focused on patients who were at least 6 months post transplantation, but there is no a priori reason not to consider earlier treatment if the patient is on stable immunosuppression and has recovered from postoperative complications. Treatment during the first 6 to 12 months post transplantation certainly seems reasonable to reduce the likelihood of treating patients with more advanced liver disease. A phase 2 study of prophylactic ledipasvir/sofosbuvir enrolled 16 genotype 1-infected liver transplant recipients (most with hepatocellular carcinoma as the indication). Treatment was initiated immediately preoperatively and continued for 4 weeks post transplantation (Levitsky, 2016). SVR12 post transplantation was attained in 88% (15/16) of patients. While these results are too preliminary upon which to base recommendations, the findings provide additional data on the safety of ledipasvir/sofosbuvir early in the post-transplantation period.

An observational HCV-TARGET cohort study provides real-world data based on experience with 347 liver, 60 kidney, and 36 dual liver kidney transplant recipients. Among the enrolled patients, 86% had genotype 1 infection, 44% had cirrhosis, 26% had a history of liver decompensation, and 54% had a prior treatment failure with a non-NS5A inhibitor regimen (Saxena, 2017). Among the 279 participants treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks, the SVR rates were 97% (152/157) for those also taking ribavirin and 95% (116/122) for patients not taking ribavirin. Patients who received ribavirin were more frequently genotype 1a (versus genotype 1b), treatment experienced, and without renal dysfunction. The rate of therapy discontinuation due to an adverse event was 1.3%, highlighting the safety of the drug combination. Acute graft rejection occurred during or after cessation of therapy in 1.4% (6/415) of patients. These episodes were not judged to not be a direct consequence of the antiviral regimen but serve to remind clinicians of the need to monitor immunosuppressive agent levels during direct-acting antiviral (DAA) therapy.

Another multicenter cohort of 162 patients (98% genotype 1) assessed treatment with ledipasvir/sofosbuvir (with or without ribavirin) for 8 weeks, 12 weeks, or 24 weeks. Duration of treatment and ribavirin use were provider determined. Overall SVR12 rates were 94% and 98% in those treated with ledipasvir/sofosbuvir without or with ribavirin, respectively (Kwok, 2016). SVR12 rates in patients treated for 8 weeks, 12 weeks, or 24 weeks with the ribavirin-free regimen were 86% (6/7), 94% (65/69), and 95% (39/41), respectively. SVR12 rates in the ribavirin inclusive groups were 97% (38/39) and 100% (6/6) for 12 weeks and 24 weeks of treatment, respectively.

Collectively, these real-world experiences indicate high SVR rates can be attained without inclusion of ribavirin in liver transplant patients. However, since all factors leading clinicians to include or exclude ribavirin cannot be discerned from these observational studies, inclusion of ribavirin is recommended for patients with unfavorable baseline characteristics (eg, cirrhosis, prior treatment experience) and ribavirin-free therapy is recommended for patients with a favorable baseline profile.

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-1 trial evaluated the efficacy and safety of a 12-week course of daily daclatasvir (60 mg) and sofosbuvir (400 mg) plus ribavirin (600 mg with possible escalation to 1000 mg as tolerated) among 60 patients with cirrhosis (CTP class A, B, or C) and 53 patients with HCV recurrence after liver transplantation. Treatment-naive and -experienced patients were enrolled. Seventy-six percent (86/113) of participants had genotype 1 infection, including 77% (41/53) in the post-transplantation group. Eleven patients with genotype 3 infection and 1 patient with genotype 6 infection were also included in the post-transplantation group. The SVR12 rate was 94% (50/53) among those with recurrent HCV infection post transplantation. Among patients with genotype 3 infection, SVR12 rates were 83% (5/6) and 91% (10/11), respectively, in those with advanced cirrhosis and recurrent HCV infection post transplantation (Poordad, 2016).

Fontana and colleagues reported on the use of daclatasvir-containing regimens with sofosbuvir (n=77), simeprevir (n=18), or both (n=2) for 24 weeks in 97 liver transplant recipients with severe recurrent HCV infection (Fontana, 2016). Thirty-five percent of the cohort received ribavirin. Ninety-three percent of patients had genotype 1 infection, 31% had biopsy-proven cirrhosis, and 37% had severe cholestatic HCV. The proportion of patients with CTP class A, B, or C cirrhosis was 51%, 31%, and 12%, respectively. The mean MELD score was 13.0 ± 6.0. The overall SVR12 rate was 87% (84/97). SVR12 rates were 91% (70/77) in the daclatasvir/sofosbuvir ± ribavirin group and 72% (13/18) in the daclatasvir/simeprevir ± ribavirin group. Although 8 patients died during or after therapy from graft dysfunction, CTP and MELD scores were stable or improved in 87% and 83% of patients, respectively. Three virologic breakthroughs and 2 relapses occurred in patients treated with daclatasvir/simeprevir. These data are consistent with findings from Herzer and colleagues who described 6 liver transplant recipients with recurrent genotype 1 infection, 4 (67%) of whom achieved SVR with a regimen of daclatasvir/simeprevir plus ribavirin (Herzer, 2015).

These data along with those from other studies suggest that daclatasvir should preferentially be combined with sofosbuvir rather than simeprevir in liver transplant recipients, particularly among patients with advanced liver disease (EASL, 2017). Daclatasvir-containing regimens appear to be well tolerated overall, with anemia noted when ribavirin is used. Cyclosporine and tacrolimus increase daclatasvir area under the curve (AUC) by 40% and 5%, respectively; these changes are not clinically significant. Daclatasvir does not cause clinically meaningful changes in calcineurin inhibitor, mammalian target of rapamycin (mTOR) inhibitor, steroid, or mycophenolate levels.

Simeprevir + Sofosbuvir

The prospective, randomized, phase 2 GALAXY study assessed the use of simeprevir (150 mg) plus sofosbuvir (400 mg), with or without weight-based ribavirin, for 12 weeks or 24 weeks in 46 liver transplant recipients (44 noncirrhotic) with recurrent genotype 1 infection (O'Leary, 2017). Among the randomized participants, the SVR12 rates were 100% with simeprevir plus sofosbuvir for 12 weeks, 82% with simeprevir plus sofosbuvir and ribavirin for 12 weeks, and 94% with simeprevir plus sofosbuvir for 24 weeks.

A retrospective multicenter analysis evaluated the efficacy and safety of simeprevir plus sofosbuvir, with or without ribavirin, among 123 liver transplant recipients with recurrent genotype 1 infection. Twenty percent of patients received ribavirin (at the discretion of the treating physician). Excluding 2 patients with nonvirologic failure, the SVR4 and SVR12 rates by modified intention-to-treat analysis were 92% and 91%, respectively (Pungpapong, 2015).

Another retrospective study from 21 HCV-TARGET centers reported on the efficacy of simeprevir plus sofosbuvir (79%; n=119) or simeprevir plus sofosbuvir and ribavirin (21%; n=32) among 151 liver transplant recipients with recurrent genotype 1 infection (Brown, 2016). Duration of therapy was 12 weeks for most patients; 10% (15/151) of participants received 24 weeks of treatment. Allograft cirrhosis had developed in 64% (97/151) of patients and 40% (60/151) had decompensated hepatic function. Overall SVR12 was 88% (133/151); 7% of patients experienced virologic relapse. Serious adverse events were reported in 12% of patients, and 3 deaths occurred that were unrelated to therapy.

In healthy volunteers, coadministration of a single dose of cyclosporine with simeprevir resulted in a 19% increase in cyclosporine concentration and simeprevir concentration similar to historical data (Olysio prescribing information, 2017).

However, the phase 2 SATURN study reported that HCV-infected liver transplant recipients with genotype 1b infection taking simeprevir plus daclatasvir and ribavirin concomitantly with cyclosporine experienced a 5-fold increase in plasma simeprevir exposure compared with phase 3 trials of simeprevir in the absence of cyclosporine (Forns, 2017b). This interaction may be caused by cyclosporine's inhibition of organic anion transporting polypeptide 1B1 (OATP1B1), P-glycoprotein (P-gp), and cytochrome P450 3A (CYP3A). Given these findings, simeprevir should not be coadministered with cyclosporine.

Coadministration of a single dose of tacrolimus with simeprevir in healthy volunteers did not result in a notable change in tacrolimus concentration (Olysio prescribing information, 2017). An interim analysis of the SATURN study data noted an 85% increase in plasma simeprevir exposure when used concomitantly with tacrolimus compared with historical data (Forns, 2017b); (Ouwerkerk-Mahadevan, 2016b). Based on phase 1 studies, a 2-fold increase in simeprevir concentration is unlikely to be clinically significant. Clinicians may consider use of sofosbuvir plus simeprevir in patients receiving tacrolimus with therapeutic drug monitoring, particularly in those expected to have difficulty tolerating ribavirin (eg, patients with impaired renal function or anemia) or in patients who are unable to forgo proton pump inhibitor therapy (these agents attenuate ledipasvir absorption).

Sofosbuvir/Velpatasvir

To date, there have been no studies evaluating the safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in liver transplant recipients. For this reason, very limited recommendations on its use post liver transplantation can be made. However, with no treatment options for liver transplant recipients with genotype 2 or 3 infection who have decompensated cirrhosis, expert opinion led to the recommendation to use sofosbuvir/velpatasvir with weight-based ribavirin for these patients. Similarly, recognition of the need for alternative options for patients with genotype 2 or 3 infection and cirrhosis—especially those who are treatment experienced—led to inclusion of sofosbuvir/velpatasvir as an alternative regimen for patients with compensated cirrhosis. The safety of sofosbuvir and other NS5A inhibitors has been demonstrated and discussed above.

In the nontransplant setting (discussed in detail in the initial and retreatment sections), the phase 3, double-blind, placebo-controlled ASTRAL-1 study reported on 742 treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were randomly assigned in a 5:1 ratio to sofosbuvir/velpatasvir or placebo for 12 weeks (Feld, 2015). All patients with genotype 5 infection (n=35) received active treatment. Thirty-two percent (201/624) of patients randomized to active therapy were treatment experienced and 19% (121/624) had compensated cirrhosis (CTP class A). The genotype distribution in the active treatment arm was 34% (n=210) genotype 1a; 19% (n=118) genotype 1b; 17% (n=104) genotype 2; 19% (n=116) genotype 4; 6% (n=35) genotype 5; and 7% (n=41) genotype 6. The overall SVR was 99% (95% CI, 98 to >99). The side effect/adverse event profile of sofosbuvir/velpatasvir was similar to placebo.

In the phase 3, open-label ASTRAL-3 study, 552 treatment-naive or -experienced patients with genotype 3 infection (with or without compensated cirrhosis) were randomized in a 1:1 ratio to 12 weeks of sofosbuvir/velpatasvir or 24 weeks of sofosbuvir plus weight-based ribavirin. The SVR12 rate was 95% (95% CI, 92 to 98) for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 rate of 80% (95% CI, 75 to 85) for patients receiving sofosbuvir plus ribavirin for 24 weeks (Foster, 2015a).

The phase 3, open-label ASTRAL-4 study enrolled 267 treatment-naive or -experienced (55%) patients with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening). Patients were randomized in a 1:1:1 ratio to 12 weeks of sofosbuvir/velpatasvir, 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin, or 24 weeks of sofosbuvir/velpatasvir. SVR12 rates were 83% (75/90) for the 12-week sofosbuvir/velpatasvir regimen, 94% (82/87) for the 12-week sofosbuvir/velpatasvir plus ribavirin regimen, and 86% (77/90) for the 24-week sofosbuvir/velpatasvir regimen (Curry, 2015b). Among patients with genotype 1 infection, SVR12 rates were 88% and 96% with 12 weeks of sofosbuvir/velpatasvir without and with ribavirin respectively, and 92% with sofosbuvir/velpatasvir for 24 weeks. Virologic relapse occurred in 12% and 9% of patients in the 12-week and 24-week sofosbuvir/velpatasvir arms, respectively, compared to 2% in the 12-week sofosbuvir/velpatasvir plus ribavirin study arm. Although the ASTRAL-4 study was not powered to generate statistical significance, these results suggest that sofosbuvir/velpatasvir with ribavirin for 12 weeks is the optimal choice for patients with genotype 1 or 3 infection who have decompensated cirrhosis. The participant numbers were too small for genotypes 2, 4, and 6 to differentiate the comparative efficacy of the

treatment arms. Reflecting the approach in nontransplant patients with decompensated cirrhosis, liver transplant recipients with hepatic decompensation are recommended to receive sofosbuvir/velpatasvir plus ribavirin for 12 weeks.

Velpatasvir is a substrate for CYP3A4, CYP2C8, and CYP2B6, a weak inhibitor of P-gp and OATP transporters, and a moderate inhibitor of the breast cancer resistance protein (BCRP) membrane transporter. As such, velpatasvir is moderately affected by potent inhibitors and, to a greater extent, potent inducers of enzyme/drug transporter systems (Mogalian, 2016). Based on this profile, which is similar to ledipasvir, clinically significant drug-drug interactions would not be expected for coadministration of sofosbuvir/velpatasvir with common immunosuppressive agents (eg, tacrolimus, cyclosporine, corticosteroids, mycophenolate mofetil, or everolimus).

Mixed Genotypes

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

Drug Interactions Between DAAs and Calcineurin Inhibitors

The interaction of DAA agents and calcineurin inhibitors is complex and unpredictable without formal studies of drug-drug interactions. A summary of drug interactions between calcineurin inhibitors and DAAs with recommended dosing is provided in the table below. Based on the metabolism of grazoprevir and elbasvir, a 15-fold increase in grazoprevir AUC and a 2-fold increase in elbasvir AUC can be expected with cyclosporine coadministration. Therefore, this combination should be avoided. Since a 40% to 50% increase in tacrolimus level is predicted during coadministration with grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored.

Table. DAA Interactions With Calcineurin Inhibitors

	Cyclosporine (CSA)	Tacrolimus (TAC)
Sofosbuvir (SOF)	4.5-fold ? in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Paritaprevir / ritonavir / ombitasvir + dasabuvir (PrOD)	5.8-fold ? in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ? in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir / grazoprevir (EBR/GZR)	15-fold ? in GZR AUC and 2-fold ? in EBR AUC; combination is not recommended	43% ? in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir / pibrentasvir (GLE/PIB)	5-fold ? in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses >100 mg/day	1.45-fold ? in TAC AUC; no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed
Sofosbuvir / velpatasvir / voxila previr (SOF/VEL/VOX)	9.4-fold ? in VOX AUC; combination is not recommended	No data; no a priori dose adjustment
AUC=area under the curve		

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Patients with Renal Impairment

Chronic hepatitis C is independently associated with the development of chronic kidney disease (CKD) (Rogal, 2016); (Fabrizi, 2015). A meta-analysis published in 2015 demonstrated that chronic HCV infection was associated with a 51% increase in the risk of proteinuria and a 43% increase in the incidence of CKD (Fabrizi, 2015). There is also a higher risk of progression to end-stage renal disease (ESRD) in persons with chronic HCV infection and CKD, and an increased risk of all-cause mortality in persons on dialysis (Lee, 2014); (Fabrizi, 2012).

Recommendations for Patients With CKD Stage[a] 1, 2, or 3

RECOMMENDED	RATING
No dose adjustment is required when using: • Daclatasvir (60 mg)[b] • Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) • Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c] • Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) • Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) • Simeprevir (150 mg) • Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg) • Sofosbuvir (400 mg)	I, A

[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 mL/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)
[b] Refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

Patients With CKD Stage[a] 4 or 5 (eGFR <30 mL/min or End-Stage Renal Disease)

RECOMMENDED	GENOTYPE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	1a, 1b, 4	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	1, 2, 3, 4, 5, 6	8 to 16 weeks[c]	I, B[c]

[a] Chronic kidney disease (CKD) stages: 1 = normal (eGFR >90 mL/min); 2 = mild CKD (eGFR 60-89 mL/min); 3 = moderate CKD (eGFR 30-59 ml/min); 4 = severe CKD (eGFR 15-29 mL/min); 5 = end-stage CKD (eGFR <15 mL/min)
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Patients in this group should be treated as would patients without CKD. Duration of glecaprevir/pibrentasvir should be based on presence of cirrhosis and prior treatment experience (please refer to appropriate section). As such, strength of rating may be lower for certain subgroups.

Recommended Regimens

Elbasvir/Grazoprevir

The C-SURFER trial evaluated the safety and efficacy of 12 weeks of the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) versus placebo among genotype 1-infected patients with CKD stage 4 or 5 (eGFR <30 mL/min). The initial study randomized eligible patients to immediate or deferred treatment with elbasvir/grazoprevir. The delayed treatment arm initially received placebo and was later treated with elbasvir/grazoprevir. Notably, both elbasvir and grazoprevir are primarily hepatically metabolized and undergo minimal renal elimination.

The data for the immediate treatment arm have been published (Roth, 2015). Seventy-five percent of the study participants were on hemodialysis, and 45% were African American. A small number of patients with compensated cirrhosis were included. Intention-to-treat (ITT) and modified intention-to-treat (mITT) SVR12 rates were 94% and 99%, respectively. There were no changes in erythropoietin use, hemoglobin or other adverse events in the treatment groups compared to placebo. None of the genotype 1a-infected patients with baseline NS5A resistance-associated substitutions (RASs) experienced viral relapse. The only reported relapse occurred in a patient with genotype 1b infection. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear but may relate to the moderately increased area under the curve (AUC) with grazoprevir and elbasvir observed in patients with stage 4/5 CKD (Zepatier prescribing information, 2017).

Based on these data, daily fixed-dose elbasvir/grazoprevir is recommended for the treatment of genotype 1 infection in patients with severely compromised renal function. While C-SURFER did not evaluate patients with genotype 4 infection, it is likely that the high efficacy of elbasvir/grazoprevir in genotype 1 and 4 infection in persons with normal renal function can be extrapolated to genotype 4-infected persons with CKD stage 4/5. Treatment with elbasvir/grazoprevir in persons with CKD has been shown to be cost-effective in the United States (Elbasha, 2016).

Glecaprevir/Pibrentasvir

The EXPEDITION-4 trial evaluated the safety and efficacy of 12 weeks of the pangenotypic NS3/NS4A protease inhibitor glecaprevir and the pangenotypic NS5A inhibitor pibrentasvir for genotype 1, 2, 3, 4, 5, or 6 infection (Gane, 2017b). This open-label study enrolled treatment-naive and -experienced patients (previous interferon or peginterferon ± ribavirin, or sofosbuvir and ribavirin ± peginterferon) with CKD stage 4 or 5, including hemodialysis dependence. Baseline characteristics of the 104 patients enrolled in the study were 76% male; 25% black; 19% compensated cirrhosis; 40% treatment experienced; and 82% hemodialysis dependent. The genotype distribution was 22% genotype 1a; 28% genotype 1b; 16% genotype 2; 11% genotype 3; 19% genotype 4; 1% genotype 5; and 1% genotype 6. In the study, the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120mg) was administered as three 100 mg/40 mg fixed-dose combination pills.

The study reported ITT and mITT SVR12 rates of 98% and 100%, respectively. There were no virologic failures. Two patients did not achieve SVR12; 1 patient discontinued the study due to diarrhea in the context of recent gastrointestinal bleeding and the other experienced a cerebral hemorrhage due to uncontrolled hypertension (had achieved SVR4). Adverse events included pruritus (20%), fatigue (14%), and nausea (12%). There were no serious adverse events related to the study drugs, and there were no grade 4 laboratory abnormalities reported.

The EXPEDITION-4 trial supports the efficacy and safety of glecaprevir/pibrentasvir in patients with CKD and ESRD. The recommended duration of therapy is the same as for patients without CKD.

Sofosbuvir-Based Regimens

Safe and effective doses of sofosbuvir in persons with an eGFR <30 mL/min have not been established. However, there is accumulating evidence on use of sofosbuvir-based regimens in those with an eGFR <30 mL/min (Desnoyer, 2016);

(Nazario, 2016).

The HCV-TARGET study is an ongoing prospective, observational cohort study that evaluates the use of direct-acting antiviral agents across clinical practices in North America and Europe. The study reported the safety and efficacy of sofosbuvir-containing regimens in patients with mild to severe renal dysfunction (eGFR groups: <30 mL/min; 31-45 mL/min; 46-60 mL/min; and >60 mL/min) (Saxena, 2016). The patients received different regimens that included sofosbuvir (peginterferon/ribavirin plus sofosbuvir; simeprevir and sofosbuvir ± ribavirin; and sofosbuvir plus ribavirin). Overall, the regimens were well tolerated with no increased discontinuation among patients with low eGFRs. The SVR12 rates were similar across the eGFR groups. Notably, there was progressive deterioration of renal function and related symptoms in patients with an eGFR <30 mL/min, suggesting the need for close monitoring of these patients. In summary, patients with low baseline renal function have a higher frequency of anemia, worsening renal dysfunction, and more severe adverse events, but treatment responses remain high and comparable to those without renal impairment.

Daclatasvir, Elbasvir, Grazoprevir, Ledipasvir, and Simeprevir

Daclatasvir, elbasvir, grazoprevir, ledipasvir, and simeprevir are primarily hepatically metabolized and undergo minimal renal elimination. While exposures to many of these agents are higher in severe renal impairment—presumably due to effects of uremic toxins, parathyroid hormone, and/or cytokines on hepatic metabolism—they do not require dose adjustments in the setting of renal impairment.

Mixed Genotypes

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

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Kidney Transplant Patients

Genotypes 1 and 4

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Kidney Transplant Patients With Genotype 1 or 4 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A[c] IIa, C[d]
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Evidence for patients without cirrhosis
[d] Evidence for patients with compensated cirrhosis

Genotypes 2, 3, 5, and 6

Recommended and alternative regimens for:

Treatment-Naive and -Experienced Kidney Transplant Patients With Genotype 2, 3, 5, or 6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A[c] IIa, C[d]
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) plus low initial dose of ribavirin (600 mg; increase as tolerated)	12 weeks	II, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Genotypes 2, 3, and 6
[d] Genotype 5

DAA Therapy in Kidney Transplant Patients

A recent phase 2, open-label clinical trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in 114 kidney transplant recipients who were more than 6 months post transplant (Colombo, 2017). Enrolled patients had genotype 1 (91%) or 4 infection; 69% were treatment naive, and 15% had compensated cirrhosis. Patients were randomized to 12 weeks or 24 weeks of ledipasvir/sofosbuvir. Median eGFR prior to treatment was 50 mL/min for patients in the 12-week study arm and 60 mL/min for those in the 24-week arm. Overall SVR12 was 100% (114/114). Adverse events were common (64%) and serious adverse events occurred in 13 patients (11%); only 1 participant discontinued treatment because of an adverse event (Colombo, 2017). Four patients with an eGFR >40 mL/min at baseline experienced a decrease to <30 mL/min during therapy. In 3 of these patients, eGFR increased to >30 mL/min at the last visit recorded; 1 patient who had interrupted study treatment had a final value of 14.4 mL/min. All but 1 of the 6 patients with compensated cirrhosis whose eGFR decreased to <40 mL/min continued study treatment without interruption; none permanently discontinued study treatment.

Several additional reports have described successful outcomes with combination direct-acting antiviral (DAA) therapy in kidney transplant recipients (Sawinski, 2016); (Kamar, 2016); (Saxena, 2017). Sawinski and colleagues treated 20 HCV-infected kidney transplant recipients (88% genotype 1; 50% with advanced fibrosis; 60% treatment-experienced with an interferon-based regimen) with sofosbuvir-based therapy. Various regimens were used, including simeprevir plus sofosbuvir (n=9); ledipasvir/sofosbuvir (n=7); sofosbuvir plus ribavirin (n=3); and daclatasvir plus sofosbuvir (n=1). SVR12 was 100% (Sawinski, 2016). Two patients required dose reductions due to anemia (associated with ribavirin use). However, no significant changes in serum creatinine or proteinuria, or graft rejection were seen before or after treatment. Forty-five percent of patients required dose reduction of immunosuppressive agents while on antiviral therapy (Sawinski, 2016).

Real-life data from the ongoing HCV-TARGET study have also demonstrated the efficacy of DAA therapy in patients with kidney transplant and in those with dual liver kidney transplant (Saxena, 2017). Various regimens were used, including sofosbuvir/ledipasvir ± ribavirin (85%); sofosbuvir plus daclatasvir ± ribavirin (9%); and ombitasvir/paritaprevir/ritonavir plus dasabuvir ± ribavirin (6%). The SVR12 rate was 94.6% in those with kidney transplant and 90.9% in dual liver kidney transplant recipients.

A pilot study conducted by Kamar and colleagues evaluated 25 kidney transplant recipients with chronic HCV infection who were treated with sofosbuvir-based regimens. The reported SVR12 was 100% (Kamar, 2016). Among the study participants, 76% were infected with genotype 1 and 44% had advanced fibrosis. All participants had an eGFR >30 mL/min. Treatment regimens included ledipasvir/sofosbuvir (n=9); daclatasvir plus sofosbuvir (n=4); sofosbuvir plus ribavirin (n=3); ledipasvir/sofosbuvir plus ribavirin (n=1); simeprevir and sofosbuvir plus ribavirin (n=1); simeprevir and sofosbuvir (n=6); and sofosbuvir plus peginterferon/ribavirin (n=1). Treatment was well tolerated without any discontinuations, dose reductions, graft rejections, or changes in serum creatinine levels. No drug interactions with calcineurin inhibitors were observed (Kamar, 2016).

Another small study that treated 3 genotype 4-infected kidney transplant patients with sofosbuvir (400 mg) plus ribavirin (1000 mg) for 24 weeks reported 100% SVR (Hussein, 2016). Anemia was reported in 2 patients related to concomitant ribavirin use. No other adverse events were reported.

The phase 3, open-label, single arm MAGELLAN-2 study evaluated a 12-week course of the pangenotypic regimen of glecaprevir/pibrentasvir in 100 liver (n=80) and kidney (n=20) transplant recipients. SVR 12 was achieved in 99% of patients (Reau 2017). The safety profile was excellent, and there was only 1 rejection episode in a liver transplant recipient. While this is an effective pangenotypic regimen as demonstrated in the nontransplant population, there were no genotype 5 transplant recipients in the study.

Drug interactions are an important consideration with antiviral therapy in renal transplant recipients. Please see Unique Patient Populations: Patients Who Develop Recurrent HCV Infection Post Liver Transplantation for a table of drug interactions with DAAs and calcineurin inhibitors.

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Management of Acute HCV Infection

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 period, there is a 20% to 50% chance of spontaneous resolution of the infection (Kamal, 2008). In the past, cure rates of acute infection with interferon-based treatment were very high (Grebely, 2014). The present guidance reflects current trends transitioning toward safer, interferon-sparing treatments for chronic infection and the implications for the approach to acute HCV treatment.

Acute HCV infection may result from exposure to the virus through various routes. The highest risk is associated with repeated parenteral exposure from contaminated equipment in an injection drug use setting. Lower rates of HCV transmission occur from needle-stick injuries in which healthcare workers are exposed to the blood of an HCV-infected patient. Heterosexual exposure risk is very low. Transmission rates among HIV-infected men who have unprotected sex with men are much higher, particularly among those who engage in high-risk sexual practices that increase trauma to the mucosal membranes and exposure to blood (Boesecke, 2012).

Diagnosis of Acute HCV

Recommended Testing for Diagnosing Acute HCV Infection	
RECOMMENDED	RATING
HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels (see Testing Algorithm figure).	I, C

Recommendations for HCV testing are also found in the HCV Testing and Linkage to Care section.

Diagnosis of acute HCV infection enables 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 virus transmission and liver disease progression (Bruneau, 2014). Indeed, some persons involved in high-risk behaviors practice serosorting, defined as using HCV antibody serostatus to determine whether to engage in high-risk behaviors with certain individuals (Smith, 2013). Thus, undiagnosed acutely-infected persons may be at greater risk of transmitting HCV to their presumably seronegative contacts than would be expected by chance.

The best laboratory evidence to support a diagnosis of acute HCV infection is: (1) a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative window period) (Cox, 2005), or (2) a positive HCV antibody test after a prior negative HCV antibody test (seroconversion). There are rare instances in which these approaches may be misleading, such as in immunosuppressed individuals with impaired antibody production (Chamot, 1990).

Discrete Exposure

The aforementioned types of clear, laboratory-based documentation of acute HCV infection are most easily achieved when there has been a discrete, known or suspected exposure (eg, after new onset or a change in drug injection practice, a percutaneous needle-stick 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 Testing Algorithm 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 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 exposure(s). The frequency of repeat testing should reflect management goals. At a minimum, repeat testing should be done 4 to 6 months after baseline testing. When earlier identification of infection or reinfection is desired, HCV RNA and ALT testing every 4 to 6 weeks for 6 months is recommended.

No Discrete Exposure

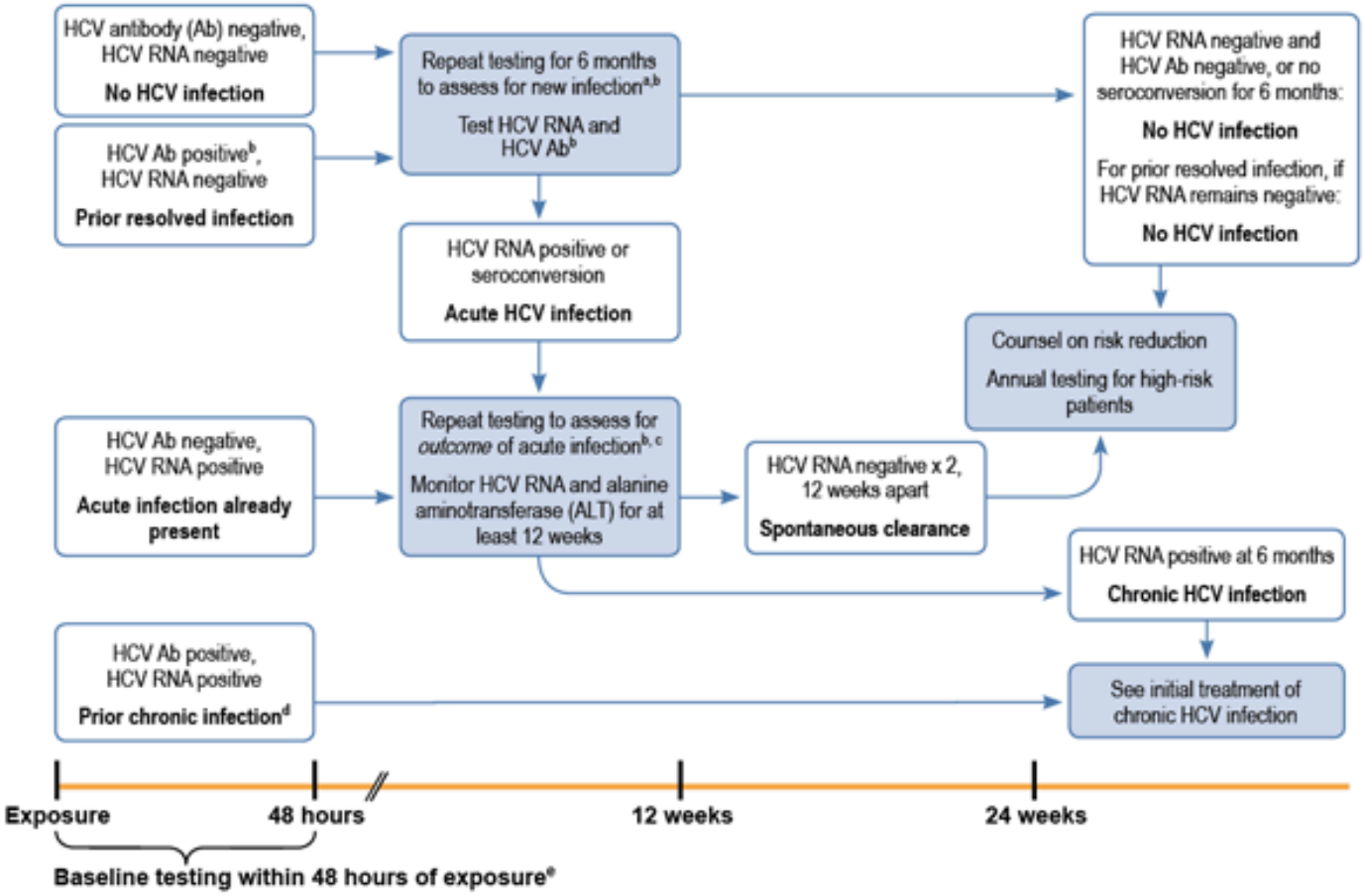
Individuals suspected of having acute HCV infection often do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult (see Blood Test Interpretation Table). Acute infection should be suspected if there is a new rise in the ALT level without 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. These patterns do not commonly occur outside of the first 6 months after HCV infection (McGovern, 2009). A low signal-to-cutoff ratio of HCV antibody along with detectable HCV RNA might also be suggestive of the early weeks of acute primary infection, although this information may need to be specifically requested from the testing laboratory (Araujo, 2011).

Patients suspected of having acute HCV infection should also have a laboratory evaluation to exclude other or coexisting causes of acute hepatitis (eg, hepatitis A virus, hepatitis B virus, hepatitis delta virus if chronically infected with hepatitis B, and autoimmune hepatitis) (Kushner, 2015). Patients should also have HIV testing.

Table. Interpretation of Blood Tests for Diagnosis of Acute HCV Infection

TEST	INTERPRETATION FOR DIAGNOSIS OF ACUTE HCV
HCV Antibody	• Test may be negative during the first 6 weeks after exposure. • Seroconversion may be delayed or absent in immunosuppressed individuals. • Presence of HCV antibody alone does not distinguish between acute vs chronic infection. • A low signal-to-cutoff ratio may be present during acute HCV infection or represent a false-positive result.
HCV RNA	• Viral fluctuations >1 $\log_{10}$ IU/mL may indicate acute HCV infection. • HCV RNA may be transiently negative during acute HCV infection. • Presence of HCV RNA alone does not distinguish between acute vs chronic infection.
ALT	• Fluctuating ALT peaks suggest acute infection. • ALT may be normal during acute HCV infection. • ALT may be elevated due to other liver insults, such as alcohol consumption.

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.

Pharmacologic Prophylaxis

Pharmacologic Prophylaxis Not Recommended	
NOT RECOMMENDED	RATING
Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.	III, C

Although direct-acting antiviral (DAA) treatment regimens are highly efficacious and more tolerable than interferon-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 an interferon-based regimen does not prevent infection (Nakano, 1995); (Arai, 1996).

Medical Management and Monitoring of Acute HCV Infection

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING
Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (eg, every 4 to 8 weeks) for 6 to 12 months is also recommended to determine spontaneous clearance versus persistence of HCV infection.	I, 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.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

Patients with acute HCV infection should be counseled to reduce behaviors that could result in virus transmission, such as sharing injection equipment and engaging in high-risk sexual practices. Because the risk of transmission of other bloodborne, sexually transmitted infections (eg, HIV and HBV) is higher in the acute infection phase, some experts counsel patients with acute HCV to consider using barrier precautions, even in a stable monogamous relationship (see HCV Testing and Linkage to Care). For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate (Litwin, 2009); (Strathdee, 2005).

Patients with acute hepatitis C are often asymptomatic or have nonspecific symptoms (eg, fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, and/or vomiting) that frequently are not recognized as being associated with acute HCV infection. A small proportion (<25%) of patients with acute HCV develop jaundice. Patients diagnosed with acute HCV should initially be monitored with hepatic panels (ALT, aspartate aminotransferase [AST], bilirubin, and international normalized ratio [INR] in the setting of an increasing bilirubin level) at 2- to 4-week intervals (Blackard, 2008). Laboratory monitoring should continue until the ALT level normalizes and HCV RNA becomes repeatedly undetectable, suggesting spontaneous resolution. If this does not occur, frequency of laboratory monitoring for patients with persistently detectable HCV RNA and elevated ALT levels should follow recommendations for monitoring patients with chronic HCV infection (see Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy).

HCV infection spontaneously clears in 20% to 50% of patients (Kamal, 2008). In at least two-thirds of patients who spontaneous clear acute HCV infection, this occurs 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 the infection at a later time (Grebely, 2014). Thus, detectable HCV RNA at 6 months after the time of infection will identify most persons who need antiviral

therapy (see When and in Whom to Initiate HCV Therapy).

Patients who spontaneous clear should not be treated with antiviral therapy. However, they should be counseled about the possibility of reinfection and tested routinely for this development if risk behaviors are ongoing (see HCV Testing and Linkage to Care). Of note, transient suppression of viremia can occur in those with acute HCV infection, even among those who progress to chronic infection. Thus, a single undetectable HCV RNA test result is insufficient to declare spontaneous clearance (see HCV Testing and Linkage to Care); (Villano, 1999); (Mosley, 2008).

Predictors of spontaneous clearance include jaundice, elevated ALT level, hepatitis B virus surface antigen (HBsAg) positivity, female sex, younger age, genotype 1 infection, 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 >1.5 and 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.

Antiviral Therapy

Recommended Treatment for Patients With Acute HCV Infection	
RECOMMENDED	RATING
If the clinician and patient decide 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).	IIa, C
If a decision is made to initiate treatment during the acute infection period, monitoring HCV RNA for at least 12 to 16 weeks before starting treatment is recommended to allow time for possible spontaneous clearance.	IIa, C

Recommended Regimens for Patients With Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

When Antiviral Therapy Is Not Recommended	
NOT RECOMMENDED	RATING
For patients in whom HCV infection spontaneously clears, antiviral treatment is not recommended.	III, B

In the interferon era, the efficacy of acute HCV infection treatment (particularly for genotype 1), including abbreviated regimens, was superior to the treatment of chronic infection (Ghany, 2009). There are emerging data on the treatment of acute HCV infection with shortened courses of all-oral, DAA regimens both in HCV monoinfection and HIV/HCV coinfection. But as yet, there are insufficient data to support a particular regimen or treatment duration. Until more definitive data are available, monitoring for spontaneous clearance for a minimum of 6 months before initiating treatment is recommended. When the decision is made to initiate antiviral therapy after 6 months, treatment as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection and When and in Whom to Initiate HCV Therapy).

There are instances wherein a clinician may decide that the benefits of early treatment outweigh waiting for possible spontaneous clearance. These include situations where importance is placed on:

- HCV transmission prevention (eg, a surgeon, a person with ongoing intravenous drug use, or an HIV-positive man who engages in sex with other men)
- Mitigation of clinical consequences (eg, a patient with cirrhosis who is acutely superinfected with HCV)
- Reduction in the likelihood of loss to follow-up (eg, a patient who may not be engaged in care in 3 to 6 months)

Referral to an addiction specialist and harm reduction counseling should be provided if relevant. If a decision is made to initiate treatment during the acute infection period, the same regimens recommended for chronic HCV infection are recommended for acute infection, given their high efficacy and safety in chronic HCV infection (see Initial Treatment of HCV Infection and When and in Whom to Initiate HCV Therapy sections).

Last update: September 21, 2017

HCV in Pregnancy

Testing

Recommendation for Universal Hepatitis C Screening in Pregnancy	
RECOMMENDED	RATING
All pregnant women should be tested for HCV infection (see Recommendations for Initial HCV Testing and Follow-Up), ideally at the initiation of prenatal care.	IIb, C

It has been estimated that up to 29,000 HCV-infected women gave birth each year from 2011 to 2014 (Ly, 2017). With the current increases in HCV among young adults, including women of childbearing age (Koneru, 2016); (Kuncio, 2016); (Watts, 2017), there is now discussion about universal screening of pregnant women (Prasad, 2016). Risk factor-based testing has never been shown to be effective (Kuncio, 2015); (Waruingi, 2015); (Fernandez, 2016) and inconsistent screening and counseling practices have been reported among obstetricians and gynecologists (Boaz, 2003). The Society for Maternal-Fetal Medicine recommends several obstetrical practices in women with HCV infection, including preference for amniocentesis over chorionic villus sampling when invasive prenatal diagnostic testing is indicated, as well as avoidance of internal fetal monitoring during labor, prolonged rupture of membranes, and episiotomies (Hughes, 2017). There are, however, no data to support elective cesarean delivery for HCV-infected women. Identifying HCV as women engage in prenatal care would allow for appropriate assessment of liver disease status and ideally facilitate linkage to HCV care after delivery. In addition, prenatal HCV diagnosis is a prerequisite for appropriate screening and care for the exposed children. Moreover, the cost-effectiveness of HCV screening in other clinical settings has improved with progressively lower costs of direct-acting antiviral-based treatment (Selvapatt, 2015); (Assoumou, 2018).

To enhance mothers' health and address public health concerns, universal testing of pregnant women for current HCV infection is recommended (see Recommendations for Initial HCV Testing and Follow-Up). Testing at the initiation of prenatal care is considered optimal to maximize opportunities for education, referral, and appropriate testing for the exposed infant. Early identification is key as women living with HCV and their exposed infants are at significant risk for not linking to appropriate evaluation or care. Women should be tested with an HCV-antibody test. If positive, this should be followed with testing for HCV RNA. HCV-infected pregnant women should be linked to care so that antiviral treatment can be initiated at the appropriate time (see the HCV Testing and Linkage to Care section). Infants of HCV-infected women should be tested and followed as described in the HCV in Children section.

Whom to Treat

Recommendation Regarding HCV Treatment and Pregnancy	
RECOMMENDED	RATING
For women of reproductive age with known HCV infection, antiviral therapy is recommended **before** considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B

Not Recommended Regarding HCV Treatment and Pregnancy	
NOT RECOMMENDED	RATING
Treatment during pregnancy is not recommended due to the lack of safety and efficacy data.	IIb, C

Women of reproductive age with HCV should be counseled about the benefit of antiviral treatment prior to pregnancy to improve the health of the mother and eliminate the low risk of mother-to-child transmission (MTCT). The safety of direct-acting antivirals (DAAs) in pregnancy is unknown, and there are no data on the effect of DAAs on male or female fertility. However, ribavirin is contraindicated in pregnancy due to its known teratogenicity. In addition, the risk for teratogenicity persists for up to 6 months after ribavirin cessation and applies to women taking ribavirin and female partners of men taking ribavirin. Women who become pregnant while on DAA therapy (with or without ribavirin) should discuss the risks versus benefits of continuing treatment with their physicians. If exposed to ribavirin, they should also have their maternal and fetal outcomes reported to the ribavirin pregnancy registry (see also, Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin).

Monitoring During Pregnancy

Recommendations for Monitoring HCV-Infected Women During Pregnancy	
RECOMMENDED	RATING
HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody–positive pregnant women to assess the risk of mother-to-child transmission (MTCT) and degree of liver disease.	I, B
All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT.	I, B
In HCV-infected pregnant women with pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy (ICP) with subsequent assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bile acids.	I, B
HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine (ie, high-risk pregnancy) obstetrician.	I, B

Pregnancy Impact on HCV Infection

Pregnancy itself does not appear to negatively affect chronic HCV infection. In general, serum ALT levels decrease during the first and third trimesters of pregnancy and increase after delivery. HCV RNA levels rise during the first and third trimesters, reaching a peak during the third trimester, and decrease postpartum (Conte, 2000); (Gervais, 2000). These effects are likely due to the immunosuppressive effects of pregnancy. HCV-infected pregnant women have a higher incidence of intrahepatic cholestasis of pregnancy (ICP) (pooled OR 20.40 [95% CI, 9.39-44.33, I2=55%]) based on a meta-analysis of 3 studies when compared to noninfected pregnant women (Wijarnpreecha, 2017). ICP is associated with an increased rate of adverse maternal and fetal outcomes; all patients with this syndrome should be immediately referred

to a high-risk obstetrical specialist for monitoring and treatment.

HCV Infection Impact on Pregnancy and Perinatal Outcomes

Although some studies show an increased risk of adverse perinatal outcomes (eg, preterm delivery, low birth weight infants, and congenital anomalies) with maternal HCV infection, these risks are confounded by comorbid conditions, such as substance use (Connell, 2011). However, pregnant women with cirrhosis are at increased risk for poor maternal outcomes (ie, preeclampsia, cesarean section, hemorrhagic complication, and death) and neonatal outcomes (ie, preterm delivery, low birth weight, and neonatal death) (Puljic, 2016); (Tan, 2008). Women with cirrhosis should be counseled about these increased risks and care should be coordinated with specialists in maternal-fetal medicine.

Hepatitis C MTCT occurs at an overall rate of 5% to 15% (Mast, 2005); (Ceci, 2001); (Shebl, 2009); (Jhaveri, 2015), with the number that progress to chronic infection being 3% to 5%. No specific risk factor predicts transmission and no specific intervention (eg, antiviral, mode of delivery, or others) has been demonstrated to reduce transmission—except for suppression of HIV replication in women with HIV/HCV coinfection (Checa Cabot, 2013). Given the potential associated risk of MTCT, it is advisable to avoid invasive procedures (eg, fetal scalp monitors and forceps delivery).

The neuropsychiatric and systemic side effects of interferon-based agents and the pregnancy category X rating of ribavirin made studies involving these drugs to interrupt MTCT untenable for safety reasons. It is important to note that DAAs have not been studied as a way to interrupt MTCT. These drugs have not demonstrated significant toxicity in animal studies, and antiviral medication use has become the standard of care for people with HIV and hepatitis B infection. Therefore, it is realistic to think that DAAs could be used in the future to interrupt MTCT. However, with a low transmission rate, improved methods to identify mothers who are likely to transmit are needed to reduce the number needed to treat below 20 to prevent 1 transmission event. DAA therapy is not recommended during pregnancy to reduce MTCT due to the current lack of safety and efficacy data.

Postpartum Issues

Recommendations Regarding Breastfeeding and Postpartum Care for HCV-Infected Women	
RECOMMENDED	RATING
Breastfeeding is not contraindicated in women with HCV infection, except when the mother has cracked, damaged, or bleeding nipples, or in the context of HIV coinfection.	I, B
Women with HCV infection should have their HCV RNA reevaluated after delivery to assess for spontaneous clearance.	I, B

HCV and Breastfeeding

Breastfeeding is not a risk for HCV MTCT (CDC, 1998) with studies showing similar rates of maternal infection in breast-fed and bottle-fed infants (Resti, 1998). However, given the associated risks of HCV transmission with blood exposure and HIV transmission with breastfeeding, we recommend that HCV-infected women who breastfeed abstain from doing so while their nipples are cracked, damaged, or bleeding, or in the context of HIV/HCV coinfection.

Spontaneous Clearance in the Postpartum Period

HCV RNA levels can fluctuate during pregnancy and the postpartum period. The most frequently observed pattern is a steady rise in HCV RNA levels during pregnancy followed by a slight or significant drop (>3-4 log) in the postpartum period

(Lin, 2000). This is most likely due to the release of tolerance in HCV-specific T lymphocyte responses that develops during pregnancy (Honegger, 2013). Spontaneous clearance of HCV can occur in the postpartum period. Previous studies with small numbers of patients demonstrated that up to 10% of postpartum women became HCV RNA undetectable (Hattori, 2003); (Lin, 2000); (Honegger, 2013). A recent study from Egypt demonstrated a 25% rate of spontaneous resolution that was strongly associated with the favorable IL28B allele (Hashem, 2017).

Given these findings, women should have their HCV RNA reevaluated after delivery. In that time, HCV RNA could become undetectable or rebound to prepregnancy levels. The possibility of spontaneous viral clearance should be considered for any woman who is being assessed for DAA treatment in the postpartum period.

Last update: May 24, 2018

HCV in Children

Testing

Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of HCV-Infected Children	
RECOMMENDED	RATING
All children born to HCV-infected women should be tested for HCV infection. Testing is recommended using an antibody-based test at or after 18 months of age.	I, A
Testing with an HCV-RNA assay can be considered in the first year of life, but the optimal timing of such a test is unknown.	IIa, C
Repetitive testing by HCV RNA is not recommended.	III, A
Children who are anti-HCV positive after 18 months of age should be tested with an HCV-RNA assay after age 3 to confirm chronic hepatitis C infection.	I, A
The siblings of children with vertically-acquired chronic HCV should be tested for HCV infection, if born from the same mother.	I, C

Although the prevalence of chronic HCV is lower in children than adults, an estimated 5 million children worldwide have active HCV infection (Gower, 2014). Data from the National Health and Nutrition Examination Survey (NHANES) collected between 2003 and 2010 indicates that 0.2% of 6- to 11-year-olds (31,000 children) and 0.4% of 12- to 19-year-olds (101,000 adolescents) in the US are chronically infected with HCV (Denniston, 2014).

As birth to an HCV-infected mother is a known risk for infection, such offspring should be evaluated and tested for HCV. The rate of mother-to-child transmission (MTCT) of HCV infection is approximately 5%, although rates are higher among women with inadequately controlled HIV coinfection, and women with higher HCV-RNA levels, or viral loads (>6 log IU/mL) (Benova, 2014); (Delotte, 2014); (Cottrell, 2013). Identifying, following, and treating exposed children is recommended. The basis for evaluation early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months. About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 3 years of age (EPHCVN, 2005); (Mast, 2005).

There is considerable debate about the utility of HCV-RNA testing within the first year of life. Proponents argue that use of a highly sensitive RNA assay early in life can increase the rate of infected infants detected, and that a negative result strongly suggests the infant is not infected while a positive result helps identify HCV cases earlier. Opponents argue that early testing does not change the need for definitive testing at or after 18 months; HCV RNA is more expensive than an antibody-based test; and there is no intervention or treatment that will occur prior to age 3—because of lack of approved drugs for this age group and to allow for possible spontaneous clearance. On balance, optional early HCV-RNA testing may facilitate more infants getting tested and retained in care if they are positive. The optimal timing of HCV-RNA testing is still unknown, but 2 to 6 months after birth is reasonable. There is no value in repeated HCV-RNA testing prior to 18 months of age, but anti-HCV testing should take place at or after 18 months of age.

Transmission and Prevention

Recommendations for Counseling Parents Regarding Transmission and Prevention in HCV-Infected Children	
RECOMMENDED	RATING
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, HCV-infected children do not pose a risk to other children and can participate in school, sports, and athletic activities, and engage in all other regular childhood activities without restrictions.	I, B
Parents should be informed that universal precautions should be followed at school and in the home of children with HCV infection. Educate families and children about the risk and routes of HCV transmission, and the techniques for avoiding blood exposure, such as avoiding the sharing of toothbrushes, razors, and nail clippers, and the use of gloves and dilute bleach to clean up blood.	I, B

HCV-infected children often face discrimination and stigmatization in school and child-care settings that is driven by inadequate public understanding of hepatitis C. HCV is not transmitted by casual contact in the absence of blood exposure. Families should not be forced to disclose a child's HCV infection status, and children should not be restricted from any routine childhood activity.

The risk of sexual transmission of hepatitis C is considered very low/rare. Sexual transmission occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men (see HCV Testing and Linkage to Care) (Schmidt, 2014). Adolescents with HIV infection and those with multiple sexual partners or sexually transmitted infections (STIs) should be encouraged to use barrier precautions to prevent sexual transmission of HCV and other STIs. Other adolescents with HCV infection should be counseled that the risk of sexual transmission is low but barrier precautions are recommended for other reasons (see Testing and Linkage to Care: Table 2 - Measures to Prevent Transmission of HCV).

Monitoring and Medical Management

Recommendations for Monitoring and Medical Management of HCV-Infected Children	
RECOMMENDED	RATING
Routine liver biochemistries at initial diagnosis and at least annually thereafter are recommended to assess for disease progression.	I, C
Appropriate vaccinations are recommended for HCV-infected children not immune to hepatitis B virus and/or hepatitis A virus to prevent these infections.	I, C
Disease severity assessment via routine laboratory testing and physical examination, as well as use of evolving noninvasive modalities (ie, elastography, imaging, or serum fibrosis markers) is recommended for all children with chronic HCV.	I, B
Children with cirrhosis should undergo hepatocellular carcinoma (HCC) surveillance and endoscopic surveillance for varices per standard recommendations.	I, B
Hepatotoxic drugs should be used with caution in children with chronic HCV after assessment of potential risk versus benefit of treatment. Use of corticosteroids, cytotoxic chemotherapy, or therapeutic doses of acetaminophen are not contraindicated in children with chronic HCV.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic HCV.	II, C
Anticipatory guidance about the potential risks of ethanol for progression of liver disease is recommended for children with HCV and their families. Abstinence from alcohol and interventions to facilitate cessation of alcohol consumption, when appropriate, are advised for all persons with HCV infection.	I, C

In children, liver disease due to chronic HCV infection generally progresses slowly, and cirrhosis and liver cancer are infrequently encountered. Although elevated serum aminotransferase levels are often noted, HCV-infected children younger than 3 years virtually never have advanced liver disease.

The initial assessment of children with chronic HCV infection includes exclusion of other causes of liver disease, assessment of disease severity, and detection of extrahepatic manifestations of HCV. Testing for concomitant HBV (HBsAg, anti-HBc, and anti-HBs), HIV (anti-HIV), and immunity to HAV (anti-HAV IgG) are recommended due to shared risk factors and the need to vaccinate all nonimmune children that may not have received routine childhood vaccines against HAV and HBV.

Disease staging in children can be accomplished via physical examination and the assessment of routine laboratory parameters including albumin, serum aminotransferase levels, total bilirubin, international normalized ratio (INR), and platelet count every 6 to 12 months. Serum fibrosis markers also hold promise to stratify disease severity but require further validation (Mack, 2012). Of note, serum aminotransferase levels are not consistently reflective of disease severity in children. In one study nearly 33% of children had normal aminotransferase levels despite substantial necroinflammation on biopsy (Casiraghi, 2004).

For children in whom advanced liver disease is a concern, liver imaging to evaluate for splenomegaly or venous collaterals is recommended initially, using liver ultrasound instead of CT or MRI due to its widespread availability and lack of ionizing radiation. Although liver biopsy is considered the gold standard regarding the grade of inflammation and stage of fibrosis, sampling artifact is problematic and most patients and practitioners prefer noninvasive alternatives, such as liver elastography, to determine the presence/absence of cirrhosis, particularly in children. Ultrasound-based liver elastography in children requires the use of specialized probes and cutoff values for advanced fibrosis/cirrhosis that differ from those used in adults, but this approach appears promising for monitoring children with chronic HCV infection (Behairy, 2016); (Geng, 2016); (Lee, 2013).

Due to the slow rate of fibrosis progression among children, there are few, if any, established bona fide risk factors for disease progression. Development of advanced liver disease in children is infrequent until more than 30 years of infection (Jhaveri, 2011); (Goodman, 2008); (Minola, 2002). However, as in adults, children with comorbid disease—such as obesity with nonalcoholic fatty liver disease and congenital heart disease with elevated right heart pressures—and those receiving hepatotoxic drugs should be monitored carefully for disease progression.

Hepatocellular carcinoma (HCC) is rarely encountered among children and has been reported almost exclusively in children with cirrhosis. There are reports that children with chronic HCV and a history of childhood leukemia may be at increased risk of developing HCC, but evidence is limited (González-Peralta, 2009). In children with cirrhosis, liver ultrasound with or without serum alpha-fetoprotein (AFP) testing every 6 months is recommended for HCC surveillance per AASLD guidelines (Bruix, 2011). A baseline endoscopy is advisable to detect esophageal varices in children with cirrhosis and every 3 years thereafter in the absence of antiviral therapy. After successful antiviral therapy, the risk for cirrhosis complications is substantially less.

In children with advanced fibrosis from chronic HCV, medications that are known to accelerate hepatic fibrosis (eg, methotrexate) should be avoided if possible. Similarly, abstinence from alcohol use is strongly advised to minimize disease progression. Although corticosteroids and other immunosuppressants may enhance HCV replication, they are not contraindicated in children with HCV and should be prescribed for appropriate indications based on overall risk vs benefit. Of note, icteric flares of HCV—as reported in children and adults with chronic HBV—have not been reported in children receiving organ transplants or cytotoxic chemotherapy. Although underlying liver disease is a risk factor for development of sinusoidal obstruction syndrome following bone marrow transplantation, the presence of HCV infection should not delay this therapy.

To remain well, untreated children with chronic hepatitis C are encouraged to maintain a healthy body weight due to the known deleterious effects of insulin resistance on fibrosis progression with HCV infection. Other commonly used medications, such as antimicrobial agents, antiepileptics, and cardiovascular agents, should be dosed per standard recommendations. However, NSAIDs and aspirin should be avoided, if possible, in children with cirrhosis and esophageal varices due to concerns of gastrointestinal bleeding and nephrotoxicity. Acetaminophen is a safe and effective analgesic for children with chronic HCV infection when dosed per package insert recommendations.

Treatment

Recommendations for Whom and When to Treat Among HCV-Infected Children

RECOMMENDED	RATING
If direct-acting antiviral (DAA) regimens are available for a child's age group, treatment is recommended for all HCV-infected children older than 3 years as they will benefit from antiviral therapy, independent of disease severity.	I, B
Treatment of children aged 3 to 11 years with chronic hepatitis C should be deferred until interferon-free regimens are available.	II, C
The presence of extrahepatic manifestations—such as cryoglobulinemia, rashes, and glomerulonephritis—as well as advanced fibrosis should lead to early antiviral therapy to minimize future morbidity and mortality.	I, C

Recommended regimens listed by evidence level and alphabetically for:

Adolescents ≥12 Years Old or Weighing ≥35 kg, Without Cirrhosis or With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naive without cirrhosis or with compensated cirrhosis[a], or treatment-experienced[b] without cirrhosis	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-experienced[b] with compensated cirrhosis[a]	24 weeks	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin[c] for patients with genotype 2 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin[c] for patients with genotype 3 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a]	24 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naive or treatment-experienced[b] without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, B

[a] Child-Pugh A
[b] Patients who have failed an interferon-based regimen, with or without ribavirin
[c] See ribavirin dosing table for recommended weight-based dosages.

Table. Dosing for Ribavirin in Combination Therapy With Sofosbuvir for Adolescents ≥12 Years Old or Weighing ≥35 kg

Body Weight (kg)	Daily Ribavirin Dosage (in 2 divided doses)
<47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
>80	1200 mg/day

Advanced liver disease due to HCV infection is uncommon during the childhood years. However, liver disease progresses over time with increasing fibrosis severity. Although uncommon, cirrhosis is occasionally seen in infected children and adolescents younger than 18. Children have a long life expectancy during which HCV complications may develop. Infected children and adolescents may also transmit HCV to others.

DAA regimens have a very high success rate in adults with chronic HCV infection. In addition, interferon-based regimens have limited success in children with genotype 1 or 4 infection. Interferon and ribavirin have general and pediatric-specific toxicities (eg, temporary growth impairment) that do not occur with DAA regimens. Several clinical trials are underway, early data have been published, and DAA regimens are now available for adolescents 12 years and older. It is anticipated that additional safe and effective DAA regimens will be available for children aged 3 through 11 in the near future.

In a phase 2, multicenter open-label study of 100 adolescents with chronic genotype 1 infection treated for 12 weeks with the adult formulation of ledipasvir-sofosbuvir, sustained virologic response (SVR) was documented in 98% of participants (Balistreri, 2017). The two patients who did not achieve SVR12 were lost to follow-up during or after treatment. Most of the patients were treatment naive (80%). One patient had cirrhosis, 42 did not, and the cirrhosis status was unknown in the remaining 57. The regimen was safe and well tolerated in this population, and the adult dosage formulation resulted in pharmacokinetic characteristics similar to those observed in adults.

The combination of sofosbuvir and ribavirin at doses approved for adults was tested in adolescents with chronic genotype 2 (12 weeks of treatment) or genotype 3 (24 weeks of treatment) infection (Wirth, 2017). Of the 52 adolescents, 75% had genotype 3 infection, and 83% were treatment naive. Cirrhosis status was negative in 40% and unknown in 60% of the participants. SVR12 rates were 100% (13/13) and 97% (38/39) in genotype 2 and 3 infections, respectively. This regimen was safe and well tolerated, and pharmacokinetic properties of sofosbuvir were equivalent to those observed in adults.

Last update: May 24, 2018

Management of Key Populations With Chronic HCV Infection

People who inject drugs (PWID), men who have sex with men (MSM), and individuals in jails and prisons bear a particularly high burden of chronic HCV infection. Injection drug use accounts for the majority of new HCV infections, and the rising opioid epidemic has become an important force in the perpetuation of the HCV epidemic. Acute HCV infection is also increasingly being reported among HIV-infected and -uninfected MSM due to a variety of risk factors. Finally, HCV infection disproportionately affects individuals in correctional institutions, where the prevalence of infection ranges from 17% to 23% (Varan, 2014); (Edlin, 2015), far exceeding the 1.0% prevalence in the general population (Denniston, 2014). More than 90% of these individuals are ultimately released and re-enter the general population, where they can contribute to HCV transmission and develop liver-related and extrahepatic complications (Macalino, 2004); (Rich, 2014).

Achieving the goal of HCV elimination will depend on diagnosing HCV and treating HCV infection in these groups, and implementing harm reduction strategies to prevent future infections. As a result, the panel has chosen to focus attention on HCV management among these key populations to reduce HCV transmission and decrease HCV-related morbidity and mortality. The first subsection of the key populations guidance focuses on recommendations for HCV testing, treatment, and harm reduction among PWID. The second subsection focuses on testing, treatment, and prevention of HCV among MSM. The final subsection provides recommendations for screening and treatment of HCV in jail and prison settings. Chronic HCV cannot be eliminated without implementation of strategies to reach these populations, and the recommendations in these subsections provide guidance in this effort.

The following subsections include guidance for management of patients with HCV in key populations.

- Key Populations: Identification and Management of HCV in People Who Inject Drugs
- HCV in Key Populations: Men Who Have Sex With Men
- HCV Testing and Treatment in Correctional Settings

Last update: May 24, 2018

Key Populations: Identification and Management of HCV in People Who Inject Drugs

Prevalence of HCV Among People Who Inject Drugs

Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence of 10% to 70% depending on geographic location and duration of IDU exposure (Hagan, 2008); (Amon, 2008); (Nelson, 2011). In this section, the term people who inject drugs (PWID) includes individuals who are actively using drugs and those who have previously used injection drugs.

The first few years after an individual begins to inject drugs constitute a high-risk period in which the rate of HCV infection can exceed 40% (Maher, 2006). According to the National Survey on Drug Use and Health, heroin use has increased across the US among men and women, most age groups, and all income levels (CDC, 2015b). IDU accounts for the majority of new HCV infections (approximately 70%) and is the driving force in the perpetuation of the epidemic. Given these facts and the absence of a vaccine against HCV, testing and linkage to care combined with HCV treatment have the potential to dramatically decrease HCV incidence and prevalence (Martin, 2013); (NAS, 2017).

Recommendations for Screening and Treatment of HCV Infection in People Who Inject Drugs (PWID)	
RECOMMENDED	RATING
Annual HCV testing is recommended for PWID with no prior testing, or past negative testing and subsequent injection drug use. Depending on the level of risk, more frequent testing may be indicated.	IIa, C
Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV-antibody testing with reflexive or immediate confirmatory HCV-RNA testing and linkage to care for those who are infected.	IIa, C
PWID should be counseled about measures to reduce the risk of HCV transmission to others.	I, C
PWID should be offered linkage to harm reduction services when available, including needle/syringe service programs and substance use disorder treatment programs.	I, B
Active or recent drug use or a concern for reinfection is **not** a contraindication to HCV treatment.	IIa, B

HCV Testing Among PWID

All individuals who currently inject drugs or have used injection drugs in the past should be tested for HCV infection. Data are limited regarding the optimal interval for repeat testing among individuals actively using drugs. An HCV-antibody test is recommended and if the result is positive, current infection should be confirmed by immediate HCV-RNA testing (see HCV Testing and Linkage to Care). This can be accomplished using phlebotomy for a combined reflex test performed by a laboratory, which is appropriate for clinical settings. In certain community settings, a point-of-care antibody test with an immediate blood draw for a confirmatory HCV-RNA test may be implemented.

Among persons at risk of HCV reinfection after previous spontaneous or treatment-related viral clearance, HCV-RNA

testing is recommended because an HCV-antibody test is expected to remain positive. Among persons with a negative HCV-antibody test who are at high risk for a new HCV infection due to current IDU, testing for HCV RNA or follow-up testing for HCV antibody is recommended if HCV exposure may have occurred within the past 6 months.

Integration of HCV testing services into harm reduction services provided by medication-assisted treatment (MAT) programs, needle/syringe programs, and acute detoxification programs provide an opportunity for routine screening in this key population (Harris, 2010); (Aronson, 2017).

Linkage to HCV Care and Treatment Adherence

Ideally, treatment of HCV-infected PWID should be delivered in a multidisciplinary care setting with services to reduce reinfection risk and manage the common social and psychiatric comorbidities in this population. Regardless of the treatment setting, recent and active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which PWID have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit HCV therapy access in this patient population (Aspinall, 2013); (Hellard, 2014); (Grebely, 2011); (Dore, 2016). Indeed, combining HCV treatment with needle/syringe exchange and opioid substitution treatment programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease.

Modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population (Martin, 2013b). Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned because they create barriers to treatment, add unnecessary cost and effort, miss an opportunity to decrease HCV transmission, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Instead, scaling up HCV treatment in PWID is necessary to positively impact the HCV epidemic in the US and globally.

In addition, recent hepatitis C test-and-link programs have identified the use of patient navigators or care coordinators to be an important intervention in overcoming challenges to linkage to and retention in care (Trooskin, 2015); (Coyle, 2015); (Ford, 2017). The Check Hep C program in New York City compared services delivered at 2 clinical care sites to 2 sites that linked patients to off-site care. Participants receiving clinical care co-located with testing services had higher odds of initiating treatment than those linked to off-site care (Ford, 2017). Ongoing assessment of efficacy and comparative effectiveness of this and additional strategies is a crucial area of future research for patients with chronic HCV. Replication and expansion of best practices and new models for linkage to HCV care will be crucial to maximize the public health impact of newer HCV treatment paradigms.

HCV Treatment Among PWID

Clinical trials among PWID reporting current IDU at the start of HCV treatment and/or continued use during therapy demonstrate SVR12 rates approaching 95% (Dore, 2016); (Grebeley, 2018). Moreover, high SVR rates among PWID are not limited to clinical trials but are also observed in clinical practice settings. A cohort study was conducted with 89 patients initiating HCV treatment between January 2014 and August 2015 at a primary care clinic in the Bronx, New York. Four patient groups were compared: no active drug use or MAT; no active drug use with MAT; active drug use without MAT; and active drug use with MAT. The study found that regardless of active drug use or MAT, patients who received direct-acting antiviral (DAA) therapy at this urban primary care clinic achieved high HCV cure rates (SVR ≥95%) (Norton, 2017).

Furthermore, MAT does not compromise HCV treatment outcomes. Similar SVR12 rates are achieved by PWID engaged in MAT compared to individuals not engaged in MAT in clinical trials involving various DAA regimens (Feld, 2014); (Lalezari, 2015); (Grebely, 2016); (Zeuzem, 2015); (Dore, 2016). HCV-infected patients receiving MAT who were treated with elbasvir/grazoprevir had high rates of adherence to antiviral treatment and SVR12 rates >89% regardless of ongoing IDU (Dore, 2016). Similarly, an SVR12 of 97.4% was reported in a clinical trial evaluating ombitasvir/paritaprevir/ritonavir plus dasabuvir and ribavirin for 12 weeks among patients receiving MAT (Lalezari, 2015). Further, an analysis of a clinical trial evaluating outcomes of sofosbuvir/velpatasvir treatment in patients receiving MAT (n=51) compared to those not receiving MAT (n=984) demonstrated that MAT did not significantly reduce treatment completion, antiviral adherence,

SVR12, or safety (Grebely, 2016).

Recommendation for Testing for Reinfection in People Who Inject Drugs (PWID)	
RECOMMENDED	RATING
At least annual HCV-RNA testing is recommended for PWID with recent injection drug use after they have spontaneously cleared HCV infection or have been successfully treated.	IIa, C

Reinfection

As HCV therapy is expanded to populations of PWID with high-risk behaviors for re-exposure, acknowledgement that HCV reinfection will occur in some individuals is critical, and appropriate strategies must be in place to maximize prevention of reinfection and offer retreatment for reinfection (Grebely, 2017). Importantly, the rate of HCV reinfection in the PWID population is lower (2.4/100 person-years) than the rate of incident HCV infection in the general population of PWID (6.1 to 27.2/100 person-years), although the rate of reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited (Aspinall, 2013); (Grady, 2013).

Data suggest that reinfection is rare in drug users who clear HCV with therapy even if they continue to inject drugs, as long as steps are taken to minimize the risk. Studies of HCV reinfection in PWID have demonstrated rates of reinfection post SVR ranging from 1 to 5/100 person-years in patients who have ever injected drugs, increasing to 3 to 33/100 person-years in patients with continued injecting risk behavior (Midgard, 2016b); (Marco, 2013); (Grebely, 2010); (Grebely, 2012); (Bate, 2010); (Currie, 2008); (Dalgard, 2002); (Grady, 2012). Relapse into drug use has been associated with HCV reinfection after cure (Midgard, 2016b) while interventions that reduce drug use, such as utilization of opiate agonist therapy and mental health services, have been associated with a reduction in HCV reinfection risk (Islam, 2017). These services should be made available to PWID. PWID found to be HCV reinfected should be retreated. Retreatment of a new reinfection should be as detailed in the Initial Treatment section.

Increasing the HCV treatment rate among the PWID population would reduce numbers of new HCV and liver-related disease cases (Jiang, 2017). In a study that evaluated reinfection and injecting risk behavior following DAA therapy, participants on MAT for ≥3 months had a reinfection rate of 2.3/100 person-years, with a persistent reinfection rate of 1.6/100 person-years and a reinfection rate of 4.2/100 person-years among those who reported IDU (Dore, 2017).

Harm Reduction

Harm reduction is a way of preventing disease and promoting health that “meets people where they are” and provides the tools and information they need to keep themselves and those around them well (Logan, 2010). Harm reduction places drug use within the larger sociopolitical spheres of poverty, criminalization, and mental health. Accepting that not everyone is ready or able to curtail or stop high-risk behavior, harm reduction focuses on promoting a spectrum of scientifically proven, practical strategies for reducing the negative consequences of drug use and other high-risk behaviors. Harm reduction strategies include but are not limited to: condom distribution; access to sterile syringes; medication-assisted treatment for opioid dependence (such as methadone, buprenorphine and naltrexone); safe injection spaces; and overdose prevention. Heroin overdose deaths in the US increased 286% from 2002 to 2013 (CDC, 2015b). Naloxone should be prescribed to all PWID. Broad implementation of harm reduction strategies has the potential to significantly impact the HCV epidemic.

Medication-Assisted Treatment

MAT options have been developed for drugs such as heroin, oxycodone, and morphine. The therapies (agonist pharmacotherapy and methadone maintenance) were identified to provide a less harmful opioid (eg, methadone) or an opioid-receptor agonist (eg, buprenorphine) under medical supervision in both specialty and outpatient clinics. Several reviews have identified opioid substitution therapy as effective in reducing illicit opioid use (Mattick, 2009); (Mattick, 2014) and opioid-related death and all-cause mortality (Degenhardt, 2009); (Sordo, 2017), and improving quality of life (Lawrinson, 2008); (Ward, 1999). Participation in methadone maintenance treatment has been demonstrated to be protective against hepatitis C incidence among PWID, with a dose-response protective effect with increasing methadone exposure on hepatitis C incidence (Nolan, 2014).

Syringe Service Programs

Syringe service programs (SSPs) were developed to reduce the spread of bloodborne diseases among injection drug users. These programs provide PWID with sterile syringes and other equipment (cookers, filters, sterile water, alcohol swabs) to reduce the risk of bloodborne disease (eg, HIV and HCV) transmission associated with sharing injection equipment. These programs were developed in the 1980s and often include drug treatment referrals, peer education, and HIV prevention. Areas with greater syringe access through SSPs have lower rates of hepatitis C among PWID. A prospective study of PWID in New York City found a significant decline in HCV rates from 1990 to 2001, corresponding to an increase in the number of syringes distributed by SSPs during this period (Des Jarlais, 2005).

Benefit of Treatment to Reduce HCV Transmission

Persons cured of chronic HCV no longer transmit the virus to others. As such, successful HCV treatment benefits public health. Several health models have shown that even modest increases in successful HCV treatment among PWID can decrease prevalence and incidence (Martin, 2013); (Durier, 2012); (Martin, 2013b); (Hellard, 2014). Models developed to estimate the impact of HCV testing and treatment on the burden of HCV at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated (Wedemeyer, 2014); (Martin, 2015). Elimination of HCV among PWID will also require scaling up harm reduction services (Fraser, 2018).

Last update: May 24, 2018

HCV in Key Populations: Men Who Have Sex With Men

Incidence and Risk Factors for HCV Infection Among HIV-Infected Men Who Have Sex With Men

Several outbreaks of sexually transmitted HCV infection among HIV-infected men who have sex with men (MSM) have been reported since 2000 (Matthews, 2007); (Urbanus, 2009); (van de Laar, 2010); (Wandeler, 2012). A recent systematic review reported an HCV incidence of 6.35/1000 person-years among HIV-infected MSM (Jin, 2017). The determinants of sexually transmitted, incident HCV among HIV-positive MSM have not been thoroughly characterized but risk factors have been identified. Group sex practices that can cause trauma to rectal mucosal tissue (eg, receptive anal intercourse without a condom, receptive fisting) and rectal bleeding are associated with HCV transmission among HIV-infected MSM (Apers, 2015); (CDC, 2011); (Danta, 2007); (Daskalopoulou, 2017); (Page, 2016); (Schmidt, 2011); (Vanhommerig, 2015); (Wandeler, 2012); (Witt, 2013).

The recent proliferation of ChemSex (also known as Party and Play or PNP)—use of crystal methamphetamine, mephedrone, or gamma-hydroxybutyrate, sometimes with phosphodiesterase type 5 inhibitors (which lowers inhibitions, creates feelings of invulnerability, increases stamina, and inhibits ejaculation) before or during sex—has also been associated with incident HCV infection (56 Dean Street, 2014); (Pufall, 2016); (Hegazi, 2017). These HCV infections have been occurring especially in men who already have ulcerative and rectal sexually transmitted infections including syphilis, lymphogranuloma venereum, and genital herpes (Bottieau, 2010); (Browne, 2004); (Gambotti, 2005); (Ghosn, 2004); (Gotz, 2005); (van de Laar, 2007).

While it is not completely clear why higher rates of incident HCV have been reported in HIV-infected compared to uninfected MSM, behavioral factors such as serosorting (sex between partners of the same HIV status with the aim of minimizing HIV transmission risk) and increased rates of anal sex without condoms by HIV-infected men have been implicated (Mao, 2011). In a recent study of 33 HIV/HCV-coinfected MSM, one-third shed HCV in their semen (Turner, 2016). In addition to being found in semen, rectal shedding of HCV has also been reported in HIV/HCV-coinfected MSM (Foster, 2017b).

Incidence and Risk Factors for HCV Infection Among HIV-Uninfected Men Who Have Sex With Men

Acute HCV infections have been recently reported among HIV-uninfected MSM who present for pre-exposure prophylaxis (PrEP) (Hoornenborg, 2017). These HIV-uninfected men became infected with HCV strains known to be circulating in HIV sexual transmission networks. Thus, there is growing concern that with the implementation of PrEP, high risk HIV-uninfected MSM may be at increased risk of incident HCV through unprotected sexual intercourse with HCV-infected MSM. The risk factors for acute HCV infection in these patients remain unknown but may be similar to those reported in HIV-infected MSM.

Testing

Recommendations for Testing and Prevention of HCV Infection in Men Who Have Sex With Men (MSM)	
RECOMMENDED	RATING
Annual HCV testing is recommended for sexually active HIV-infected adolescent and adult MSM. Depending on the presence of high-risk sexual or drug use practices, more frequent testing may be warranted.	IIa, C
HCV testing at HIV pre-exposure prophylaxis (PrEP) initiation and at least annually thereafter (while on PrEP) is recommended in HIV-uninfected MSM. Depending on sexual or drug use risk practices, more frequent testing may be warranted.	IIa, C
All MSM should be counseled about the risk of sexual HCV transmission with high-risk sexual and drug use practices, and educated about measures to prevent HCV infection or transmission.	IIa, C

Screening for HCV Infection Among MSM

Practitioners treating HIV-infected adolescent and adult MSM should be on high alert for acute HCV infection, which is most often asymptomatic (see the HCV in Children section). In accordance with Centers for Disease Control and Prevention sexually transmitted diseases (STDs) screening recommendations, HCV screening should be performed at least annually and may be done more frequently, depending on the presence of local and individual factors such as high HCV prevalence and/or incidence locally, high-risk sexual behavior (eg, unprotected [by a condom] receptive anal intercourse, group sex, fisting, ChemSex), and ulcerative STD(s) or STD-related proctitis (Apers, 2015); (Bottieau, 2010); (Browne, 2004); (CDC, 2011); (56 Dean Street, 2014); (Danta, 2007); (Daskalopoulou, 2017); (CDC, 2015); (Pufall, 2016); (Gambotti, 2005); (Ghosn, 2004); (Gotz, 2005); (Page, 2016); (Schmidt, 2011); (van de Laar, 2007); (Vanhommerig, 2015); (Wandeler, 2012); (Witt, 2013).

Screening should be performed using an HCV-antibody test in most instances. However, individuals with self-reported recent high-risk exposures and/or newly elevated alanine aminotransferase (ALT) levels should have HCV screening with both HCV-antibody and HCV-RNA tests due to concern for acute HCV infection. Those found to be chronically HCV-infected should be offered antiviral treatment to prevent liver disease progression and transmission to others. These patients should also be counseled about risk factors for HCV transmission and the potential for HCV reinfection after cure (Ingiliz, 2014); (Ingiliz, 2017); (Lambers, 2011). Subsequent care for acute HCV should be as detailed in the Management of Acute HCV section.

Prevention of HCV Infection

To reduce the risk of sexually transmitted HCV and other STDs, MSM should be counseled to use condoms with all sex acts. They should also be informed about the high risk of HCV transmission associated with sharing any equipment used for preparing and injecting or snorting drugs. If indicated (and available), providers should offer referrals to syringe service programs and culturally competent counseling/drug treatment, and encourage patients to seek testing for sexually transmitted infections if they have been at risk. Among patients who are using opioids, discussion of preventing HCV infection is also an opportunity to provide opioid education and naloxone distribution (OEND), which is an effective

intervention to prevent overdose death.

Although PrEP can prevent sexual transmission of HIV, it is not protective against HCV or other sexually transmitted infections. HIV-uninfected MSM who present for PrEP should receive risk reduction counseling. HIV-uninfected MSM on PrEP should also receive at least annual HCV screening for identification of incident infections.

Treatment

Recommendation on Treatment of HCV in Men Who Have Sex With Men (MSM)	
RECOMMENDED	RATING
Antiviral treatment for HCV-infected MSM should be coupled with ongoing counseling about the risk of HCV reinfection, and education about methods to reduce HCV reinfection risk after cure.	I, B

Since MSM may be at high risk of transmitting HCV to others, HCV infection should be treated both for individual benefit and to prevent HCV transmission. HIV-infected MSM are considered an important population for HCV elimination through treatment as prevention (Martin, 2015). The population-level benefit of expansion of HCV treatment in populations of HIV-infected MSM has been evaluated in modeling studies (Martin, 2016); (Salazar-Vizcaya, 2016). Additionally, real-world data support the potential for HCV treatment as prevention in cohorts of HIV/HCV-coinfected MSM. Analysis of data from the Dutch acute HCV in HIV study group (DAHHS) showed a 50% reduction in acute HCV incidence between 2014 and 2016 within 1 year of expansion of HCV therapy through unrestricted direct-acting antiviral (DAA) availability to HIV-infected MSM (Boerekamps, 2017).

HCV treatment should be coupled with education addressing the potential for HCV reinfection and risk factors for transmission to reduce the risk of transmission to others and subsequent reinfection after HCV cure. Brief counseling interventions delivered in clinical settings have been shown to reduce HIV transmission risk and may be effective in reducing HCV transmission risk (Boerekamps, 2017); (Myers, 2010); (Richardson, 2004).

Testing for HCV Reinfection

Recommendation on Prevention of HCV Reinfection in Men Who Have Sex With Men (MSM)	
RECOMMENDED	RATING
At least annual (and risk-based, if indicated) HCV testing with HCV RNA is recommended for sexually active MSM after successfully treated or spontaneously cleared HCV infection.	IIa, C

High HCV reinfection rates, ranging from 7.3 to 15.2/100 person-years, have been reported after HCV treatment and cure among HIV-infected MSM (Ingiliz, 2017); (Lambers, 2011); (Martin, 2015b). The risk of HCV reinfection may also increase with each subsequent infection treated or cleared. In an analysis of 606 MSM from 8 centers in Europe, an increase in

HCV reinfection incidence rates was reported with each subsequent reinfection (HCV reinfection incidence 7.3/100 person-years for the first reinfection and 18.8/100 person-years for the second reinfection) (Ingiliz, 2017). For this reason, it is important to provide patients with clear, nonjudgmental, accurate information about reducing their risk for sexually transmitted HCV. This counseling should be ongoing. Additionally, clinicians should monitor and test for HCV reinfection in sexually active MSM after cure, regardless of HIV status. Individuals found to be HCV reinfected should be retreated. HCV treatment in this setting should be as detailed in the Initial Treatment of HCV section.

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HCV Testing and Treatment in Correctional Settings

Prevalence of HCV infection in Correctional Settings

HCV infection disproportionately affects individuals in correctional institutions, which include jails (short-stay facilities that typically house persons for sentences of up to 1 year) and prisons (long-term facilities for persons with a felony conviction). A 2003 Centers for Disease Control and Prevention (CDC) survey based on data derived from 8 states estimated that 16% to 41% of US inmates had serological evidence of prior HCV exposure and 12% to 35% had chronic infection (Allen, 2003); (Weinbaum, 2003). More recent analyses suggest that the seroprevalence of HCV infection in incarcerated populations ranges from 17.4% to 23.1% (Varan, 2014); (Edlin, 2015). However, HCV prevalence in correctional populations is not geographically uniform and can vary by state and region (Varan, 2014). These estimates far exceed the 1.0% HCV prevalence in the general population (Denniston, 2014). Injection drug use is the most common risk factor for HCV transmission in correctional settings (Ruiz, 1999); (Spaulding, 2006). HCV-associated liver disease is a frequent cause of death in inmates and has recently surpassed death from HIV (Spaulding, 2011); (Spaulding, 2015).

Approximately 30% of all persons with HCV infection in the US spend at least part of the year in a correctional institution (Hammett, 2002); (Varan, 2014). Unfortunately, most HCV-infected individuals in correctional facilities are unaware of their infection (Spaulding, 2012). Given the high prevalence of HCV infection in correctional settings coupled with the fact that more than 10 million individuals pass through jails and prisons each year, as many as 1 million persons with undiagnosed HCV infection might come into contact with the correctional system each year (Spaulding, 2012); (Rich, 2014). More than 90% of these individuals are eventually released and re-enter the general population, where they can contribute to HCV spread in the community (Macalino, 2004); (Rich, 2014) and may have little contact with the healthcare system (Fox, 2005); (Bushway, 2006); (Rich, 2014b); (Neate, 2016). Moreover, 68% of prisoners are reincarcerated for a new crime within 3 years of their release from prison (Durose, 2014). Recidivism can further promote the spread of HCV within correctional settings.

Both the US Preventive Services Task Force and the World Health Organization recommend that all incarcerated persons undergo HCV testing (WHO, 2016); (Moyer, 2013b). Despite these recommendations and the high prevalence of HCV infection in correctional institutions, HCV testing is not universally performed in this setting.

Current Approaches to HCV Testing and Treatment in Jails

HCV testing and treatment have been historically uncommon in jails, primarily because of the short duration of incarceration and lack of available resources (Maurer, 2015). With approximately 11 million jail admissions annually (Minton, 2016), jails represent an important public health setting in which to test for HCV infection and treat persons with chronic HCV.

Jails have also not had the resources and systems to enable continuation of community-initiated HCV therapy. If detainees are unable to continue HCV treatment while incarcerated in jail, the interruption in therapy will adversely affect the likelihood of achieving a cure and could promote development of viral resistance. Without systems to facilitate continuation of HCV therapy, jails may interfere with community HCV treatment efforts and societal payers will suffer losses on investments.

Current Approaches to HCV Testing and Treatment in Prisons

The bulk of the evidence on current HCV testing and treatment in the prison setting is based on a 2015 national survey conducted by the American Correctional Association and the Coalition of Correctional Health Authorities research and health outcomes working group (Maurer, 2015). According to this survey, some type of HCV testing is performed in the majority of prisons but routine opt-out testing is generally not conducted across the prison system. Additionally, there are major differences in approaches to HCV testing and prevention counseling. The most common triggers for HCV testing in a prison setting were physician request, identified risk factors, and inmate request. Only 16% of prison facilities tested all inmates with an HCV-antibody test upon entry. Selection of patients for antiviral therapy also varied across prison systems. The survey found that antiviral therapy for chronic HCV was available in 90% of prisons. However, few inmates actually received treatment, primarily due to antiviral therapy expense and lack of availability of trained staff. Moreover,

despite the fact that injection drug use was the major risk factor for HCV transmission in this population, only half of the prison facilities combined substance use disorder treatment with HCV therapy.

More recently, investigators at Yale University administered a survey to the directors of the departments of corrections in all 50 US states that inquired about current HCV practices within state correctional facilities (Beckman, 2016). This survey included questions about the number of inmates in the state's prisons known to be HCV-infected on or about December 31, 2014; the number of prisoners receiving any form of HCV treatment at that time; and the availability of relevant resources for inmates with known HCV infection. Representatives from 41 states completed the questions on the number of inmates with chronic HCV infection and the proportion receiving antiviral treatment. The overall number of inmates who were reported to have chronic HCV in the 41 reporting states was 106,266 prisoners, corresponding to 10% of the overall prison population in these states. Among these inmates, only 0.89% (n=949) received any form of HCV treatment on or about December 31, 2014. States used a variety of factors to prioritize HCV treatment among inmates, particularly cirrhosis, sentence length, likelihood of recidivism, potential for antiviral adherence, and chance of HCV reinfection. States with a relatively high proportion of inmates reported to have HCV infection did not treat a greater number of patients than states with a low proportion of infections.

Representatives from 49 of the state departments of corrections completed the questions on resources related to HCV infection. Seventeen states reported offering routine opt-out HCV testing of inmates. Among the 32 states without routine opt-out HCV testing, the main indications for HCV testing were abnormal results from other tests, HIV infection, or a substance use disorder. Medication-assisted treatment programs for substance use disorders were available through 14 state departments of corrections. Four states reported that they followed all of the Federal Bureau of Prisons guidelines (FBP, 2016).

Increased HCV Testing and Treatment in Correctional Institutions Will Aid HCV Elimination

Given the high prevalence of HCV among persons in the US correctional system, the success of the national HCV elimination effort will depend on identifying chronically infected individuals in jails and prisons, linking these persons to medical care for management, and providing access to antiviral treatment (NAS, 2017). Diagnosis of chronic HCV in correctional settings followed by linkage to care and successful antiviral treatment can ultimately reduce the risk of liver-related and extrahepatic complications, and has the potential to decrease HCV transmission in correctional facilities and the community after release (van der Meer, 2012); (Harris, 2016); (He, 2016).

Recommendations for Screening and Treatment of HCV Infection in Jails

RECOMMENDED	RATING
Jails should implement opt-out HCV testing consisting of HCV-antibody testing followed by confirmatory HCV-RNA testing if antibody-positive. • Chronically infected individuals should receive counseling about HCV infection and be provided linkage to follow-up community healthcare for evaluation of liver disease and treatment upon release. • Chronically infected individuals whose jail sentence is sufficiently long to complete a recommended course of antiviral therapy should receive treatment for chronic HCV infection according to AASLD/IDSA guidance while incarcerated. Upon release, patients should be provided linkage to community healthcare for surveillance for HCV-related complications.	IIa, C

Recommendations for Screening and Treatment of HCV Infection in Prisons	
RECOMMENDED	RATING
Prisons should implement opt-out HCV testing. Chronically infected individuals should receive antiviral therapy according to AASLD/IDSA guidance while incarcerated. Upon release, patients should be provided linkage to community healthcare for surveillance for HCV-related complications.	IIa, C
To prevent HCV reinfection and reduce the risk of progression of HCV-associated liver disease, prisons should provide harm reduction and evidence-based treatment for underlying substance use disorders.	IIa, C

Recommendation for Continuation of HCV Treatment in Jail and Prison Settings	
RECOMMENDED	RATING
Jails and prisons should facilitate continuation of HCV therapy for individuals on treatment at the time of incarceration.	IIa, C

Opt-Out Testing for HCV Infection in Jails and Prisons

Interventions to reduce HCV transmission and HCV-related liver disease can only be implemented if infected patients are diagnosed. Given the variable approaches to HCV testing across correctional facilities (Maurer, 2015), patients with chronic HCV in these settings may not have the opportunity to be diagnosed (Varan, 2014). Universal opt-out testing of inmates for chronic HCV is highly cost-effective and has been shown to reduce ongoing HCV transmission and the incidence of advanced liver disease (He, 2016). Based on a microsimulation model of HCV transmission and disease progression, this approach would enable diagnosis of 122,700 new HCV infections in prisons in the next 30 years; prevent 12,700 new HCV infections caused by release of infected inmates; and avert 11,700 liver-related deaths (He, 2016).

In October 2016, the Federal Bureau of Prisons recommended an opt-out strategy of testing for HCV infection for all sentenced inmates (FBP, 2016). With this approach, an inmate is informed of the indications and plan for HCV testing, and the test is ordered and performed unless the inmate declines it. However, the Federal Bureau of Prisons clinical guidelines state that HCV testing is not required by policy or law. Thus, it is unclear if prisons are conforming to these recommendations.

HCV-infected individuals in jails frequently cycle in and out of this setting, are unaware of their infection, and can contribute to HCV transmission in the community (Rich, 2014). Therefore, providing opt-out HCV testing in jails followed by linkage to community healthcare providers for those found to be infected is an advantageous approach to HCV case finding in these settings. A recent prospective cohort study evaluated an HCV testing and linkage-to-care program implemented in selected jails in North Carolina and South Carolina from December 2012 to March 2014 (Schoenbachler, 2016). HCV testing and linkage-to-care services were conducted by noncorrectional staff in parallel with correctional healthcare staff. Forty-eight percent of detainees with chronic HCV who were referred for management after release attended a follow-up appointment. Similar programs have been established in New York (Akiyama, 2016), Texas (de la Flor, 2017), and Rhode Island (Beckwith, 2016) with the latter using rapid, point-of-care HCV-antibody testing. These studies demonstrate the feasibility of HCV testing in jails followed by linkage to medical care after release for those who

are chronically infected.

HCV DAA Treatment in Jails

A recent observational cohort study demonstrated the feasibility of initiating and completing direct-acting antiviral (DAA) HCV treatment in a jail setting (MacDonald, 2017). In this study, 104 detainees in the New York City jail system received DAA treatment between January 1, 2014 and June 30, 2016, of whom 60% (n=62) entered the jail on DAA therapy and 40% (n=42) initiated DAA treatment in jail. HCV viral loads were undetectable in 94% of community-initiated patients and 97% of jail-initiated patients. This study provides evidence that jail-based initiation of HCV treatment is feasible and prompt access to DAAs in jail can preserve the effectiveness of community-initiated HCV regimens.

HCV DAA Treatment in Prisons

HCV DAA therapy for chronic HCV is now logistically feasible within the prison setting and would aid the HCV elimination effort (Spaulding, 2013). The availability of all-oral DAA regimens that commonly require no more than 12 weeks of therapy and cause few adverse effects overcomes many of the logistical challenges associated with interferon-based HCV treatment (Spaulding, 2013). Directly observed therapy is the norm in prison settings, and the risk of drug diversion is low. Returning inmates to their communities cured of chronic HCV would be an invaluable step toward HCV elimination. In addition to these clinical benefits, treating chronic HCV in incarcerated persons is cost-effective. A recent analysis found that sofosbuvir-based treatment for HCV genotype 1 monoinfection met the benchmark for cost-effectiveness in terms of the benefits gained (Liu, 2014).

Treatment of Substance Abuse Disorders

Given that injection drug use is the major risk factor for initial HCV infection and reinfection, and because alcohol abuse/dependence is a major cofactor in HCV-related liver disease progression, treatment of concomitant substance use disorders along with HCV therapy is of major importance in the incarcerated population. The most effective way to prevent HCV transmission in people who inject drugs is to combine harm reduction strategies that improve the safety of injection (ie, needle/syringe exchange) with interventions that treat the underlying addiction, particularly medication-assisted treatment (MacNeil, 2011); (Volkow, 2014) (see Identification and Management of HCV in People Who Inject Drugs). Alcohol prevention and treatment programs have not been given the same priority as those for drug addiction in correctional settings, and access to treatment for alcohol abuse/dependence after release is often limited. Addressing hazardous alcohol use among inmates with chronic HCV could help slow liver disease progression, decrease HCV transmission, and might reduce recidivism. However, according to the 2015 survey by the American Corrections Association (Maurer, 2015), slightly more than half of correctional systems treat the fundamental substance use disorders among patients receiving HCV antiviral therapy.

Overcoming Barriers to HCV Testing and Treatment in Correctional Settings

To expand HCV testing and prevention counseling and increase access to HCV therapy in correctional institutions, it will be necessary to overcome several important barriers. First, appropriately trained staff are needed to screen inmates for HCV infection and, depending on the result, provide counseling on HCV prevention, linkage to care, and access to antiviral treatment. Offsite providers can assist in these endeavors but add expense and logistical complications. The use of telemedicine to link inmates to specialists has been shown to be effective for the evaluation and treatment of chronic HCV in underserved settings (Arora, 2011). The National Commission on Correctional Health Care supports telemedicine in corrections. However, only 30 of the 45 states responding to the 2016 National Survey of Prison Health Care reported using telemedicine (Maruschak, 2016).

Second, unplanned transfers and releases could disrupt ongoing HCV treatment (Spaulding, 2013). Most state correctional facilities do not have a process in place to smoothly transition a patient receiving DAA treatment in a prison setting to continuing community-based care without a lapse in antiviral therapy. However, the New York State Hepatitis C Continuity Program demonstrated that it is possible to establish a network of community-based providers to facilitate continuation of HCV treatment without interruption after release (Klein, 2007). In this program, inmates who initiated HCV treatment in prison were transitioned to a community-based provider for completion of therapy after release. Inmates diagnosed with chronic HCV who remained untreated while incarcerated were referred to a community provider for

treatment evaluation after release.

Finally, the costs of HCV testing and antiviral treatment in correctional facilities are also formidable barriers. Strategies for financing HCV treatment have been put forward by the National Academy of Medicine's Committee for a National Strategy for the Elimination of Hepatitis B and C (NAS, 2017). These strategies might help to overcome cost barriers to HCV testing and treatment in correctional settings.

Addressing these barriers will help ensure that persons residing in jails and prisons can undergo HCV testing and be diagnosed; have access to HCV prevention counseling; and receive treatment for chronic HCV and underlying substance use disorders. Improving the diagnosis and management of HCV infection in correctional settings will greatly facilitate efforts to eliminate HCV infection in the US.

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