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

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version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this.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.

Last update: November 6, 2019

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.

Last update: November 6, 2019

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 recommendations	The guidance is presented in the form of recommendations. Each recommendation is rated in terms of the level of the evidence and strength of the recommendation using a modification of the scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (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 recommendations and supporting information	Draft recommendations are developed by subgroups of the full panel with interest and expertise in particular sections of the guidance. Following development of supporting text and references, the sections are reviewed by the full panel and chairs. A penultimate draft is submitted to the AASLD and IDSA governing boards for final review and approval before posting online on the website, www.hcvguidelines.org. Subgroups of the panel meet regularly by conference call as needed to update recommendations and supporting evidence. Updates may be prompted by new publications or presentations at major national or international scientific conferences, new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety warnings, or other information that may have a substantial impact on the clinical care of patients. Updates and changes 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)

Last update: November 6, 2019

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.

Last update: August 27, 2020

HCV Testing and Linkage to Care

One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing

RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy.	I, B
Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP).	IIa, C

Risk Activities

- Injection drug use (current or ever, including those who injected only once)
- Intranasal illicit drug use
- Men who have sex with men

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 needlestick, sharps, or mucosal exposure to HCV-infected blood
- Children born to HCV-infected women
- Recipients of a prior transfusion or organ transplant, 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
- Chronic liver disease and/or chronic hepatitis, including unexplained elevated alanine aminotransferase (ALT) levels
- Solid organ donors (living and deceased) and solid organ transplant recipients

Recommendations for One-Time Hepatitis C Testing

Based on the 2013-2016 NHANES data among the general noninstitutionalized US population, an estimated 4.1 million people have had HCV exposure (HCV-antibody–positive), including 2.4 million with active HCV infection (HCV-RNA–positive) (Hofmeister, 2019). Total HCV burden in the US also includes those not accounted for in NHANES data—incarcerated, institutionalized, or unsheltered homeless persons—with estimates ranging from 380,000 to 800,000 additional HCV-antibody–positive persons (Hofmeister, 2019); (Edlin, 2015). Approximately 50% of all infected persons are unaware that they have HCV (Holmberg, 2013); (Denniston, 2012).

HCV screening is recommended because of the known 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 (Chou, 2020); (Owens, 2020); (Schillie, 2020); (Smith, 2012).

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 is generally inefficient except among HIV-infected men who have unprotected sex with men (Pakianathan, 2018).

Injection drug use (IDU) poses the greatest 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 in the US prior to 1992 (after which routine screening of the blood supply was implemented); receipt of clotting factor concentrates in the US before 1987; receipt of blood or blood products in other countries (risk depends on country and screening practices); long-term hemodialysis; needlestick injuries among healthcare workers; and patient-to-patient transmission resulting from poor infection control practices. Other risk factors include having been born to an HCV-infected mother, incarceration, and percutaneous or parenteral exposures in an unregulated setting. Examples include tattoos received outside of licensed parlors and medical procedures performed 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 (Schillie, 2020); (Owens, 2020). An estimated 12% to 39% of incarcerated persons in North America are HCV-antibody–positive, supporting the recommendation to test this population for HCV (Larney, 2013); (Allen, 2003); (Weinbaum, 2003).

Because of shared transmission modes, persons with HIV infection are at risk for HCV. Annual HCV testing is recommended for sexually active HIV-infected adolescent and adult men who have sex with men. The presence of concomitant ulcerative sexually transmitted infections, proctitis related to sexually transmitted infections, or high-risk sexual or drug use practices may warrant more frequent testing. Sexual transmission is particularly a risk for HIV-infected men who have unprotected sex with men (Hosein, 2013); (van de Laar, 2010). Testing sexually active, non-HIV–infected persons for HCV infection before starting and while receiving pre-exposure prophylaxis (PrEP) for HIV prevention should also be considered (Hoornenborg, 2020); (Volk, 2015).

Data also support testing in all deceased and living solid organ donors because of the risk of HCV infection posed to the recipient (Lai, 2013); (Seem, 2013). Although hepatitis C testing guidelines from the US CDC and the USPSTF do not specifically recommend testing immigrants from countries with a high HCV prevalence (eg, Egypt and Pakistan), such persons 18 years or older are included in the one-time, opt out HCV testing recommendation.

CDC established risk-based HCV testing guidelines in 1998 (CDC, 1998). These guidelines were expanded in 2012 with a recommendation to offer one-time HCV testing to all persons born from 1945 through 1965 without prior ascertainment of HCV risk factors. This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify >50% of HCV infections, due in part to patient underreporting of their risk and provider limitations in ascertaining risk factor information. The USPSTF also recommended 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.

Since the birth cohort recommendation was adopted, however, there has been an increase in the number of acute and chronic HCV infections reported in individuals born after 1965 (Zibbell, 2018); (Ly, 2017); (Suryaprasad, 2014). The increase in HCV incidence and prevalence among a younger cohort results from the opioid epidemic and increased IDU. This shift in HCV epidemiology and the known failures of risk-based testing warranted an expansion of the recommendation. Accordingly, CDC updated screening recommendations in 2020 to include HCV screening at least once in a lifetime for all adults aged ≥18 years as well as HCV screening of all pregnant women during each pregnancy, except in settings where the prevalence of HCV infection (ie, HCV-RNA positivity) is <0.1%. Both recommendations were based on extensive literature review and estimates of cost-effectiveness of screening. In their recommendation, CDC noted that no states have an estimated HCV-RNA prevalence <0.1% (Schillie, 2020). USPSTF also recently issued recommendations for one-time, routine, opt out testing of adults aged 18 through 79 years (Owens, 2020).

For the CDC 2020 testing guidelines, a systematic review included a harms assessment for hepatitis C screening during pregnancy. This review was augmented by input from subject matter experts, studies not captured through the formal literature review, and the peer-review process. Despite several plausible harms (including insurability and employability issues, legal ramifications and potential loss of infant custody, unnecessary cesarean deliveries, and unnecessary avoidance of breastfeeding), CDC concluded that identified or potential harms did not outweigh the benefits of HCV screening (Schillie, 2020).

Generally, routine HCV testing is cost-effective because of increasing HCV incidence and prevalence among people who inject drugs (PWID) and the decreasing cost of DAA therapy. Many patients at greatest risk for HCV infection and transmission do not readily report their highly stigmatized risk activities. Studies conducted in US urban emergency departments, for example, reveal that 15% to 25% of patients with previously unidentified HCV infection were born after 1965 and/or have no reported history of IDU and are, therefore, missed by even perfect implementation of risk-based testing guidance (Schechter-Perkins, 2018); (Hsieh, 2016); (Lyons, 2016). Reinfection among those actively using drugs is common, but because HCV testing is a low-cost intervention and therapy is both highly effective and cost-effective, routine testing provides good economic value (ie, cost-effectiveness) even when many people need to be tested and treated more than once during their lifetime.

Several cost-effectiveness studies published since release of the birth cohort recommendations have demonstrated that routine, one-time HCV testing among all adults in the US would likely identify a substantial number of HCV cases that are currently being missed, and that doing so would be cost-effective. One research group employed simulation modeling to compare several versions of routine guidance, including routine testing for adults aged ≥40 years, ≥30 years, and ≥18 years. The investigators found that routine HCV testing for all adults ≥18 years was cost-effective compared to current guidance, and potentially cost-saving compared to testing only those aged ≥30 years or ≥40 years (Barocas, 2018). The study further demonstrated that routine testing remained cost-effective unless HCV infection had no impact on healthcare utilization and no impact on quality of life. Another research team similarly found that routine HCV testing for all adults aged ≥18 years is likely cost-effective compared to current guidance, provided the HCV prevalence among those born after 1965 is >0.07% (Eckman, 2019). Notably, these studies reached similar conclusions despite being conducted independently and employing different simulation modeling approaches. Further, a variety of studies have tested the cost-effectiveness of routine HCV testing in specific venues, including correctional settings (He, 2016), substance use treatment centers (Schackman, 2018); (Schackman, 2015), and federally qualified health centers (Assoumou, 2018). All of these studies demonstrated that routine HCV testing and treatment was cost-effective, even when linkage to HCV treatment after testing was poor and the rate of HCV reinfection among injection drug users was high.

Analyses focusing on pregnant women have demonstrated similar findings. One analysis calculated an incremental cost-effectiveness ratio (ICER) of $2,826 per quality-adjusted life-year (QALY) gained for universal screening of pregnant women compared with risk-based screening at an HCV-RNA positivity prevalence of 0.73% (Chaillon, 2019). Although real-world data informing screening during each pregnancy are lacking, a modeled analysis suggested that hepatitis C screening during each pregnancy would be cost-effective. Using a hepatitis C prevalence of 0.38% among pregnant women, the analysis found that universal hepatitis C screening during the first trimester of each pregnancy compared with the current practice of risk-based screening had an ICER of $41,000 per QALY gained (Tasillo, 2019). Universal screening reduced HCV-attributable mortality by 16% and increased the proportion of infants identified as HCV-exposed, from 44% to 92%. ICER remained at or below $100,000 per QALY gained if hepatitis C prevalence was higher than

0.16% (Schillie, 2020).

Evidence regarding the frequency of HCV testing in persons at risk for ongoing exposures to the virus is lacking. Clinicians should, therefore, determine the periodicity of testing based on the risk of infection or reinfection. Because of the high incidence of HCV infection among PWID and HIV-infected men who have unprotected sex with men, HCV testing at least annually using an assay that detects HCV RNA (ie, a quantitative HCV-RNA test) if they have been previously exposed, is recommended among such individuals (Newsum, 2017); (Aberg, 2014); (Witt, 2013); (Bravo, 2012); (Linas, 2012); (Wandeler, 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).

Initial HCV Testing and Follow-Up

Recommendations for Initial HCV Testing and Follow-Up

RECOMMENDED	RATING
HCV-antibody testing with reflex HCV RNA polymerase chain reaction (PCR) testing is recommended for initial HCV testing.	I, A
Among persons with a negative HCV-antibody test who were exposed to HCV within the prior 6 months, HCV-RNA or follow-up HCV-antibody testing 6 months or longer after exposure is recommended. HCV-RNA testing can also be considered for immunocompromised persons.	I, C
Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, HCV-RNA testing is recommended because a positive HCV-antibody test is expected.	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 may be considered for those in whom it may alter treatment recommendations.	I, A
Persons found to have a positive HCV-antibody test and negative results for HCV RNA by PCR should be informed that they do not have evidence of current (active) HCV infection but are not protected from reinfection.	I, A

All persons for whom HCV screening is recommended 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. Point-of-care assays are valuable in the community setting and allow for sample collection with a finger stick rather than standard phlebotomy. If point-of-care assays are used, reporting of results to the medical record and health authorities should follow protocols used for laboratory-based HCV-antibody tests. When possible, positive point-of-care antibody tests should be followed-up with immediate HCV-RNA confirmatory testing rather than referring the patient to another provider or setting to have the test performed. Table 1 lists FDA-approved, commercially available HCV-antibody screening assays.

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 Assay	Siemens Healthcare Malvern, PA, USA	CLIA[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)
Elecsys™ Anti-HCV II	Roche Diagnostics Indianapolis, IN, USA	ECLIA[e] (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. Rochester, NY, USA	CLIA[b] (automated)

[a] EIA: enzyme immunoassay
[b] CLIA: chemiluminescent immunoassay
[c] CMIA: chemiluminescent microparticle immunoassay
[d] MEIA: microparticle enzyme immunoassay
[e] ECLIA: electrochemiluminescent immunoassay

A positive HCV-antibody test indicates current (active) HCV infection (acute or chronic), past infection that has resolved, or rarely a false positive result (Pawlotsky, 2002). A test to detect HCV viremia is therefore necessary to confirm active HCV infection and guide clinical management, including initiation of HCV treatment. Many reference laboratories now offer HCV-antibody testing that automatically reflexes to HCV-RNA PCR testing if the antibody test is positive. This should be considered the optimal testing approach in a clinical setting because it requires only a single blood draw without the need to bring people back to care for confirmatory testing, a major barrier in the continuum of care (Mera, 2016). Collection of dried blood spot (DBS) samples also allows for assessment of HCV antibodies and reflex HCV-RNA testing by testing spots sequentially. DBS samples can be collected using a finger stick rather than phlebotomy and can be transported without an intact cold chain, making it useful in rural areas and in people for whom phlebotomy may be a testing barrier (Lange, 2017).

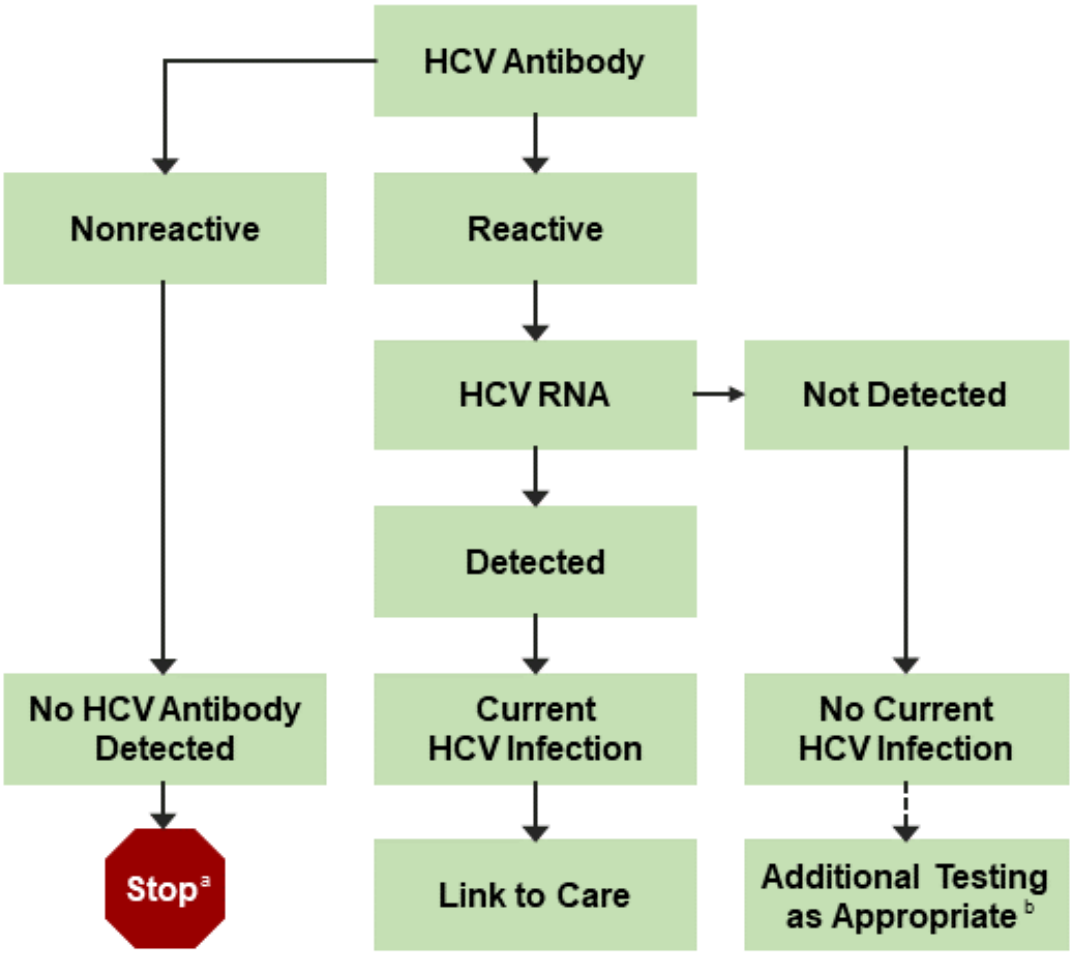
HCV-RNA testing should also be performed in persons with a negative HCV-antibody test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or might have been exposed to HCV within the last 6 months because these persons may be HCV antibody negative. An HCV-RNA test is also needed to detect reinfection in HCV-antibody–positive persons after previous spontaneous or treatment-related viral clearance.

Detection of HCV core antigen in the blood also indicates active HCV infection. Because the sensitivity of HCV core

antigen testing is less than that of HCV-RNA testing, if an HCV core antigen test is used to assess viremia, antibody-positive samples that test negative for HCV core antigen should have a confirmatory HCV-RNA test to exclude a false negative core antigen result (van Tilborg, 2018).

An FDA-approved quantitative or qualitative HCV-RNA test with a detection level of ≤25 IU/mL should be used to detect HCV RNA. Figure 1 shows the CDC-recommended HCV testing algorithm.

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).

Persons who have a positive HCV-antibody test and negative results for HCV RNA by 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, resolved HCV infection 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 2 different assays because they target different regions of the virus, making it very unlikely that both would falsely detect a cross-reactive antigen (CDC, 2013); (Vermeersch, 2008).

Prior to initiation of antiviral therapy, quantitative HCV-RNA testing should 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).

With the advent of pangenotypic HCV treatment regimens, HCV genotyping is no longer required prior to treatment initiation for all individuals. In those with evidence of cirrhosis and/or past unsuccessful HCV treatment, treatment regimens may differ by genotype and thus pretreatment genotyping is recommended (see Treatment-Naive and Treatment-Experienced sections). For noncirrhotic treatment-naive patients, although genotyping may impact the preferred treatment approach, it is not required if a pangenotypic regimen is used (see Simplified Treatment Algorithm).

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 noninvasive tests (serum panels, elastography) or liver biopsy, if required, 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

Recommendations for Counseling Persons With Active HCV Infection	
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 prevent 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 (Safdar, 2004); (Harris, 2001); (Bellentani, 1999); (Corrao, 1998); (Wiley, 1998); (Poynard, 1997); (Noda, 1996).

Daily consumption of >50 g of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of lesser amounts of alcohol also exerts a deleterious effect on the liver; these data, however, are controversial (Hagström, 2017); (Younossi, 2013b); (Westin, 2002). Persons who abuse alcohol and have 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 (Puoti, 2017b); (Kruse, 2014); (Thein, 2008a); (Zarski, 1998). 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.) Persons who test positive for HBsAg require monitoring during HCV treatment because of HBV reactivation risk (Lee, 2018). Anti-HBV therapy may also be considered (see reactivation of HBV in the Monitoring section). For persons who test negative for HBsAg but positive for hepatitis B core antibodies (anti-HBc), with or without hepatitis B surface antibodies (anti-HBs), have resolved HBV infection; the risk of clinically significant HBV reactivation with HCV therapy is very low and no further workup is required (Mücke, 2018). Patients should be counseled about how to reduce their risk of acquiring these infections and HBV vaccination is recommended when appropriate.

Assessment of Liver Disease Severity

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Noninvasive tests using serum biomarkers, elastography, or liver imaging allow for accurate diagnosis of cirrhosis in most individuals (see pretreatment workup in When and in Whom to Initiate HCV Therapy). Liver biopsy is rarely required but may be considered if other causes of liver disease are suspected.

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
- Transient elastography
- Liver imaging (eg, ultrasound or CT scan)

Simple calculations derived from routine blood tests—such as the serum AST-to-platelet ratio index (APRI) (Wai, 2003) and FIB-4 score (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 cirrhosis and associated 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). Elastography provides instant information regarding liver stiffness and vibration-controlled transient elastography at the point of care and can reliably distinguish patients with a high vs low likelihood of cirrhosis (Bonder, 2014); (Castera, 2012). A more detailed discussion regarding fibrosis assessment is found in the When and In Whom to Initiate Therapy section.

Persons with known or suspected bridging fibrosis and cirrhosis are at increased risk for developing complications of advanced liver disease and 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 (Fontana, 2010); (Sangiovanni, 2006). 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 PWID 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 (Urbanus, 2009); (van de Laar, 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 about harm reduction related to illicit drug use, including entering substance use treatment programs. 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 healthcare provider who is knowledgeable in and prepared to provide comprehensive management.	IIa, C

Improved identification of active HCV infection and treatment advances 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 should be evaluated by a healthcare provider with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation may be required for persons with HCV infection who have advanced fibrosis or cirrhosis (Metavir stage ≥F3), including possible referral for consideration of liver transplantation in those with evidence of hepatic decompensation.

Only an estimated 13% to 18% of HCV-infected persons in the US 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) (Clark, 2012); (Arora, 2011); (Khokhar, 2007).

Common healthcare provider-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 HCV treatment cost (Reilley, 2014); (McGowan, 2013); (Morrill, 2005).

Data do not support exclusion of HCV-infected persons from consideration for hepatitis C therapy based alcohol intake or use of illicit drugs (see Identification and Management of HCV in People Who Inject Drugs). Some possible strategies to address HCV treatment barriers are listed in Table 3.

Table 3. Common Barriers to and Misconceptions Regarding HCV Treatment and Potential Strategies

Barrier	Strategy
Comorbid conditions (eg, substance use psychiatric disorders, uncontrolled chronic medical conditions)	• Conduct counseling and education. • Refer for services (eg, mental health services, medications for opioid use disorder [MOUDs], and syringe service programs). • Co-localize services (eg, primary care, medical homes, and drug treatment).
Competing priorities and loss to follow-up	• Conduct counseling and education. • Engage case managers and patient navigators. Consider other strategies such as incentives, peer navigators, and transportation assistance. • Co-localize services (eg, primary care, medical homes, and drug treatment).
Long treatment duration and adverse effects	• Conduct counseling and education. • Consider other strategies like incentives, peer navigators, and transportation assistance. • Utilize directly observed therapy.
Lack of access to treatment (eg, out-of-pocket costs, high copays, lack of insurance, geographic distance, and/or lack of specialist availability)	• 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 and copay assistance programs. • Co-localize services (eg, primary care, medical homes, and 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).

Co-localization of HCV screening, evaluation, and treatment with other medical or social services (ie, integrated care) is a strategy that addresses several treatment barriers. Co-localization has already been applied to settings with high HCV prevalence (eg, correctional facilities, needle exchange programs, substance abuse treatment centers, and harm reduction programs) but this type of care is not uniformly available (Burton, 2019); (Harrison, 2019); (Morey, 2019); (Schulkind, 2019); (Bruggmann, 2013); (Islam, 2012); (Stein, 2012). A recent study 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 SVR without serious adverse events (Ho, 2015).

A strategy that addresses lack of access to specialists—a primary barrier to hepatitis C care—is participation in models involving close collaboration between primary care practitioners and subspecialists (Beste, 2017b); (Rossaro, 2013); (Miller, 2012); (Arora, 2011). Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists (Rossaro, 2013); (Arora, 2011) or the availability of experienced providers in a methadone or correctional setting (Morey, 2019); (Talal, 2019). 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 HCV treatment access 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 primary care providers engaged in HCV management and treatment. This expansion will support the goals of HCV elimination and overcome barriers associated with the need for subspecialty referrals. The ASCEND trial utilized a real-world cohort of patients at urban federally qualified health centers and found that HCV treatment administered by nonspecialist providers was as safe and effective as that provided by specialists (Kattakuzhy, 2017).

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 (Ford, 2018); (Coyle, 2015); (Trooskin, 2015). There are also data suggesting that financial incentives and peer navigation may be useful to support treatment adherence in patients with substance use disorders (Ward, 2019); (Wohl, 2017). 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: August 27, 2020

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. 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 During Pregnancy and in Children, Acute HCV Infection, 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 acute or 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). While follow-up studies after cure using DAAs are limited, durability of SVR appears to be just as high (Sarrazin, 2017); (Reddy, 2018). 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 post-treatment 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, 2014b); (Gerber, 2016). Conversely, patients who do not achieve SVR after treatment have a continued worsening in health-related quality of life (Younossi, 2019).

Despite convincing data from observational studies demonstrating the benefit of SVR on all-cause and liver-related mortality, the lack of randomized, placebo-controlled trials of HCV DAA treatment focusing on clinical endpoints (eg, mortality, HCC, liver decompensation, etc) and reliance on surrogate endpoints (eg, HCV RNA) have led some to question the benefits of HCV treatment. In further support of the dramatic benefit of HCV cure, a French cohort study that prospectively followed almost 10,000 patients with chronic HCV infection (including 2,500 who remained untreated for HCV) for a median of 33 months demonstrated a 52% reduction in all-cause mortality and a 34% reduction in HCC (Carrat, 2019).

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 hepatitis C 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 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, 2016); (Matsuda, 2016).

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, 2016). A US Veterans Administration dataset analysis that used very limited endpoints 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% (Matsuda, 2016).

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 HCV-related cirrhosis 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 SVR of 70% post transplant (Curry, 2015). Post-transplant 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 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-drug interactions and the need for close monitoring), patients with a 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 the CD4 cell count may mitigate this to some extent but the effect is not completely reversed (Benhamou, 2001); (Bräu, 2006); (Lo Re, 2014). Thus, 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 infection 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 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 arthralgia, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels (Agnello, 1992). Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli (Johnson, 1993). 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. Limited data with DAA therapy in the setting of vasculitis end-organ disease related to cyroglobulinemia have demonstrated responses in 20% to 90% of patients (Comarmond, 2017); (Emery, 2017). Despite this, patients with severe end-organ disease may still require treatment with plasmapheresis or rituximab (Emery, 2017).

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 plasma HCV RNA load 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, HCV antiviral therapy 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 to 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. 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 HCV DAA therapy 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). The safety and efficacy of treating women who are already pregnant, however, 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 DAAs 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 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).

Some of the best examples of HCV treatment as prevention of transmission have come from well characterized cohorts of HIV/HCV coinfected MSM. In the Dutch acute HCV in HIV study (DAHHS) cohort, a 51% decrease in HCV incidence among MSM living with HIV was realized in just 2 years after implementing a comprehensive HCV screening and

immediate treatment program (Boerekamps, 2017). Similarly, in the Swiss HIV cohort study (SHCS), a 92.5% reduction in HCV prevalence and 51% decrease in incident HCV infections was realized shortly after implementing universal screening and treatment within an MSM cohort living with HIV (Braun, 2018).

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 cost concerns (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 DAA regimens 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 HCV prevalence in this at-risk population (He, 2016), although research is needed in this area.

Persons on Hemodialysis

HCV prevalence is markedly elevated in persons on hemodialysis, ranging from 2.6% to 22.9% in a large multinational study (Fissell, 2004). US studies found a similarly elevated prevalence 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 to 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 noninvasive markers and/or elastography, and rarely liver biopsy, is recommended for all persons with HCV infection to facilitate decision making regarding HCV treatment strategy and 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 1/3 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 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, successful HCV treatment 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 accelerated 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 levels are associated with more rapid fibrosis progression (Ghany, 2003). However, even patients with a normal ALT level 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.

HCV RNA level 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 (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 of 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 • 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, 2020). Reduced access to treatment, however, 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. Although these terms may sound similar, the following discussion seeks to clarify them regarding HCV therapy. This section aims to be informational. As explained, actual costs are rarely known. Accordingly, the HCV guidance does not currently utilize cost-effectiveness analysis to guide recommendations.

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, states have loosened their Medicaid treatment restrictions with a growing number providing treatment to all infected persons. Many 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

Estimating and interpreting the ICER requires answering 3 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 outcome 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 per 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*
   From a societal perspective, 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 (Wong, 2017a). 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 HCV therapies 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 per 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 relative cost-effectiveness. 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, persons who inject drugs, and adolescents—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.

Cost-Effectiveness of Screening for HCV

Several cost-effectiveness studies demonstrate that routine, one-time testing for HCV among all adults in the US would likely identify a substantial number of cases of HCV that are currently being missed, and that doing so would be cost-effective. One study employed simulation modeling to compare several versions of routine guidance, including routine testing for adults over the ages of 40 years, 30 years, and 18 years and found that routine testing for all adults aged ≥18 years was cost-effective compared to risk-based screening, and potentially cost-saving compared to testing only those aged ≥30 years or aged ≥40 years (Barocas, 2018). The study further found that routine testing remained cost-effective unless HCV infection had no impact on healthcare utilization and no impact on quality of life. Another research group similarly found that routine testing of all adults aged ≥18 years is likely cost-effective compared to risk-based screening, so long as the prevalence of HCV among those born after 1965 exceeds 0.07% (Eckman, 2019). Notably, these studies reached similar conclusions despite being conducted entirely independently and employing different simulation modeling approaches. Further, a variety of studies have examined the cost-effectiveness of routine HCV testing in specific venues, including correctional settings (He, 2016), prenatal care settings (Chaillon, 2019); (Tasillo, 2019), substance use treatment centers (Schackman, 2018); (Schackman, 2015), and federally qualified health centers (Assoumou, 2018). All of them found that routine testing and treatment for HCV was cost-effective, even when linkage to HCV treatment after testing was poor, and even when the rate of HCV reinfection among injection drug users is common.

Generally, routine HCV testing is cost-effective because the incidence and prevalence of HCV remain high in people who inject drugs with a notable rising prevalence in young adults who may not readily report their stigmatized risk behaviors. Studies conducted in urban emergency departments in the US, for example, reveal that 15% to 25% of patients with previously unidentified HCV infection were born after 1965 and/or have no reported history of injection drug use and are, therefore, missed by even perfect implementation of risk-based screening (Schechter-Perkins, 2018); (Hsieh, 2016); (Lyons, 2016). Reinfection among those actively using drugs is common but because screening is a low-cost intervention, and therapy is both highly effective and cost-effective, routine testing provides good economic value (ie, cost-effective) even when many people need to be tested and treated more than once during their lifetime.

Conclusions

Many studies have demonstrated the economic value of HCV screening (Chaillon, 2019); (Eckman, 2019); (Tasillo, 2019); (Assoumou, 2018); (Barocas, 2018); (Schackman, 2018); (Schechter-Perkins, 2018); (Lyons, 2016); (Hsieh, 2016); (Schackman, 2015) and treatment (Goel, 2018); (Chhatwal, 2017); (He, 2017); (Chahal, 2016); (Chhatwal, 2015); (Chidi, 2016); (Martin, 2016a); (Linas, 2015); (Najafzadeh, 2015); (Rein, 2015); (Tice, 2015); (Younossi, 2015a) and made it clear that HCV screening and therapy are cost-effective. In response, in 2020, both the US Centers for Disease Control (CDC) and Prevention and the US Preventive Service Task Force (USPSTF) recommended routine, one-time HCV testing for all US adults aged ≥18 years without effort to identify risk factors, as well as repeat testing for those with ongoing risk factors (Owens, 2020); (Schillie, 2020). The high cost of HCV medications and the high prevalence of disease have led to limited 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 difficult to estimate the true budgetary impact of providing HCV drugs. Competition and negotiated pricing have reduced prices substantially but cost continues to limit the public health impact of 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.

Last update: August 27, 2020

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 virus (HCV) infection who are starting direct-acting antiviral (DAA) treatment, are on treatment, or have completed therapy. It is divided into 4 parts: pretreatment and on-treatment monitoring; post-treatment follow-up for persons in whom treatment failed to clear the virus; post-treatment follow-up for those who achieve a sustained virologic response (SVR; virologic cure); and additional considerations if treatment includes ribavirin.

Pretreatment and On-Treatment Monitoring

Recommended Assessments Prior to Starting DAA 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 DAA therapy and, when possible, an interacting co-medication should be stopped or switched to an alternative with less risk for potential interaction during HCV treatment. (See Table of Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications below or use an online resource such as University of Liverpool interaction checker.) Patients should 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 need to inform the healthcare provider about any changes to their medication regimen. **The following laboratory tests are recommended within 6 months prior to starting DAA 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 anytime prior to starting DAA therapy:** • Quantitative HCV RNA (HCV viral load) • If a non-pan–genotypic DAA will be prescribed, then test for HCV genotype and subtype.	I, C
The safety of ribavirin-free DAA regimens in humans has not been established during pregnancy and for nursing mothers, so counseling should be offered to women of childbearing age before beginning HCV treatment. (See ribavirin pregnancy recommendations below.)	I, C

Recommended Assessments Prior to Starting DAA Therapy

All patients initiating DAA therapy should be assessed for active hepatitis B virus (HBV) coinfection with HBV surface antigen (HBsAg) testing, and for evidence of prior infection with HBV core antibody (anti-HBc) and HBV surface antibody (anti-HBs) testing.	IIa, B
Patients found or known to be HBsAg-positive should be assessed for whether their HBV DNA level meets AASLD criteria for HBV treatment and initiation of antiviral therapy for HBV.	Strong, Moderate[a]
All patients initiating DAA therapy should be assessed for HIV coinfection.	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. Additional information about RAS testing can be found in the HCV Resistance Primer.	IIb, B
Patients scheduled to receive an HCV NS3 protease inhibitor (ie, grazoprevir, voxilaprevir, glecaprevir) should be assessed for a history of decompensated liver disease and 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 score ≥7 should **not** receive treatment with regimens that contain NS3 protease inhibitors due to increased blood levels and/or lack of safety data.	I, A

[a] Unlike the AASLD/IDSA HCV guidance, the AASLD guidelines for treatment of chronic hepatitis B uses the GRADE approach to rate recommendations; please see that document for further information about this rating system.

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 (see table of Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications below), especially with newly prescribed medications.	I, B
Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. On-treatment and post-treatment monitoring for hypoglycemia is recommended.	I, C
Inform patients taking warfarin of the potential for changes in their anticoagulation status. On-treatment and post-treatment INR monitoring for subtherapeutic anticoagulation is recommended.	I, C
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 ALT values from baseline at any time during treatment should prompt discontinuation of DAA therapy (especially with signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR). An increase in ALT <10-fold from baseline that is accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or INR should also prompt discontinuation of DAA therapy.	I, B

Recommended Monitoring During Antiviral Therapy	
Asymptomatic increases in ALT <10-fold from baseline should be closely monitored with repeat testing at 2-week intervals. If levels remain persistently elevated, consideration should be given to discontinuation of DAA therapy.	
Quantitative HCV viral load testing is recommended 12 or more weeks after completion of therapy to document SVR (cure).	I, B
For HBsAg-positive patients not already receiving HBV suppressive therapy because their baseline HBV DNA level does not meet treatment criteria, one of two approaches may be taken: • Initiate prophylactic HBV 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 monthly during and immediately after DAA therapy. 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

The recommended pretreatment testing 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

Concomitant Medications	LDV/SOF	EBR/GZR	VEL/SOF	GLE/PIB	SOF/VEL/VOX
Acid-reducing agents	Antacids H2RA PPI		Antacids H2RA PPI	H2RA PPI	Antacids H2RA PPI
Alpha-1 blockers	Silodosin	Prazosin Silodosin	Prazosin Silodosin	Prazosin Silodosin	Prazosin Silodosin
Antiarrhythmics	Amiodarone Dronedarone	Amiodarone Dronedarone Quinidine	Amiodarone Dronedarone	Amiodarone Dronedarone Quinidine	Amiodarone Dronedarone
	Digoxin Quinidine		Digoxin Quinidine		Digoxin Quinidine
Anticoagulant and antiplatelet agents	Apixaban Dabigatran Edoxaban Rivaroxaban Ticagrelor Warfarin	Apixaban Dabigatran Edoxaban Rivaroxaban Ticagrelor Warfarin	Apixaban Dabigatran Edoxaban Rivaroxaban Ticagrelor Warfarin	Dabigatran	Dabigatran Edoxaban
				Apixaban Edoxaban Rivaroxaban Ticagrelor Warfarin	Apixaban Rivaroxaban Ticagrelor Warfarin
Anticonvulsants and barbiturates	Amobarbital Carbamazepine Eslicarbazine Oxcarbazepine Phenobarbital Phenytoin Primidone Rufinamide	Amobarbital Carbamazepine Eslicarbazine Oxcarbazepine Phenobarbital Phenytoin Primidone	Amobarbital Carbamazepine Eslicarbazine Oxcarbazepine Phenobarbital Phenytoin Primidone Rufinamide	Amobarbital Carbamazepine Eslicarbazine Oxcarbazepine Phenobarbital Phenytoin Primidone	Amobarbital Carbamazepine Eslicarbazine Oxcarbazepine Phenobarbital Phenytoin Primidone Rufinamide
	Zonisamide	Rufinamide		Rufinamide	
Antihypertensives	Aliskiren Amlodipine Diltiazem Eplerenone Felodipine Irbesartan Isradipine	Eplerenone Felodipine Isradipine	Diltiazem	Aliskiren	Aliskiren Enalapril Irbesartan Isradipine Non-DHP CCB Olmesartan Telmisartan Valsartan
				Enalapril Eplerenone Irbesartan Isradipine Non-DHP CCB Olmesartan Telmisartan	
Antipsychotics – first generation	Pimozide	Pimozide		Pimozide	
				Droperidol Thioridazine	
Antipsychotics – second generation	Paliperidone	Aripiprazole Quetiapine		Aripiprazole Clozapine Paliperidone Quetiapine	Paliperidone
Antiretrovirals	See HIV/HCV Coinfection Section				
Azole antifungals		Ketoconazole		Ketoconazole Posaconazole	
Benzodiazepines	Midazolam	Midazolam			
Bronchodilators				Theophylline	

Buprenorphine/ naloxone					
Calcineurin inhibitors		Cyclosporine Tacrolimus		Cyclosporine Tacrolimus	Cyclosporine Tacrolimus
Cholesterol-lowering agents	Rosuvastatin Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Simvastatin	Atorvastatin Fluvastatin Gemfibrozil Lovastatin Rosuvastatin Simvastatin	Atorvastatin Fluvastatin Lovastatin Pitavastatin Rosuvastatin Simvastatin	Atorvastatin Lovastatin Simvastatin Ezetimibe Fluvastatin Gemfibrozil Pitavastatin Pravastatin Rosuvastatin	Rosuvastatin Pitavastatin Pravastatin Atorvastatin Fluvastatin Lovastatin Simvastatin
Cisapride					
Ergot derivatives					
Ethinyl estradiol containing products					
Glucocorticoids		Dexamethasone		Dexamethasone	Dexamethasone
Heart failure agents		Bosentan Ambrisentan	Bosentan	Bosentan Ambrisentan	Bosentan Ambrisentan
Herbals	St. John's wort	St. John's wort	St. John's wort	St. John's wort	St. John's wort
Loop diuretics					
Macrolide antimicrobials	Telithromycin	Telithromycin		Erythromycin Telithromycin	Erythromycin Telithromycin
Phosphodiesterase -5 inhibitors					
Rifamycin antimicrobials	Rifabutin Rifampicin Rifapentine	Rifabutin Rifampicin Rifapentine Rifaximin	Rifabutin Rifampicin Rifapentine	Rifabutin Rifampicin Rifapentine Rifaximin	Rifabutin Rifampin Rifapentine Rifaximin

H2RA=Histamine H_2 Antagonist; PPI=proton pump inhibitor; DHP CCB=dihydropyridine calcium channel blocker; Non-DHP CCB=non dihydropyridine calcium channel blocker

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and red indicates the combination should be avoided. Specific concomitant medications or medication classes with actual or theoretical potential for interaction are listed in the box.

The education of patients and caregivers about potential adverse effects of DAA therapy and their management is an integral component of treatment and is important for a successful outcome in all patient populations. During DAA 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. This includes on-treatment and post-treatment monitoring for hypoglycemia or subtherapeutic INR levels among patients taking diabetes medicines or warfarin, respectively. Real-world data indicate an association between DAA therapy and related changes in hepatic function and alterations in dose-response relationships with these medications (Drazilova, 2018); (Abdel Alem, 2017); (Rindone, 2017); (Pavone, 2016); (DeCarolis, 2016); (Soriano, 2016). Inform patients on these medications about the potential for these developments; make dose adjustments as needed. 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.

Routine testing for HCV RNA during treatment is not recommended unless the ALT level fails to decline (when elevated) or there are concerns regarding patient adherence with DAA treatment. There are no data to support stopping treatment based on detectable HCV RNA during the first 4 weeks of treatment, or that detectable HCV RNA at this time point signifies medication nonadherence.

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 HCV infection. Virologic relapse is rare 12 weeks or longer after treatment completion (Sarrazin, 2017); (Simmons, 2016). 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 participants 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, 2019).

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 and Nursing Mothers

Few adequate and well-controlled human studies are available to establish whether DAAs pose a risk to pregnancy outcomes or whether DAAs and their metabolites are present in breastmilk. An open-label, phase 1 study of HIV-negative pregnant women with chronic genotype 1 infection evaluated a 12-week course of ledipasvir/sofosbuvir initiated between 23 to 24 weeks of gestation (Chappell, 2019). Among 7 evaluable patients, all achieved SVR12 and adverse events related ledipasvir/sofosbuvir were ≤ grade 2. All 7 participants delivered at term with undetectable HCV viral loads at delivery. One-year follow-up of the infants is ongoing.

Given the dearth of data on this topic, clinicians should discuss with female patients that DAAs should be used during pregnancy only if the potential benefit of DAA therapy justifies the potential risk of harm to the fetus. The health benefits of DAA therapy for nursing mothers should be weighed against the health benefits of breast feeding and the possible adverse effects of the DAA regimen on the breastfed child. Given the relatively short duration of treatment and the availability of ribavirin-free regimens in most patients, the potential risk of harms and benefits of delaying pregnancy until HCV DAA therapy is completed should be considered. For additional information about 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 (Mücke, 2018); (Bersoff-Matcha, 2017); (Chen, 2017). Therefore, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg testing, and for evidence of prior infection with anti-HBc and anti-HBs testing. HBV vaccination is recommended for all susceptible individuals. Testing for HBV DNA should be performed 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 HBV therapy at the same time or before HCV DAA therapy is initiated (Terrault, 2018).

Patients with a low or undetectable HBV DNA level can either receive prophylactic HBV treatment for the duration of DAA treatment until assessment for 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-HBc and anti-HBs (resolved infection). However, the possibility of HBV reactivation should be considered in these patients in the event of an unexplained increase in liver aminotransferase levels 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
Retreatment for chronic HCV is recommended utilizing the regimens recommended in the Retreatment section.	I, C
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
Surveillance for hepatocellular carcinoma with liver ultrasound examination, with or without alpha fetoprotein (AFP), every 6 months is recommended for patients with cirrhosis[a] in accordance with the AASLD guidance on the diagnosis, staging, and management of hepatocellular carcinoma.	Low, Conditional[b]
For patients with cirrhosis, endoscopic surveillance for varices should be performed in accordance with the AASLD guidance on portal hypertension bleeding in cirrhosis.	Guidance[b]

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Unlike the AASLD/IDSA HCV guidance, the AASLD guidelines for treatment of chronic hepatitis B uses the GRADE approach to rate recommendations; please see that document for further information about this rating system.

The Following Monitoring Is Not Recommended During or After Therapy	
NOT RECOMMENDED	RATING
Monitoring for HCV drug resistance-associated substitutions (RASs) during or after therapy is not recommended unless retreatment will be performed and RAS testing is recommended in advance of this therapy. See the Retreatment section for recommendations regarding RAS testing prior to retreatment. Additional information about RAS testing can be found in the HCV Resistance Primer.	IIb, C

Patients who do not achieve SVR retain the possibility of continued liver injury, progression of hepatic fibrosis, and the potential to transmit HCV infection to others. Such patients should be considered for retreatment per the Retreatment of Persons in Whom Prior Therapy Has Failed section.

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 one or more of the antivirals at the time of virologic breakthrough (Lawitz, 2014a); (Schneider, 2014). There is no evidence to date, however, that the presence of RASs results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. Additional information about RASs and RAS testing can be found in the HCV Resistance Primer section. If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert regarding the treatment of HCV infection may be useful.

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 noncirrhotic patients, recommended follow-up is the same as if they were never infected with HCV.	I, B
Assessment for HCV recurrence is recommended only if the patient develops unexplained hepatic dysfunction, or annual assessment if the patient has ongoing risk factors for HCV infection. In such cases, a quantitative HCV RNA test, rather than an HCV antibody test, is recommended to assess for HCV recurrence.	I, A
Surveillance for hepatocellular carcinoma is recommended for patients with cirrhosis[a], in accordance with the AASLD guidance on the diagnosis, staging, and management of hepatocellular carcinoma.	Strong, Moderate[b]
For cirrhotic patients, upper endoscopic surveillance is recommended in accordance with the AASLD guidance on portal hypertension bleeding in cirrhosis.	Guidance[b]
Assessment for 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.
[b] Unlike the AASLD/IDSA HCV guidance, the AASLD guidelines for treatment of chronic hepatitis B uses the GRADE approach to rate recommendations; please see that document for further information about this rating system.

Patients with undetectable serum HCV RNA, as assessed by a sensitive polymerase chain reaction (PCR) assay, ≥12 weeks after treatment completion are deemed to have achieved SVR (cure). The likelihood of achieving SVR with DAA therapy 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 (Morgan, 2013); (Morisco, 2013); (Morgan, 2010); (Singal, 2010); (George, 2009). Liver fibrosis and liver function test results improve in most patients who achieve SVR (Morgan, 2013); (Morisco, 2013); (Morgan, 2010); (Singal, 2010); (George, 2009). Because of lack of progression, noncirrhotic patients who achieve SVR should receive standard medical care that is recommended for patients who were never infected with HCV unless they remain at risk for non-HCV–related liver disease, such as nonalcoholic fatty liver disease or alcoholic liver disease.

Among cirrhotic patients who achieve SVR, decompensated liver disease (with the exception of hepatocellular carcinoma [HCC]) rarely develops during follow-up and overall survival is prolonged (Morgan, 2013); (Morisco, 2013); (Morgan, 2010); (Singal, 2010); (George, 2009). Bleeding from esophageal varices is rare after SVR (Morgan, 2013); (Morisco, 2013); (Morgan, 2010); (Singal, 2010); (George, 2009). Cirrhotic patients should undergo surveillance endoscopy every 2 years if known to have small varices and every 3 years in the absence of known varices in accordance with AASLD guidance on portal hypertension bleeding (Garcia-Tsao, 2017).

Importantly, cirrhotic patients remain at risk for developing HCC and should, therefore, undergo surveillance for HCC every 6 months utilizing ultrasound (with or without AFP testing) despite the lowered risk that results after viral eradication

(Marrero, 2018). Although multiple studies of cirrhotic patients who achieved SVR with peginterferon/ribavirin reported a reduction in the risk of developing HCC (Morgan, 2013); (Morisco, 2013); (Morgan, 2010); (Singal, 2010); (George, 2009) and a meta-analysis of persons achieving SVR with DAAs found that the HCC risk did not exceed that seen in patients who experienced SVR with interferon-based treatment after adjustment for baseline risk factors for HCC (Waziry, 2017b), one report found a higher than expected frequency of HCC in patients with HCV-related cirrhosis despite successful DAA treatment (Reig, 2016). However, a prospective observational study of 3045 cirrhotic patients found an adjusted hazard ratio for HCC of 0.57 (95% CI 0.40 to 0.81) following DAA-based therapy, implying a 43% reduction in HCC incidence (Carrat, 2019).

Bleeding from esophageal varices is uncommon after SVR (Morgan, 2013); (Morisco, 2013); (Morgan, 2010); (Singal, 2010); (George, 2009). Nevertheless, patients with compensated cirrhosis who achieve SVR should continue to receive endoscopic surveillance for esophageal varices, in accordance with the AASLD guidance on portal hypertension bleeding (Garcia-Tsao, 2017). Current AASLD recommendations for patients with compensated cirrhosis without known varices is surveillance endoscopy every 2 years if there is evidence of ongoing liver injury from associated conditions, such as obesity or alcohol use, and every 3 years if liver injury is quiescent, such as after alcohol abstinence. Patients with compensated cirrhosis and known varices should undergo surveillance endoscopy annually if there is evidence of ongoing liver injury from associated conditions, such as obesity or alcohol use, and every 2 years if liver injury is quiescent, such as after alcohol abstinence.

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 hepatic 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 have HCV recurrence due to reinfection or late relapse (Sarrazin, 2017); (Simmons, 2016). A systematic review suggests 5-year recurrence risks of 1%, 11%, and 15% in monoinfected low-risk HCV, monoinfected high-risk HCV (ie, people who currently or formerly injected drugs, imprisonment, or men who have sex with men [MSM]), and HIV/HCV coinfected patients, respectively (Simmons, 2016). At least 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). Because HCV antibody remains positive in most patients following SVR, testing for HCV recurrence 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 SVR and are receiving immunosuppressive drug therapy (eg, systemic corticosteroids, antimetabolites, chemotherapy, biologics agents, 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 acute liver injury in these patients. Approximately 23% of patients with active HCV infection—especially those with a hematologic malignancy—experience 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, 2018). Among patients who have recovered from HCV infection, 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.

Additional Considerations If Treatment Includes Ribavirin

Recommended Monitoring During Antiviral Therapy That Includes Ribavirin	
RECOMMENDED	RATING
More frequent assessment for drug-related adverse effects (ie, CBC for patients receiving ribavirin) is recommended as clinically indicated.	I, C

Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin	
RECOMMENDED	RATING
Women of childbearing potential and their partners should not receive ribavirin during or for at least 6 months prior to pregnancy.	I, C
Women of childbearing potential 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 potential 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 potential prior to beginning treatment with a regimen that includes ribavirin.	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

Ribavirin causes hemolysis. Patients receiving ribavirin should have hemoglobin levels checked during treatment, often after 2 weeks, and the ribavirin dose reduced if the patient develops significant anemia, often defined as hemoglobin <10 g/dL.

Ribavirin causes fetal death and fetal abnormalities in animals. Ribavirin should not be administered to pregnant women or to women who might become pregnant during or for 6 months after completing ribavirin treatment. Similarly, ribavirin may cause birth defects in offspring of women whose partner was receiving ribavirin when the woman became pregnant. In the very rare instances when ribavirin is used, it is imperative for persons of childbearing potential 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.

Last update: August 27, 2020

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, 2018b). 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 both baseline and selected RASs on treatment outcome varies according to regimen (ie, coadministered drugs); patient factors that impact treatment response (eg, 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 with and without 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 (without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or another recommended regimen should be used.	I, A

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

[a] Clinically important = ≥100-fold shift in the in vitro EC_{50} to ledipasvir

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 the utility of RAS testing at this time 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, 2017).

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

Elbasvir/Grazoprevir

Elbasvir/grazoprevir is indicated for treatment-naive and -experienced patients with genotype 1 or 4. 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 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). These RASs, however, 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 baseline RASs had minimal impact on SVR rates with glecaprevir/pibrentasvir in registration trials that predominantly enrolled noncirrhotic patients. 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 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 patients with cirrhosis or prior treatment experience. All genotype 3 patients with Y93H prior to treatment achieved SVR12.

Ledipasvir/Sofosbuvir

Several comprehensive analyses of genotype 1 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 who received ledipasvir/sofosbuvir, 93.5% (316/338) of those with baseline NS5A RASs achieved SVR12 compared to an SVR12 of 98.4% (1,741/1,770) in patients without baseline NS5A RASs (Sarrazin, 2016). In this analysis, the reduction in SVR was driven predominantly by patients with genotype 1a NS5A RASs. The SVR12 rates for genotype 1a patients with and without NS5A RASs were 92.3% and 98.3%, respectively. A slightly lower SVR12 of 90% was observed for genotype 1a 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. When RASs with >100-fold resistance were present, however, SVR12 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 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.

Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir is a pangenotypic therapy indicated for treatment-naive and -experienced patients with or without cirrhosis. In the ASTRAL studies, the presence of NS5A RASs had no impact on SVR12 for patients with genotype 1, 2, 4, 5, or 6 infection treated with 12 weeks of sofosbuvir/velpatasvir (Hézode, 2018). The presence of Y93H in genotype 3 patients decreased the SVR12 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. However, a subsequent trial that randomized patients with genotype

3 and cirrhosis to sofosbuvir/velpatasvir with or without ribavirin demonstrated lower relapse rates in patients receiving ribavirin (Esteban, 2018).

Sofosbuvir/Velpatasvir/Voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir fills an important role as a pangenotypic regimen for patients who have experienced treatment failure with DAA therapy. Although data are limited, the presence of NS3, NS5A, or NS5B RASs prior to treatment did not influence the likelihood of SVR12, and 12 weeks of treatment produced a high SVR12 (96%) in DAA-experienced patients. RAS testing has not been demonstrated to impact SVR rates with sofosbuvir/velpatasvir/voxilaprevir therapy (Bourlière, 2017); (Sarrazin, 2018).

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

DAA	Genotype 1a				Genotype 1b		Genotype 3a	
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N	A30K	Y93H
Ledipasvir	20x	>100x	>100x / >100x	>1000x / >10,000x	>100x >50x	>100x / --	NA	NA
Elbasvir	20x	>100x	>10x >100x	>1000x / >1000x	<10x	>100x / --	50x	>100x
Velpatasvir	<10x	<3x	20x / 50x	>100x / >1000x	<3x	<3x / --	50x	>100x
Pibrentasvir	<3x	<3x	<3x	<10x	<3x	<3x	<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	NA
Elbasvir/grazoprevir	M28A/T Q30H/R L31M/V Y93C/H/N	Y93H	NA
Sofosbuvir/velpatasvir	NA	NA	Y93H

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

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

Last update: November 6, 2019

Initial Treatment of Adults with 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 investigational, or US Food and Drug Administration (FDA) approved.

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 (NAS, 2017).

- Simplified Pangenotypic HCV Treatment for Treatment-Naive Adults Without Cirrhosis
- Simplified Pangenotypic HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis

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 or clinical setting. 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.

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 or regimen selection. All patients should have access to an HCV care provider during treatment, although preset clinic visits and/or blood tests depend on the treatment regimen and may not be required for all regimens/patients. Patients receiving ribavirin require additional monitoring for anemia during treatment (see Monitoring section).

The following pages include guidance for management of treatment-naive patients by genotype (although most patients will fall into the simplified treatment algorithms above).

- 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 is recommended in this circumstance (Chiu, 2020). When the correct combination or duration of treatment is unclear, expert consultation should be sought.

Last update: August 27, 2020

Simplified HCV Treatment* for Treatment-Naive Adults Without Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who do not have cirrhosis and have not previously received hepatitis C treatment

Pretreatment Assessment*

- Calculate FIB-4 score.
- **Cirrhosis assessment:** Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.
  - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
  - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
  - Prior liver biopsy showing cirrhosis
- **Medication reconciliation:** Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.
- **Pretreatment laboratory testing:**
  - *Within 6 months of initiating treatment:*
    - Complete blood count (CBC)
    - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
    - Calculated glomerular filtration rate (eGFR)
  - *Any time prior to starting antiviral therapy:*
    - Quantitative HCV RNA (HCV viral load)
    - HIV antigen/antibody test
    - Hepatitis B surface antigen

- *Before initiating antiviral therapy*:
  - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

Recommended Regimens*

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

On-Treatment Monitoring

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth/phone visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

Post-Treatment Assessment of Cure (SVR)

- Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

Follow-Up After Achieving Virologic Cure (SVR)

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.
- Advise patients to avoid excess alcohol use.

Follow-Up for Patients Who Do *Not* Achieve a Virologic Cure

- Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance.
- Until retreatment occurs, assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended.
- Advise patients to avoid excess alcohol use.

*More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment, including the treatment of patients with cirrhosis, can be found here.

Last update: August 27, 2020

Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7)
- Prior hepatitis C treatment
- End-stage renal disease (ie, eGFR <30 mL/min/m^2) (see Patients with Renal Impairment section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

(see HCV guidance for treatment recommendations for these patients)

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment

Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.

- Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
- Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
- Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm^3, etc)
- Prior liver biopsy showing cirrhosis

Pretreatment Assessment*

- Calculate FIB-4 score.
- Calculate CTP score**:** Patients with a CTP score ≥7 (ie, CTP B or C) have decompensated cirrhosis and this simplified treatment approach is not recommended.
- **Ultrasound of the liver** (conducted within the prior 6 months): Evaluate to exclude HCC and subclinical ascites.
- **Medication reconciliation:** Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the AASLD/IDSA guidance or the University of Liverpool drug interaction checker.
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.

- **Pretreatment laboratory testing:**
  - *Within 3 months of initiating treatment:*
    - Complete blood count (CBC)
    - International normalized ratio (INR)
    - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
    - Calculated glomerular filtration rate (eGFR)
  - *Any time prior to starting antiviral therapy:*
    - Quantitative HCV RNA (HCV viral load)
    - HIV antigen/antibody test
    - Hepatitis B surface antigen
    - HCV genotype (if treating with sofosbuvir/velpatasvir)
  - *Before initiating antiviral therapy*:
    - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

Recommended Regimens*

- **Genotype 1-6**:
  Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks

- **Genotype 1, 2, 4, 5, or 6**
  Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks
  NOTE: Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, see HCV guidance for treatment recommendations.

On-Treatment Monitoring

- Providers may order blood tests to monitor for liver injury during treatment because hepatic decompensation (eg, jaundice, etc) occurs rarely among patients with cirrhosis receiving HCV antiviral treatment.
- Patients should see a specialist if they develop worsening liver blood tests (eg, bilirubin, AST, ALT, etc); jaundice, ascites, or encephalopathy; or new liver-related symptoms.
- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- An in-person or telehealth/phone visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

Post-Treatment Assessment of Cure (SVR)

- Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

Follow-Up After Achieving Virologic Cure (SVR)

- Ultrasound surveillance for HCC (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis in accordance with AASLD guidance.

- Upper endoscopic surveillance for esophageal varices is recommended in accordance with AASLD guidance on portal hypertensive bleeding in cirrhosis.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.
- Patients should abstain from alcohol to avoid progression of liver disease.

Follow-Up for Patients Who Do *Not* Achieve a Virologic Cure

- Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance.
- Ultrasound surveillance for hepatocellular carcinoma (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis, in accordance with AASLD guidance.
- Assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, creatinine, and INR is recommended.
- Patients should abstain from alcohol to avoid progression of liver disease.

*More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment can be found here.

Last update: August 27, 2020

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). In clinical settings where RAS testing is unavailable, regimens for which the presence of specific RAS(s) factor into treatment selection should be avoided. For further guidance, please see the HCV Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with a higher rate 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
- Simplified HCV Treatment for Treatment-Naive Adults Without Cirrhosis

Last update: August 27, 2020

Treatment-Naive Genotype 1a Without Cirrhosis

Recommended 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 for elbasvir[a]	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 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

[a] Includes genotype 1a resistance-associated substitutions (RASs) at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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 >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.

In the phase 3 open-label C-EDGE TE trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, 58 genotype 1a-infected patients received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, and 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), another recommended regimen should be used (additional information is available in the RAS section).

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 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.

In an integrated analysis of 602 DAA-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 99.2% (597/602) (Naganuma, 2019). Real-world cohorts from Germany (63% genotype 1a) and Italy (32% genotype 1a) show similarly high efficacy in treatment-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir. Using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up), SVR was 100% in both the German (228/228) (Berg, 2019) and the Italian (307/307) (D'Ambrosio, 2019) cohorts.

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 two 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 SVR12 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 who received 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). 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.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% (Su, 2017); (Ioannou, 2016); (Wilder, 2016); (O'Brien, 2014). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found similar SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) (Marcus, 2018). Similarly, a Maryland Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively (Tang, 2018). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see HIV/HCV Coinfection section). For others with potential negative prognostic factors, shortening treatment duration should be done at the discretion of the practitioner.

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 SVR12 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 infection—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 for 12 weeks, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR12 with a single relapse observed with each subtype.

In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) (Wei, 2019). Of the 129 participants with genotype 1 infection (17% genotype 1a), 100% achieved SVR.

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Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended 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 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)[c]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.
[c] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy.

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 (Zeuzem, 2017); (Lawitz, 2015c).

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 >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 are 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) 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 position 28, 30, 31, or 93), another recommended regimen should be selected.

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; SVR12 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, 2018). 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.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1 (n=95, genotype 1a), 2, 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures (Brown, 2018).

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 two 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 SVR12 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 SVR12 with no difference in SVR12 observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (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 SVR12 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% of whom had

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: August 27, 2020

Treatment-Naive Genotype 1b Without Cirrhosis

Recommended 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[a]	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 HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

[a] An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV coinfected patients, a treatment duration of 12 weeks is recommended.

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 (genotype 1, 4, or 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.

A phase 3, global STREAGER trial of 89 treatment-naive patients with genotype 1b infection and low fibrosis stage (defined as a transient elastography score <9.5 or a Fibrotest® score <0.59 [F0 to F2]) evaluated the efficacy of 8 weeks of elbasvir/grazoprevir and found an SVR rate of 98% (87/89), supporting the option of using a shorter treatment duration for genotype 1b patients with low scores using these fibrosis staging modalities (Abergel, 2018).

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.

CERTAIN-1 evaluated 8 weeks of glecaprevir/pibrentasvir among 129 Japanese DAA-naive noncirrhotic patients (97% genotype 1b); SVR12 was of 99% (128/129) (Chayama, 2018). Real-world cohorts from Germany (34% genotype 1a) and Italy (67% genotype 1a) demonstrate similarly high efficacy among treatment-naive, noncirrhotic genotype 1 patients treated with 8 weeks of glecaprevir/pibrentasvir using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up). SVR rates were 100% in both the German (228/228) (Berg, 2019) and the Italian (307/307) (D'Ambrosio, 2019) cohorts.

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%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% (Su, 2017); (Ioannou, 2016); (Wilder, 2016); (O'Brien, 2014). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found comparable

SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) (Marcus, 2018). Similarly, a Maryland Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively (Tang, 2018). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see HIV/HCV Coinfection section).

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 infection 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 SVR12 with no difference observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (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—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.

Last update: August 27, 2020

Treatment-Naive Genotype 1b With Compensated Cirrhosis

Recommended 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 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)[b]	8 weeks[c]	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

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 (Zeuzem, 2017); (Lawitz, 2015c).

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.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1 (n=136, genotype 1b), 2, 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures (Brown, 2018).

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 cirrhotic. There was no difference in SVR12 rate in cirrhotic (97%) versus noncirrhotic patients (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 SVR12 with no difference in SVR12 observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (99%). Baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR12 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 infection—19% of whom had compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) 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.

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Treatment-Naive Genotype 2

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

Last update: August 27, 2020

Treatment-Naive Genotype 2 Without Cirrhosis

Recommended 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

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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. In an integrated analysis of 297 DAA-naive, noncirrhotic patients with genotype 2 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 98% (252/257) (Naganuma, 2019). Additionally, a real-world cohort of treatment-naive, noncirrhotic genotype 2 patients from Italy treated with glecaprevir/pibrentasvir for 8 weeks achieved an SVR rate of 98% (173/175) (D'Ambrosio, 2019).

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 (100 mg) 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).

In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) (Wei, 2019). Of the 62 patients with genotype 2 infection, 100% achieved SVR.

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Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended 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]	8 weeks[c]	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

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.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1, 2 (n=26), 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures (Brown, 2018). Real-world data support the use of 8 weeks in cirrhotic patients (Flamm, 2020).

Last update: August 27, 2020

Treatment-Naive Genotype 3

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

Last update: August 27, 2020

Treatment-Naive Genotype 3 Without Cirrhosis

Recommended 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

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

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/pibrentasvir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence at this time to recommend testing for RASs or extension of therapy in the setting of an A30K substitution.

In addition, data from real-world cohorts support the effectiveness of an 8-week regimen of glecaprevir/pibrentasvir therapy for treatment-naive, noncirrhotic patients with genotype 3 infection (Drysdale, 2019); (Sterling, 2019). Among treatment-naive patients with genotype 3, 99% (162/164) of patients in a German cohort (Berg, 2019) and 96% (46/48) of patients in an Italian cohort (D'Ambrosio, 2019) treated with 8 weeks of glecaprevir/pibrentasvir achieved SVR12.

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.

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.

A subsequent open-label study conducted in Russia and Sweden demonstrated similar response rates in noncirrhotic genotype 3 patients (Isakov, 2019). Additionally, an observational cohort study from Germany supports the effectiveness of 12 weeks of sofosbuvir/velpatasvir among treatment-naive patients with genotype 3 infection (von Felden, 2018). Of 167 treatment-naive genotype 3 patients (25% cirrhosis in overall cohort), 162 were cured and there were no virologic failures. Other real-world data from cohorts across North America, Canada, and the United Kingdom also demonstrate high SVR rates with 12 weeks of sofosbuvir/velpatasvir among genotype 3, treatment-naive, noncirrhotic patients (Drysdale, 2019); (Mangia, 2019).

Another recent study provided information about the use of sofosbuvir/velpatasvir in patients with genotype 3b, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial of patients enrolled from Asia treated with sofosbuvir/velpatasvir reported an overall SVR of 86% among 84 patients with genotype 3 infection, with or without cirrhosis (Wei, 2019). Among patients with genotype 3a, 95% (40/42) achieved SVR12. In the subgroup of noncirrhotic patients with genotype 3b, 89% (25/28) achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir. All patients with genotype 3b enrolled in this trial had NS5A RASs at A30K or L31M, or both. Another study among 90 noncirrhotic treatment-naive patients—most receiving opioid agonist therapy—treated with only 8 weeks of sofosbuvir/velpatasvir demonstrated an SVR rate of 96% (86/90) (Boyle, 2020).

Last update: August 27, 2020

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]	8 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H for velpatasvir	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS Y93H for velpatasvir	12 weeks	IIa, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H for velpatasvir	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

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).

A recent real-world cohort of 723 Italian treatment-naive and -experienced patients with or without cirrhosis were treated with glecaprevir/pibrentasvir according to the manufacturer's prescribing information. One hundred percent (21/21) of patients with genotype 3 infection who received 12 or 16 weeks of glecaprevir/pibrentasvir (likely indicative of more advanced liver disease or treatment experience) achieved SVR12, compared to 95.8% (46/48) who received an 8-week regimen (D'Ambrosio 2019). Comparably high SVR12 rates were reported with 12 weeks of glecaprevir/pibrentasvir among cirrhotic persons with genotype 3 infection in other real-world cohorts (Drysdale, 2019); (Sterling, 2019).

EXPEDITION-8 included an evaluation of glecaprevir/pibrentasvir for a reduced duration of 8 weeks in treatment-naive patients with compensated cirrhosis including genotype 3 (n=63). Patients with a prior history of decompensation,

hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. Among the participants with genotype 3, 95% (60/63) achieved SVR12 with a single participant experiencing virologic failure (relapse) and 2 participants lost to follow-up (Brown, 2019).

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, 16% (n=43) 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 compared to 97% (242/249) in those without this RAS (Foster, 2015a). Ribavirin use was not evaluated in this study.

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.

To explore whether ribavirin is required for patients with genotype 3 infection and cirrhosis, a randomized, open-label study of 204 genotype 3 patients with compensated cirrhosis (including participants with NS3/4 protease inhibitor and NS5B inhibitor treatment experience) was conducted at 29 sites in Spain. SVR12 was achieved in 91% without ribavirin (5% relapse rate) and 96% with ribavirin (2% relapse rate). Baseline NS5A RASs affected response rates. Among patients with Y93H RAS, 50% (2/4) treated with sofosbuvir/velpatasvir without ribavirin achieved SVR12 compared to 89% (8/9) among those receiving ribavirin as part of their treatment regimen (Esteban, 2018). In 293 patients with genotype 3 infection (25% with cirrhosis and 4% with DAA experience) enrolled in a multicenter cohort study from Germany in which patients received 12 weeks of sofosbuvir/velpatasvir with or without ribavirin, there was only 1 virologic failure in a patient with DAA treatment experience (von Felden, 2018). All 5 genotype 3 cirrhotic patients with RASs were prescribed ribavirin along with sofosbuvir/velpatasvir and achieved SVR. Pending further data on optimal therapy in the setting of a baseline Y93H substitution, patients with compensated cirrhosis should have ribavirin added to the regimen of sofosbuvir/velpatasvir or another regimen should be considered.

Another recent study provided information about use of sofosbuvir/velpatasvir therapy in patients with genotype 3b infection, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial enrolled patients from Asia (predominantly China) and treated them with 12 weeks of sofosbuvir/velpatasvir. Ninety percent (60/67) of patients with cirrhosis achieved SVR12 (Wei, 2019). In the subset of 14 patients with genotype 3b infection and cirrhosis, however, only 50% (7/14) achieved SVR12. All patients with genotype 3b enrolled in this trial had NS5A RASs at either A30K or L31M, or both. The influence of subtype and RASs on SVR rates warrants consideration in the use of sofosbuvir/velpatasvir among cirrhotic patients with genotype 3 infection, although genotype 3b is rare in non-Asian populations.

Alternative Regimen

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.

Last update: August 27, 2020

Treatment-Naive Genotype 4

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

Last update: August 27, 2020

Treatment-Naive Genotype 4 Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 4 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)[b]	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[b] An 8-week regimen can be considered in patients with favorable baseline characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

Recommended Regimens

Elbasvir/Grazoprevir

The phase 3 C-EDGE treatment-naive trial of elbasvir/grazoprevir included 18 patients with genotype 4 infection. With 12 weeks of therapy, SVR was 100% (18/18) (Zeuzem, 2015). A similar SVR12 of 96% (54/56) was seen in treatment-naive patients with genotype 4 infection from the combined phase 2/3 elbasvir/grazoprevir database of HIV/HCV-coinfected patients treated for 12 weeks (Rockstroh, 2015).

An integrated analysis of a phase 2/3 trial evaluated elbasvir/grazoprevir with or without ribavirin among 111 treatment-naive patients with genotype 4 infection (predominantly subtype 4a and 4d); 26% of participants had HIV/HCV coinfection and 13% had cirrhosis. Elbasvir/grazoprevir without ribavirin for 12 weeks resulted in an SVR12 of 96% (97/101) (Asselah, 2018c). Baseline RASs and subtype did not appear to impact SVR12 rates. In a study among treatment-naive participants with genotype 4 infection that compared 8 weeks versus 12 weeks of elbasvir/grazoprevir treatment for those with F0 to F2 fibrosis (all with F3 to F4 fibrosis received 12 weeks of treatment), SVR rates were 94% (50/53) in the 8-week arm and 96% (26/27) in the 12-week arm (Asselah, 2020).

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, 93% (43/46) of patients with genotype 4, 100% (2/2) with genotype 5, and 90% (9/10) with genotype 6 achieved SVR12; 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 100% (16/16) with genotype 4, 100% (2/2) with genotype 5, and 100% (7/7) 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.

Ledipasvir/Sofosbuvir

In the HEPNED-001 study from the Netherlands, 40 treatment-naive, noncirrhotic patients with (n=30) and without (n=10) HIV coinfection were treated with ledipasvir/sofosbuvir for 8 weeks; 93% (28/30) of HIV/HCV-coinfected patients and 100% (10/10) of HCV-monoinfected patients achieved SVR12 (Boerekamps, 2019). Patients were predominantly infected with genotypes 4a and 4d; 2.5% each were infected with 4c and 4t. In another study that evaluated 8 weeks of ledipasvir/sofosbuvir among treatment-naive, noncirrhotic patients from Saudi Arabia with genotype 4 infection, SVR12 was 98% (Babatin, 2019). Notably, 91% of patients had a baseline HCV RNA level <6 million IU/mL. These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection, with 8-weeks therapy a consideration for those with favorable characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

In a study from Rwanda, 300 treatment-naive patients with genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. The major subtypes among participants were 4k (n=134), 4r (n=48), 4q (n=42), and 4v (n=24). Overall SVR was 87% with subtype differences evident; SVR for 4r infection was 56% compared to 93% for other subtypes (Gupta, 2019). The influence of subtype on SVR warrants consideration of the use of ledipasvir, although 4r is rare in non-African populations.

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).

Last update: August 27, 2020

Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended 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]	8 weeks[c]	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

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

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, 99% (145/146) 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 SVR12 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.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 280 treatment-naive patients with compensated

cirrhosis and genotype 1, 2, 4 (n=13), 5, or 6 infection. SVR12 was 99% with no virologic failures (Brown, 2018). Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the study.

Elbasvir/Grazoprevir

In an integrated analysis of phase 2/3 trials, 15 treatment-naive patients with genotype 4 infection and cirrhosis were treated with 12 weeks of elbasvir/grazoprevir with or without ribavirin, resulting in an SVR of 96% (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 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 was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Another open-label, single-arm study evaluating 12 weeks of ledipasvir/sofosbuvir that included 22 genotype 4, treatment-naive patients (one with cirrhosis) reported an SVR12 of 95% (21/22) in this patient population (Abergel, 2016).

Last update: August 27, 2020

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[c]	I, A[d]
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)[e]	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.
[d] For compensated cirrhosis, rating is I, B.
[e] Not recommended for genotype 6e if subtype is known.

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 SVR12; there were no known virologic failures. Further, ENDURANCE-5,6 was a phase 3b, single-arm, open-label, multicenter study of the efficacy of glecaprevir/pibrentasvir among DAA-naive patients with genotype 5 (n=23) or 6 (n=61) infection. Participants without cirrhosis received an 8-week regimen; those with cirrhosis (11% of patients) received 12 weeks of treatment (Asselah, 2019). Overall SVR was 98% with 2 virologic failures; treatment failed in a patient with genotype 6f and cirrhosis, and in another noncirrhotic participant with genotype 5a.

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 100% (2/2) with genotype 5 and 100% (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 6 infection.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 280 treatment-naive patients with compensated cirrhosis and genotype 1, 2, 4, 5 (n=1) or 6 (n=9) infection. SVR12 was 99% with no virologic failures (Brown, 2018). Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the study.

An integrated analysis of the 181 participants with genotype 5 or 6 from phase 2/3 studies including those above showed comparable response rates between 8 weeks and 12 weeks of treatment with no signal of poorer performance among cirrhotic patients with an 8-week regimen (Yao, 2020).

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, 96% (23/24) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12. An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

Two real-world cohort studies evaluated 12 weeks of sofosbuvir/velpatasvir among predominantly treatment-naive patients with genotype 6 infection. SVR was 100% in a cohort of patients (n=23) from Southwest China, none of whom had clinical cirrhosis (Wu, 2019). SVR was also 100% in a cohort of predominantly Vietnamese patients (n=43) residing in the United States, 12% of whom had cirrhosis (Nguyen, 2019).

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 EC50 of 15 nM and 0.081 nM, respectively. An open-label, single-arm study that included 41 genotype 5-infected patients demonstrated an overall SVR12 rate of 95% (39/41) (Abergel, 2016). The SVR12 rate was also 95% specifically among 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% 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).

In the largest US study, 60 patients with genotype 6 infection were randomized to 8 weeks (treatment-naive, no cirrhosis) or 12 weeks (treatment-naive or -experienced, with or without cirrhosis) of ledipasvir/sofosbuvir; SVR rates were 95% in both treatment groups (Nguyen, 2017). A real-world cohort of 92 treatment-naive patients with genotype 6 infection (predominantly Vietnamese patients residing in the United States, 51% with cirrhosis) was treated with 12 weeks of ledipasvir/sofosbuvir; SVR12 was 96.6% (Nguyen, 2019). Subtype data were not available.

A recent systematic review that examined the response to DAA therapy among persons with genotype 6 infection highlighted the heterogeneity of SVR rates in response to ledipasvir/sofosbuvir treatment across Asian countries (64% in Myanmar versus 100% in Vietnam) (Mettikanont, 2019). The reasons for this difference are likely multiple; the variable distribution of subtypes within the populations is a potential explanation. Pending more data, a conservative approach is recommended, with subtype 6e patients best treated with an alternative regimen.

Last update: August 27, 2020

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 shorter 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. In certain situations, an alternative regimen may be optimal for a specific patient.

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. Persons 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).

Scope and Need for Direct Acting Antiviral (DAA) Failure Retreatment

The success of initial DAA therapy has led to treatment of hundreds of thousands of patients in the US. With this massive scale-up, there will inevitably be failures. Even with a 2% to 3% failure rate, there will still be thousands who need retreatment. Since the last iteration of this section, additional published evidence has emerged to support recommendations for retreatment. To simplify and consolidate the guidance, this section no longer contains retreatment recommendations for interferon or interferon plus first generation protease inhibitor failures because the cure rates with modern DAA regimens in these populations were comparable to treatment naive patients. In addition, pangenotypic regimens without the addition of ribavirin have shown high efficacy for patients with prior failure across all genotypes except genotype 3. Therefore, recommendations are categorized by regimen failure.

Prior DAA exposure may result in the selection of resistance-associated substitutions (RASs), particularly in NS5A, which could theoretically compromise the retreatment regimen. To date, however, a negative impact of NS5A RASs on the efficacy of retreatment regimens consisting of 3 DAAs with unique mechanisms of action (eg, sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir plus glecaprevir/pibrentasvir) has not been demonstrated in clinical trials. Persons experiencing multiple DAA regimen failures with complex RAS patterns in NS3 and/or NS5A represent a unique and understudied population where RASs may impact treatment response. For a full discussion, see HCV Resistance Primer section.

The following pages include guidance for management of treatment-experienced patients in the following categories:

- Sofosbuvir-based and elbasvir/grazoprevir treatment failures, including:
  - Sofosbuvir/ribavirin ± interferon
  - Sofosbuvir/ledipasvir
  - Sofosbuvir/velpatasvir
  - Elbasvir/grazoprevir
- Glecaprevir/pibrentasvir treatment failures
- Multiple DAA regimen failures, including:
  - Sofosbuvir/velpatasvir/voxilaprevir
  - Sofosbuvir plus glecaprevir/pibrentasvir

Last update: January 21, 2021

Sofosbuvir-Based and Elbasvir/Grazoprevir Treatment Failures

In general, persons who have experienced treatment failure with a sofosbuvir-based regimen should be retreated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir. The main exception is persons with genotype 3 and cirrhosis, in whom addition of ribavirin to sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is recommended. Sixteen weeks of glecaprevir/pibrentasvir is an alternative regimen.

Elbasvir/grazoprevir treatment failure patients should also be retreated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir. However, glecaprevir/pibrentasvir for 16 weeks is not recommended as an alternative for this group of patients.

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

Sofosbuvir-Based Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)[b]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) except for NS3/4 protease inhibitor inclusive combination DAA regimen failures[c] • **Not** recommended for genotype 3 infection with sofosbuvir/NS5A inhibitor experience.	16 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Genotype 3: Add weight-based ribavirin if cirrhosis is present and there are no contraindications.
[c] This regimen is not recommended for patients with prior exposure to an NS5A inhibitor plus NS3/4 PI regimens (eg. Elbasvir/grazoprevir).

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 263 persons with a prior NS5A inhibitor-containing DAA regimen failure. The majority (55%) had experienced a sofosbuvir/ledipasvir failure (Bourliere, 2017). Virologic failure was rare (2%; 3/145) among those retreated with sofosbuvir/velpatasvir/voxilaprevir. All 3 individuals whose retreatment failed had cirrhosis; 2 persons had genotype 1a and 1 had genotype 4d. The treatment-failure patients with genotype 1a also had baseline RASs at Q80K, Z30T, and Y93H.

In the same study, a small number of persons who had a prior treatment failure with sofosbuvir/velpatasvir were retreated with sofosbuvir/velpatasvir/voxilaprevir. Two patients experienced virologic failure. Both had cirrhosis, genotype 3, and the Y93H RAS in the NS5A region at baseline. Because of the higher failure rates in the subgroup of genotype 3 patients with cirrhosis, the regimen of sofosbuvir/velpatasvir/voxilaprevir plus ribavirin for 12 weeks is recommended. If ribavirin cannot be used, extension to 24 weeks can be considered. Several real-world cohort reports also identified lower response rates after sofosbuvir/velpatasvir/voxilaprevir retreatment for 12 weeks in persons with genotype 3 and cirrhosis, lending further support to the need for regimen modification (Papaluca, 2020); (Llaneras, 2019). Serious adverse events were similar in the placebo and treatment arms; a single patient discontinued therapy due to an adverse event. Headache, diarrhea, and nausea were more common in those participants receiving sofosbuvir/velpatasvir/voxilaprevir compared to placebo.

Results from deferred treatment of the placebo arm in POLARIS-1 further support the high efficacy of 12 weeks of sofosbuvir/velpatasvir/voxilaprevir for retreatment of persons with a prior sofosbuvir/NS5A inhibitor treatment failure (Bourliere, 2018). Overall SVR in the deferred treatment group was 97% (n=147), including 96% SVR (n=76) in those with prior sofosbuvir/NS5A inhibitor experience (n=76).

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of the daily fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of sofosbuvir/velpatasvir in NS5A inhibitor-naive, DAA-experienced patients (Bourliere, 2017). Eleven percent had prior exposure to simeprevir/sofosbuvir. Cirrhosis was common, 46% in both arms. SVR12 rates were higher for sofosbuvir/velpatasvir/voxilaprevir (98%; 178/182) compared to sofosbuvir/velpatasvir (90%; 136/151). This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for patients with a prior treatment failure with a sofosbuvir-containing regimen, regardless of the presence of compensated cirrhosis.

Data from both clinical trials (Bourliere, 2018); (Bourliere, 2017) and real-world cohorts (Da, 2020); (Belperio, 2019); (Degasperi, 2019); (Llaneras, 2019) that evaluated the efficacy and safety of sofosbuvir/velpatasvir/voxilaprevir among DAA-experienced persons support the use of this regimen for persons with a prior elbasvir/grazoprevir treatment failure.

Alternative Regimen

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 patients with genotype 1 who had previously been treated with either an NS5A inhibitor or an NS3/4A protease inhibitor were retreated with glecaprevir/pibrentasvir (Poordad, 2018); (Poordad, 2017). Twenty-four percent of the study participants had cirrhosis; 79% had genotype 1a. In the subgroup of persons previously treated with an NS5A inhibitor (ledipasvir or daclatasvir) and not concomitantly treated with a NS3/4A protease inhibitor, the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 16 weeks achieved an SVR of 94% (16/17). The single patient who did not respond to therapy had an on-treatment virologic failure.

A phase 3b open-label study further supports the efficacy of 16 weeks of glecaprevir/pibrentasvir for retreatment of individuals with genotype 1 infection and a history of sofosbuvir/NS5A inhibitor treatment failure (Lok, 2019). The study randomized sofosbuvir/NS5A inhibitor-experienced, genotype 1 patients without cirrhosis to 12 weeks (n=78) or 16 weeks (n=49) of glecaprevir/pibrentasvir. Participants with cirrhosis were randomized to 12 weeks (n=21) or 16 weeks (n=29) of glecaprevir/pibrentasvir plus weight-based ribavirin. Enrollment in the 12-week plus ribavirin arm for participants with cirrhosis was halted early due 2 viral breakthroughs on therapy and 1 case of early relapse. SVR was numerically higher in the 16-week study arms (94% and 97% without and with cirrhosis, respectively) compared to the 12-week arms (90% and 86% without and with cirrhosis, respectively). No clear impact of ribavirin was detected in the study and the majority of virologic failures were among those with genotype 1a treated for 12 weeks without ribavirin. No virologic failures were seen in genotype 1b patients. These data further support glecaprevir/pibrentasvir for 16 weeks as an efficacious retreatment approach for sofosbuvir/NS5A inhibitor experienced patients.

Glecaprevir/Pibrentasvir for Genotype 3 Sofosbuvir/Ribavirin Treatment Failures

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) among treatment-naive or interferon-experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3 patients without cirrhosis or with compensated cirrhosis. Among the 34 treatment-experienced participants with prior exposure to sofosbuvir who were treated for 16 weeks, regardless of cirrhosis status, SVR12 was 97% (33/34). The lone virologic failure was due to relapse in a patient with cirrhosis. No NS5A RASs were present prior to treatment, however, the L31F and Y93H substitutions were present at retreatment failure (Wyles, 2018). Sixteen weeks of glecaprevir/pibrentasvir is an alternative regimen for genotype 3 patients with prior exposure to sofosbuvir plus ribavirin given the high SVR and lack of need for the addition of ribavirin. This regimen was not evaluated for genotype 3 patients who experienced a prior treatment failure with a regimen containing both sofosbuvir and an NS5A inhibitor. Given the lack of data this regimen is not recommended for genotype 3 infection with prior sofosbuvir/NS5A inhibitor experience.

Last update: January 21, 2021

Glecaprevir/Pibrentasvir Treatment Failures

Recommended regimens listed by evidence level and alphabetically for:

Glecaprevir/Pibrentasvir Treatment Failures (All Genotypes), With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIa, B
For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended.	12 weeks	IIa, C

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

Recommended Regimens

Glecaprevir/Pibrentasvir Plus Sofosbuvir and Ribavirin

For the small number of persons in whom treatment with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) fails, the addition of ribavirin and sofosbuvir is an attractive retreatment option. MAGELLAN-3 evaluated the safety and efficacy of glecaprevir/pibrentasvir in combination with sofosbuvir (400 mg) and weight-based ribavirin as a 12- or 16-week retreatment regimen for individuals who experienced virologic failure to glecaprevir/pibrentasvir (Wyles, 2019). Importantly, many study participants had received other regimens before their nonresponse to glecaprevir/pibrentasvir. Noncirrhotic, glecaprevir/pibrentasvir nonresponders with genotype 1, 2, 4, 5, or 6 who were naive to protease and NS5A inhibitors received 12 weeks glecaprevir/pibrentasvir plus sofosbuvir and weight-based ribavirin. Participants with genotype 3, and/or compensated cirrhosis, and/or protease or NS5A inhibitor experience (prior to their initial glecaprevir/pibrentasvir treatment) received 16 weeks of therapy with the same regimen. Overall, 96% (22/23) of these patients achieved SVR12 with a single relapse in a cirrhotic patient with genotype 1a. This individual had prior treatment failures with multiple other regimens and had multiple complex NS3 and NS5A RASs, including NS5A, Q30K, and Y93H prior to treatment. This study provides the rationale to recommend the combination of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin for 16 weeks for persons without cirrhosis or with compensated cirrhosis who experienced treatment failure with initial glecaprevir/pibrentasvir treatment.

Sofosbuvir/Velpatasvir/Voxilaprevir

A prospective, nonrandomized observational study evaluated the efficacy of retreatment with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) among patients who experienced

treatment failure with initial glecaprevir/pibrentasvir therapy (Pearlman, 2019). SVR12 was 94% (29/31). The cohort had higher proportions of patients with factors traditionally associated with virologic failure, including black race, cirrhosis, and genotype 3. Two patients relapsed at week 4 following the completion of therapy. One patient had genotype 3 infection, was noncirrhotic, and had an A30K mutation at baseline and at relapse. The other patient had genotype 1a infection, compensated cirrhosis, a Y93 variant detected at baseline, and L31M and Y93 variants at relapse. The addition of ribavirin was not evaluated in this study. For patients with cirrhosis, however, it may be helpful to add ribavirin based on prior studies of DAA failures.

Last update: January 21, 2021

Multiple DAA Treatment Failures (All Genotypes), Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir

Recommended regimens listed by evidence level and alphabetically for:

Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failures, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks[b]	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Extension of treatment to 24 weeks should be considered in extremely difficult cases (eg, genotype 3 with cirrhosis) or failure following sofosbuvir plus glecaprevir/pibrentasvir.

Recommended Regimens

Glecaprevir/Pibrentasvir Plus Sofosbuvir and Ribavirin

There is 1 case report examining retreatment of patients in whom therapy with sofosbuvir/velpatasvir/voxilaprevir failed. In this study, a quad regimen of sofosbuvir, glecaprevir/pibrentasvir, and ribavirin for 24 weeks was successful (Bernhard, 2020). Of note, pibrentasvir has improved in vitro activity compared to other NS5A inhibitors against most NS5A RASs (Ng, 2017b). A small study demonstrated the efficacy of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin for heavily DAA-experienced patients (including those with genotype 3 and/or cirrhosis), although no sofosbuvir/velpatasvir/voxilaprevir failures were included (Wyles, 2019). Sixteen weeks of glecaprevir/pibrentasvir plus sofosbuvir and ribavirin is recommended based on the improved resistance profile of pibrentasvir and high response rate seen with this duration of therapy among genotype 3 patients in the MAGELLAN-3 trial (Wyles, 2019). Extension to 24 weeks or longer with this regimen could be considered; while there are case report data using this duration (Bernhard, 2020); (Fierer, 2020), no clinical trial data are available to support such an approach.

Sofosbuvir/Velpatasvir/Voxilaprevir Plus Ribavirin

Although there are no published studies examining retreatment of patients in whom therapy with sofosbuvir/velpatasvir/voxilaprevir failed, in the POLARIS-1 study—which studied sofosbuvir/velpatasvir/voxilaprevir treatment among patients who had a prior DAA therapy failure—treatment failure with this triple antiviral regimen was seen more commonly in persons with cirrhosis (7% cirrhosis vs 1% without cirrhosis), and those with genotype 3 or 4 (5% genotype 3, 9% genotype 4 vs 0% genotype 1) (Bourliere, 2017). Baseline RASs did not affect SVR nor did failure select for additional RAS variants. The recommendation to treat with longer therapy in conjunction with ribavirin when retreating

with the same DAA regimen (sofosbuvir/velpatasvir/voxilaprevir) is based on extrapolation from prior studies showing benefit with this strategy in different populations (Gane, 2017).

Last update: January 21, 2021

Management of Unique & Key Populations With HCV Infection

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

Last update: August 27, 2020

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 (Fierer, 2013); (Kirk, 2013); (de Ledinghen, 2008); (Thein, 2008a). As such, HCV treatment in HIV-infected patients should be a priority for providers, payers, and patients. If HCV treatment is delayed for any reason, however, 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).

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 (Rockstroh, 2018); (Bhattacharya, 2017); (Wyles, 2017b); (Naggie, 2015); (Rockstroh, 2015); (Sulkowski, 2015); (Wyles, 2015). Treatment of HIV/HCV-coinfected patients, however, 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). The University of Liverpool drug interactions website (www.hep-druginteractions.org) is another resource for screening for drug-drug interactions with DAAs.

Risk for Hepatitis B Virus Reactivation

Due to shared modes of transmission, HIV/HCV-coinfected patients are at risk for hepatitis B virus (HBV) infection. HBV reactivation 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 with 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.

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
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, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, maraviroc, raltegravir, 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, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir.	IIa, B

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications

Given the increase in glecaprevir exposures and 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.	
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 tenofovir levels, when given as tenofovir disoproxil fumarate, may increase with sofosbuvir/velpatasvir, 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 in patients taking tenofovir disoproxil fumarate and cobicistat or ritonavir with sofosbuvir/velpatasvir. 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. 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 taking cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, C
For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.	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: abacavir, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir alafenamide. 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 concomitantly receiving sofosbuvir/velpatasvir/voxilaprevir and tenofovir disoproxil fumarate, renal monitoring is recommended during the dosing period.	IIa, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. 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, efavirenz, etravirine, nevirapine, or ritonavir-containing antiretroviral regimens.	III, B
Sofosbuvir/velpatasvir should **not** be used with efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir/velpatasvir/voxilaprevir should **not** be used with efavirenz, etravirine, nevirapine, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir.	III, B
Sofosbuvir-based regimens should **not** be used with tipranavir.	III, B
Ribavirin should **not** be used with didanosine, stavudine, or zidovudine.	III, B

Clinical Trial, Pharmacokinetic, and Drug Interaction Data

Extensive recommendations for antiretroviral therapy use (including for persons anticipating HCV treatment) are available at 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, response(s) to antiretroviral therapy, resistance profiles, and drug tolerance (DHHS, 2020); (Gunthard, 2014). 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 (Thorpe, 2011); (Tedaldi, 2008). 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 (Rockstroh, 2018); (Dieterich, 2015); (Naggie, 2015); (Osinusi, 2015); (Rockstroh, 2015); (Rodriguez-Torres, 2015); (Sulkowski, 2015); (Wyles, 2015); (Wyles, 2015b); (Dieterich, 2014b); (Sulkowski, 2014); (Sulkowski, 2013). Thus, results from HCV monoinfection studies largely justify the recommendations for HIV/HCV coinfection (discussed in the Initial Treatment, and Retreatment sections). Discussion specific to HIV/HCV coinfection research is included here.

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 the lack of data, it is highly likely that response rates are similar to those of HCV-monoinfected patients because no study to date in the DAA era has shown 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-drug interactions.

Elbasvir/Grazoprevir

The safety, tolerability, and efficacy of the second-generation NS3/4A serine protease inhibitor grazoprevir plus the NS5A inhibitor elbasvir 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, etravirine, or nevirapine (Feng, 2016). Drug interaction studies showed no clinically significant interactions between elbasvir/grazoprevir and dolutegravir, raltegravir, doravirine, or tenofovir disoproxil fumarate (Ankrom, 2019); (Feng, 2019a); (Feng, 2019b).

Glecaprevir/Pibrentasvir

The safety and efficacy of glecaprevir (a pangenotypic NS3/4A protease inhibitor) coformulated with pibrentasvir (a pangenotypic NS5A inhibitor) were evaluated in the phase 3, multicenter EXPEDITION-2 study (Rockstroh, 2018). 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.

Eight weeks of glecaprevir/pibrentasvir achieves similar SVR rates to those achieved with 12 weeks of treatment in HCV-monoinfected, treatment-naive patients with cirrhosis (Brown, 2020). However, there are no data evaluating the 8-week treatment duration in HIV/HCV-coinfected patients with cirrhosis. Thus, a shortened treatment course for HIV/HCV-coinfected patients with cirrhosis cannot be recommended at this time.

Pharmacology and Drug Interaction Data

Glecaprevir is metabolized by CYP3A as a secondary pathway, and glecaprevir and pibrentasvir are substrates for P-gp and breast cancer resistance protein (BCRP). Glecaprevir is also a substrate for the hepatic uptake transporter organic anion-transporting polypeptide (OATP) 1B1/3. Glecaprevir and pibrentasvir are weak inhibitors of CYP3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1. Glecaprevir and pibrentasvir inhibit P-gp, BCRP, and OATP1B1/3. Compounds that inhibit P-gp, BCRP, or OATP1B1/3 may increase glecaprevir and pibrentasvir concentrations. In contrast, drugs that induce P-gp/CYP3A may decrease glecaprevir and pibrentasvir concentrations.

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, 2020). A single 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.

No clinically significant interactions were observed with glecaprevir/pibrentasvir in a drug interaction study with dolutegravir, raltegravir, rilpirivine, abacavir, lamivudine, emtricitabine, or tenofovir (Kosloski, 2020). Boosted protease inhibitors are not recommended with glecaprevir/pibrentasvir. Glecaprevir and pibrentasvir exposures were both at least 47% lower when coadministered with efavirenz compared to observed concentrations when given alone in other studies and, therefore, concomitant use is not recommended (Kosloski, 2020). Etravirine and nevirapine should not be used due to the potential for decreased glecaprevir/pibrentasvir exposures.

Glecaprevir absorption is pH dependent and glecaprevir exposures are reduced approximately 50% with 40 mg of omeprazole daily. Despite the reduced glecaprevir exposures, pooled data from the phase 2/3 glecaprevir/pibrentasvir trials found that patients receiving proton pump inhibitors had similar SVR rates compared to patients not receiving a gastric acid modifier (Flamm, 2019).

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 the 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, one 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. 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 (Naggie, 2015); (Osinusi, 2015). There are limited data regarding an 8-week course of ledipasvir/sofosbuvir in HIV/HCV-coinfected patients (Vega, 2019); (Isakov, 2018); (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 (97%). Therefore, a shortened treatment course for HIV/HCV-coinfected persons is not recommended at this time.

Pharmacology and Drug Interaction Data

Ledipasvir and sofosbuvir are P-gp and BCRP substrates; ledipasvir is also an inhibitor of both P-gp and BCRP transporters.

Drug interaction studies of ledipasvir (with or without sofosbuvir) with antiretroviral drugs in uninfected persons did not identify clinically significant interactions with abacavir, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, raltegravir, rilpivirine, or tenofovir alafanamide (Ankrom, 2019); (Garrison, 2018); (Garrison, 2015); (German, 2014). Interactions with maraviroc are not expected based on its pharmacologic profile. 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. 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).

Data are limited regarding the renal safety of tenofovir when given as tenofovir alafenamide with ledipasvir/sofosbuvir. However, a small pharmacokinetic study among persons with HIV on a boosted protease inhibitor and tenofovir alafenamide containing regimen found that the addition of ledipasvir/sofosbuvir did not worsen renal biomarkers (Brooks, 2020). 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.

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, 2017b). 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.

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 OATP1B1/1B3/2B1 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 and those requiring ritonavir- or cobicistat-containing antiretroviral therapy, consider use of tenofovir alafenamide in place of tenofovir disoproxil fumarate. If the combination of tenofovir disoproxil fumarate with a ritonavir- or cobicistat-containing antiretroviral therapy is required or in those with an eGFR <60 mL/min, renal parameters should be checked at baseline and regularly thereafter while on sofosbuvir/velpatasvir.

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.

Drug-drug interaction studies in healthy volunteers found no clinically significant interaction between sofosbuvir/velpatasvir and atazanavir/ritonavir, darunavir/ritonavir, bictegravir, dolutegravir, elvitegravir/cobicistat, raltegravir, rilpivirine, emtricitabine, or tenofovir alafenamide (Garrison, 2018); (Mogalian, 2018). Velpatasvir exposures are significantly reduced with efavirenz and this combination is not recommended. Etravirine and nevirapine have not been studied with sofosbuvir/velpatasvir but are 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.

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. There are limited data on sofosbuvir/velpatasvir/voxilaprevir in HIV/HCV-coinfected patients. The RESOLVE study included 17 individuals with HIV coinfection and a previous DAA treatment failure (Wilson, 2019). SVR12 was 82% by intention-to-treat and 93% by per

protocol analysis. While these data are limited, they suggest response rates in HIV/HCV-coinfected patients are similar to those of HCV-monoinfected patients. Therefore, the respective guidance from the aforementioned treatment and retreatment sections should be followed, with consideration of drug-drug interactions.

Pharmacology and Drug Interaction Data

Voxilaprevir is a substrate for P-gp, OATP1B1/3, BCRP, CYP3A, CYP1A2, and CYP2C8. Voxilaprevir inhibits OATP1B1/3, 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 bictegravir, emtricitabine, 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. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs—Recommended Regimens

		Ledipasvir/ Sofosbuvir (LDV/SOF)	**Sofosbuvir/ Velpatasvir (SOF/VEL)**	**Elbasvir/ Grazoprevir (ELB/GRZ)**	**Glecaprevir/ Pibrentasvir (GLE/PIB)**	**Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)**
Protease Inhibitors	**Boosted Atazanavir**	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	ND, A	A			ND
NNRTIs	**Doravirine**		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase Inhibitors	**Bictegravir**			ND	ND	
	Cobicistat-boosted elvitegravir	C	C			C

		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (ELB/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
	Dolutegravir					ND
	Raltegravir					ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	**Abacavir**		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C, D
	Tenofovir alafenamide	D	D	ND		D

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and red indicates the combination should be avoided.
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.

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 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

Last update: August 27, 2020

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); (Welzel, 2016); (Charlton, 2015); (Curry, 2015). Improvements, however, 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. Predictors of improvement or decline have not been clearly identified, although 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 antiviral treatment (El-Sherif, 2018); (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 (Beste, 2017); (Prenner, 2017). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (± ribavirin), overall SVR rates were 91% in patients without HCC versus 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 SVR can be overcome with an extended duration of therapy is unknown.

In a more recent large, multicenter, real-world cohort of 642 patients with advanced cirrhosis (defined as cirrhosis and MELD score ≥10) treated with a variety of DAA regimens, the overall SVR12 rate was 90.5%. Age <60, male sex, ascites, albumin level <3.5 mg/dl, hepatocellular carcinoma, proton-pump inhibitor use, MELD score <16 and CTP class B/C were significantly associated with decreased odds of SVR12. In long-term follow up, at a median of 4 years after the end of treatment, a clinically meaningful decrease in MELD score of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%. These data highlight that a proportion of patients with advanced cirrhosis who receive DAA therapy may not achieve significant long-term improvement in liver function (Verna, 2020).

Decompensated Cirrhosis Genotype 1-6

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1-6 and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated to weight-based dose)	12 weeks	I, A[b]
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	12 weeks	I, A[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 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.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1-6 and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[b]
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[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.

Recommended regimens listed by evidence level and alphabetically for:

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

RECOMMENDED	DURATION	RATING
Prior sofosbuvir-based treatment failure, genotype 1, 4, 5, or 6 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]
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	24 weeks	II, C[d]

Recommended regimens listed by evidence level and alphabetically for:

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

[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.

Protease inhibitor-containing regimens (eg, glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir) are not recommended in patients with decompensated liver disease (see “Protease-Inhibitor Containing Regimens” discussion below for details).

Ledipasvir/Sofosbuvir

The US-based, multicenter, randomized, open-label, phase 2 SOLAR-1 trial included 108 patients with genotype 1 or 4 and decompensated cirrhosis; 59 were categorized as CTP class B (score 7 to 9) and 49 were 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, SVR rates were 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 patients with genotype 1 or 4 and 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 arm (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-

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 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 6-16), 26% of patients had varices, and 13% had a low serum albumin level. The SVR12 rates were 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache, and pruritus; 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.

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. 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. Investigators from the United Kingdom reported on the use of 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg)/sofosbuvir (400 mg), with or without ribavirin, among 235 genotype 1 patients (Foster, 2016). SVR rates were similar in the 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. SVR12 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 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 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 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 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.

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, 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.

SVR rates among the 12 patients with CTP class B cirrhosis and genotype 2 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, 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 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.

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.

Sofosbuvir/velpatasvir has also been studied in a small number of patients with CTP class C cirrhosis. In a Japanese phase 3, open-label study of patients with CTP class B (77%) and CTP class C (20%) cirrhosis, 102 patients with genotype 1, 2, or 3 were randomized to 12 weeks of sofosbuvir/velpatasvir with or without ribavirin (Takehara, 2019). Ribavirin dosing was weight based in CTP class B patients (600 mg/d ≤60 kg; 800 mg/d >60 to 80 kg; 1000 mg/d >80 kg) and 600 mg daily for all CTP class C patients. Overall SVR12 rates were 92% in each arm, but only 75% among patients with CTP class C cirrhosis.

There are no data on the outcomes of patients with decompensated cirrhosis and a history of prior sofosbuvir plus an NS5A inhibitor failure. However, in a phase 2, open-label, single-arm study using 24 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin among patients with a history of treatment failure with an NS5A inhibitor-containing regimen, among 69 patients (28% with compensated cirrhosis) treated with sofosbuvir/velpatasvir plus ribavirin for 24 weeks, SVR rates were 97% for genotype 1 (83% with compensated cirrhosis), 93% for genotype 2 (no patients with cirrhosis), and 78% for genotype 3 (75% with compensated cirrhosis) (Gane, 2017). 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. The study included 35 patients with genotype 5 and 41 patients with genotype 6 (Feld, 2015). Overall SVR12 rates were 97% (34/35) in genotype 5 patients and 100% (41/41) in those with genotype 6. 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.

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
Any protease inhibitor-containing regimen (eg, glecaprevir, grazoprevir, and voxilaprevir).	III, B
Interferon-based regimens	III, B

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 not been studied in patients with decompensated cirrhosis and, pending additional safety data, is not recommended.

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 (50 mg/50 mg) for 12 weeks was completed in 30 genotype 1 patients with CTP class B cirrhosis (Jacobson, 2019). SVR12 was 90% (27/30); 1 patient died of liver failure at post-treatment week 4 and 2 patients relapsed. At follow-up week 12, MELD scores improved in 41% (12/29) of treated patients, were unchanged in 38% (11/29), and worsened in 21% (6/29). 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.

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 that 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.

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 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.

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.

Interferon-Based Regimens

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.

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Patients Who Develop Recurrent HCV Infection Post Liver Transplantation

Post Liver Transplantation: Genotype 1-6

Recommended regimens listed by evidence level and alphabetically for:

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

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

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

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: 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, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, C

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

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

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)[b]	12 to 24 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ ribavirin starting at 600 mg and increased as tolerated[b]	12 to 24 weeks[c]	I, B

[a] Includes CTP class B and class C patients.
[b] The starting dose of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.
[c] 24-week treatment duration is recommended if treatment experienced.

Recommended regimen for:

DAA-Experienced Patients With Genotype 1-6 Infection in the Allograft, With or Without Compensated Cirrhosis[a]

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

[a] Excludes CTP class B and class C patients.
[b] For patients with cirrhosis plus multiple negative baseline characteristic, consideration should be given to adding ribavirin. The starting dose of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.

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 and 24% had genotype 3. Except for genotype 3 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. Cirrhotic patients were excluded. 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, 2018). 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. A multicenter study from Japan treated 24 liver transplant recipients with recurrent HCV with 8 weeks or 12

weeks of glecaprevir/pibrentasvir (including 21% with F3/F4); 96% achieved SVR12. All 13 patients (genotype 1 or 2, without cirrhosis) treated for 8 weeks achieved SVR (Ueda, 2019). As data on the efficacy of glecaprevir/pibrentasvir in transplant recipients with cirrhosis and use of shorter treatment course (8 weeks versus 12 weeks) in those without cirrhosis are very limited, pending additional real-world data, a 12-week course is recommended regardless of stage. Additionally, for patients with cirrhosis plus other negative baseline factors, adding low-dose (600 mg) ribavirin may be a consideration.

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 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/d [<75 kg] to 1200 mg/d [≥ 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.

An observational HCV-TARGET cohort study provides real-world data based on experience with 347 liver, 60 kidney, and 36 dual liver and kidney transplant recipients. Among the enrolled patients, 86% had genotype 1, 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 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.

The multicenter ANRS CO23 CUPILT study investigators reported their experience with sofosbuvir + an NS5A inhibitor (daclatasvir or ledipasvir ± ribavirin) among 512 liver transplant recipients with recurrent HCV who met inclusion criteria for analysis (Houssel-Debry, 2018). The genotype distribution of the participants was 70% (n=359) genotype 1, 1% (n=7) genotype 2, 18% (n=93) genotype 3, 10% (n=50) genotype 4, and <1% (n=3) genotype 5. Twenty-one percent had cirrhosis and 34% had prior treatment experience. The regimens and treatment durations were sofosbuvir + an NS5A inhibitor without ribavirin for 12 weeks (n=156) or 24 weeks (n=239), and sofosbuvir + an NS5A inhibitor and ribavirin for 12 weeks (n=47) or 24 weeks (n=70). SVR12 rates were 94%, 99%, 96%, and 93%, respectively. Twenty patients experienced treatment failure and in a multivariate analysis, fibrosis stage, prior treatment, genotype, and baseline HCV viral load did not adversely impact SVR12 rates in the 4 treatment groups. The investigators concluded that 12 weeks of sofosbuvir + an NS5A inhibitor without ribavirin was an effective regimen regardless of fibrosis stage, genotype, and prior treatment experience.

Collectively, these real-world experiences indicate high SVR rates can be attained without inclusion of ribavirin in liver transplant patients. However, all factors leading clinicians to include or exclude ribavirin cannot be discerned from these observational studies. The safest presumption is that ribavirin may contribute to the high SVR rates and be relevant for patients with unfavorable baseline characteristics (eg, cirrhosis, prior treatment experience). Thus, ribavirin-free therapy is recommended for patients with a favorable baseline profile and ribavirin-inclusive therapy is recommended for those with an unfavorable baseline profile.

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 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.

Sofosbuvir/Velpatasvir

The safety and efficacy of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was evaluated in 79 (5 with cirrhosis, 4 DAA experienced) liver transplant recipients with genotype 1, 2, 3, or 4 (Agarwal, 2018). Treatment was well tolerated with 99% of patients completing treatment. Overall SVR12 rates by genotype were 93% genotype 1a (n=15); 96% genotype 1b (n=22); 100% genotype 2 (n=3); 97% genotype 3 (n=35); and 100% genotype 4 (n=4). Eighteen (23%) patients required a change in immunosuppression during treatment but none were for rejection or drug-drug-interactions. Most patients were on calcineurin inhibitor-based immunosuppression (71% on tacrolimus, 14% on cyclosporine).

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 who were randomly assigned in a 5:1 ratio to sofosbuvir/velpatasvir or placebo for 12 weeks (Feld, 2015). All patients with genotype 5 (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 (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. SVR12 was 95% (95% CI, 92 to 98) for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 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 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, 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 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 to 24 weeks, depending upon presence of other negative prognostic features at baseline (ie, treatment experienced, genotype 3, presence of hepatocellular carcinoma).

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).

Sofosbuvir/Velpatasvir/Voxilaprevir

There is limited experience with sofosbuvir/velpatasvir/voxilaprevir in liver transplant recipients. In a single case report of a prior DAA regimen failure, successful treatment of recurrent HCV after liver transplant with sofosbuvir/velpatasvir/voxilaprevir was achieved (Cardona-Gonzalez, 2018). The patient had genotype 3 infection and acute hepatitis post liver transplant. He was treated with sofosbuvir/velpatasvir/voxilaprevir for 16 weeks with ribavirin added during the last 8 weeks of therapy.

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-Drug Interactions Between DAAs and Calcineurin Inhibitors

The interactions of DAA agents and calcineurin inhibitors are complex and unpredictable without formal studies of drug-drug interactions. A summary of drug-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
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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Treatment of HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors

With the large disparity between patients in need of organ transplantation and available donor organs, some transplant programs are turning to use of organs from HCV-viremic donors. In the past, organs from HCV-viremic donors were primarily used in recipients with chronic hepatitis C or discarded. With the advent of safe and effective HCV DAA regimens, however, organs from HCV-viremic donors may be considered for use in recipients without HCV infection. Use of these organs increases the pool of available organs, patient access to transplantation (Sageshima, 2018), and potentially reduces waitlist time (Bhamidimarri, 2017); (Scalea, 2015) and related mortality (Sawinski, 2019); (Shelton, 2018); (Kucirka, 2012).

All organ donors undergo HCV-antibody and HCV nucleic acid testing (NAT). Nonhepatic donors who are HCV antibody positive but HCV RNA negative likely pose a negligible risk of HCV transmission to the recipient, although more data are needed to confirm this. However, among increased-risk donors (as defined by the US Public Health Service [PHS] guidelines) who had a recent HCV exposure, HCV RNA may not yet be detectable and transplant recipients from these donors should be monitored for HCV in addition to HBV and HIV per the increased-risk donor testing protocols (Levitsky, 2017); (Seem, 2013b). Emerging data indicate that transplant recipients who receive a liver from an HCV-antibody–positive/HCV-RNA–negative donor should be monitored more closely after transplantation given the potential risk for HCV transmission (Bari, 2018). Donors who are HCV RNA positive (with or without anti-HCV) pose the highest risk for HCV transmission to transplant recipients. Because of the significant risk for HCV infection when transplanting an organ from an HCV-viremic donor into an HCV-uninfected recipient, rigorous informed consent and post-transplantation, HCV-related follow-up processes are recommended.

Recommendations When Considering Use of HCV-Viremic Donor Organs in HCV-Uninfected Recipients

RECOMMENDED	RATING
Informed consent should include the following elements: • Risk of transmission from an HCV-viremic donor (and with a PHS-defined increased risk donor, the potential risks for other viral infections) • Risk of liver disease if HCV treatment is not available or treatment is unsuccessful • Risk of graft failure • Risk of extrahepatic complications, such as HCV-associated renal disease • Risk of HCV transmission to partner • Benefits, specifically reduced waiting time and possibly lower waiting list mortality • Other unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure is attained)	I, C
Transplant programs should have a programmatic strategy to: • Document informed consent • Assure access to HCV treatment and retreatment(s), as necessary • Ensure long-term follow-up of recipients (beyond SVR12)	I, C

Recommendations When Considering Use of HCV-Viremic Donor Organs in HCV-Uninfected Recipients

Recent data indicate increasing acceptance of organs from HCV-viremic donors among HCV-uninfected recipients (Cotter, 2019); (Potluri, 2019); (Bowring, 2018). Although no published data are available regarding the long-term (beyond 1 to 2 years) consequences to HCV-negative recipients transplanted with organs from HCV-viremic donors who are treated post-transplant with DAAs, limited short-term data from liver, kidney, heart, and lung transplant programs are encouraging.

Liver Transplantation

Among 10 HCV-negative liver transplant recipients of organs from HCV-viremic donors, 100% achieved SVR12 with 12 to 24 weeks of various DAA regimens (Kwong, 2019). The median time from transplantation to treatment initiation was 43 days (interquartile range [IQR] 20-59 days). Noteworthy was the high rate of acute cellular or antibody-mediated rejection (30%) during or after DAA therapy in this study. In another study of 14 HCV-negative liver transplant recipients from HCV-viremic donors, treated with glecaprevir/pibrentasvir for 12 weeks starting within 5 days of transplant, SVR rates were 100% and only one patient experienced acute rejection (Bethea, 2020). A retrospective study of deceased donor liver transplantations in the US from January 2008 through January 2018 demonstrated that 2-year graft survival was similar, regardless of HCV status concordance or discordance between the allograft donor and recipient (Cotter, 2019). Unlike with other organs, shorter durations of HCV therapy should not be used in recipients of livers from HCV-viremic donors because of the large reservoir of HCV in the transplanted organ. The possibility of high risk for immunologic complications (eg, rejection) in liver recipients from HCV-viremic donors treated with DAA therapy requires further study, but vigilance is appropriate.

Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Liver Transplant

RECOMMENDED	RATING
Early[a] treatment with a pangenotypic DAA regimen is recommended when the patient is clinically stable.	II, B

[a] Early treatment refers to starting within the first month after liver transplant but preferably within the first week when the patient is clinically stable.

Recommended[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors

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

[a] Other considerations in selection of the DAA regimen:

- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided

Recommended[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors

- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Transplantation of Other Organs

In the THINKER trial, 10 HCV-uninfected kidney transplant recipients received allografts from genotype 1 HCV-viremic donors and were treated with 12 weeks of elbasvir/grazoprevir; 100% achieved SVR (Goldberg, 2017). In a 1-year follow-up study that included 10 additional participants (n=20) who received 12 to 16 weeks of elbasvir/grazoprevir (± ribavirin), all achieved SVR12. Kidney function in those who received kidneys from HCV-infected donors was comparable to matched controls who received allografts from HCV-uninfected donors (Reese, 2018). A separate open-label trial similarly demonstrated 100% SVR12 with 12 weeks of elbasvir/grazoprevir (± sofosbuvir) therapy initiated immediately prior to transplantation in 10 HCV-uninfected kidney transplant recipients of allografts from HCV-viremic donors (Durand, 2018). Notably, organ recipients in this study received the first dose of elbasvir/grazoprevir on call to the operating room. Of the 10 patients treated, only 3 had detectable HCV viremia compared to 100% in the THINKER trial, which utilized the same regimen but initiated therapy on day 3 after transplantation. Other regimens (including glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, and sofosbuvir/velpatasvir) have been studied in HCV discordant kidney donors and transplant recipients and demonstrated high SVR12 rates and no treatment-related toxicities (Franco, 2019); (Friebus-Kardash, 2019).

A study of HCV-uninfected recipients who received a heart transplant from an HCV-viremic donor showed that using a 12-week course of elbasvir/grazoprevir initiated a few days after transplantation (once the recipient became viremic) resulted in SVR12 in 9 out of the 10 evaluable patients (McLean, 2019). In another clinical trial of 44 HCV-uninfected lung (n=36) and heart transplant (n=8) recipients from HCV-viremic donors, sofosbuvir/velpatasvir was administered prophylactically/preemptively, starting within a few hours after transplantation, and continued for 4 weeks (compared to the standard 12-week course). Among the initial 35 patients with at least 6 months of follow-up after transplantation, 100% achieved SVR and had excellent graft function (Woolley, 2019). There was an increase in the proportion of the HCV-viremic lung cohort who had acute cellular rejection compared to the non-HCV lung cohort, although this finding was not statistically significant and longer-term follow-up is needed to assess for chronic rejection. In a study of 20 HCV-uninfected heart transplant recipients of allografts from HCV-viremic donors, patients were treated prophylactically/preemptively with glecaprevir/pibrentasvir beginning just prior to transplantation and continued for 8 weeks. All participants achieved SVR12, and patient and graft survival were 100% with a median follow-up of 10.7 months (Bethea, 2019). Another clinical trial evaluated 22 HCV-uninfected lung transplant recipients of allografts from HCV-viremic donors; the 20 patients who became viremic after transplantation were treated with 12 weeks of sofosbuvir/velpatasvir beginning 2 to 6 weeks after transplantation (median 21 days; IQR 16.76-24.75 days). All lungs from HCV-viremic donors were treated with ex-vivo

lung perfusion ± ultraviolet C perfusate irradiation to reduce HCV RNA concentration and infectivity, likely contributing to a slower rise in HCV viral load among recipients. Although all 20 DAA-treated patients had undetectable HCV RNA at the end of treatment, 2 patients experienced post-treatment relapse. One patient experienced severe hepatitis with early signs of fibrosing cholestatic hepatitis [FCH] on liver biopsy, and both patients exhibited complex NS3A and NS5A RASs at relapse. Both relapsed patients were successfully retreated with 24 weeks of sofosbuvir/velpatasvir/voxilaprevir plus ribavirin and achieved SVR12 (Cypel, 2019).

While these early results are encouraging, the overall number of published cases is small and treatment approaches notably variable. Known reported risks include DAA treatment failure with emergence of complex RASs and possible severe or rapidly progressive liver disease (fibrosing cholestatic hepatitis) (Cypel, 2019); (Kapila, 2019); (Molnar, 2019). Additionally, ethical and scientific issues remain, including avoidance of selection bias, optimal timing of DAA therapy, and long-term graft and patient outcomes. Due to the limited and heterogeneous experience and lack of longer-term safety data, strong consideration should be given to performing these transplantations under IRB-approved protocols as recommended by the American Society of Transplantation consensus panel (Levitsky, 2017).

Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Non-Liver Solid Organ Transplant

RECOMMENDED	RATING
Prophylactic[a]/preemptive[b] treatment with a pangenotypic DAA regimen is recommended.	II, B

[a] Prior to HCV RNA results, typically immediately pre-transplant or day 0 post-transplant
[b] Day 0 to within the first week post-transplant, typically as soon as the patient is deemed clinically stable

Recommended[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Non-Liver Organs from HCV-Viremic Donors

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, C

[a] Other considerations in selection of the DAA regimen:

- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the

Recommended[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Non-Liver Organs from HCV-Viremic Donors

prescribing information.

Initiation of DAA therapy for HCV-negative recipients of a nonliver allograft from an HCV-viremic donor can occur prophylactically/preemptively (ie, perioperatively without confirmation of viremia in the recipient) or reactively after documentation of HCV viremia. The goal is to undertake DAA therapy as early as clinically possible to avoid the development of acute hepatitis and other complications of HCV infection. Emerging data suggest that initiating prophylactic/preemptive DAA therapy before viremia occurs may reduce the likelihood of complications, such as FCH (Bethea, 2019); (Cypel, 2019); (Kapila, 2019); (Woolley, 2019); (Durand, 2018). A prophylactic/preemptive treatment approach may also allow for a shorter duration of DAA therapy in nonliver transplant recipients of organs from HCV-viremic donors (Woolley, 2019). A recent trial evaluated the use glecaprevir/pibrentasvir combined with ezetimibe 10 mg (as an inhibitor of HCV entry) in 30 recipients of nonhepatic organs (lung, heart, kidney) from HCV-viremic donors. The drugs were administered with 1 dose before and for 7 days after transplantation. With this short therapy, none of the 30 individuals developed chronic HCV infection. It is unknown if infection occurred and was rapidly cleared or if it was prevented entirely (Feld, 2020). Although intriguing, short duration approaches are not currently recommended outside of a clinical trial setting and have only been studied in the context of non-liver transplantation.

Selection of the DAA therapy for HCV-negative recipients of a nonliver allograft(s) from an HCV-viremic donor should follow the same principles as for those who develop recurrent HCV infection post liver transplantation (see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation). Importantly, since genotyping of HCV-viremic donors is not routinely performed, only pangenotypic regimens should be utilized if a prophylactic/preemptive treatment approach is used. If treatment is delayed until the recipient has quantifiable HCV RNA, the recipient's genotype can be used to guide DAA treatment selection if a pangenotypic regimen is not used. Selection of regimens that avoid the use of ribavirin (to reduce ribavirin-associated side effects) and regimens that do not require baseline RAS testing are preferred. Thus, although there are data supporting the safety and efficacy of elbasvir/grazoprevir among HCV-negative kidney and heart transplant recipients of allografts from HCV-viremic donors, the regimen is designated an alternative regimen due to the necessity for baseline RAS testing and its limited genotype coverage. Similarly, ledipasvir/sofosbuvir is designated as an alternative regimen due to lack of pangenotypic coverage.

Notably, organs from HCV-viremic donors may be used in transplant candidates with current or prior HCV infection (see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation).

Drug-Drug Interactions Between DAAs and Calcineurin Inhibitors

The interactions of DAA agents and calcineurin inhibitors are complex and unpredictable without formal studies of drug-drug interactions. A summary of interactions between calcineurin inhibitors and DAAs with recommended dosing is provided in the DAA Interactions With Calcineurin Inhibitors table.

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 with coadministration of grazoprevir, no dosing adjustments are anticipated but tacrolimus levels should be monitored. No clinically significant drug-drug interactions have been observed between sofosbuvir-inclusive regimens and tacrolimus.

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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 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).

Successful HCV antiviral treatment improves clinical outcomes. Antiviral therapy has been associated with a survival benefit in persons on dialysis in Swedish nationwide registry study (Söderholm, 2018). Among diabetic patients with ESRD receiving care at 4 US health systems, achieving a sustained virologic response (SVR) reduced the risk of developing extrahepatic manifestations of HCV disease, regardless of cirrhosis (sHR=0.46) compared to untreated patients (Li, 2019).

Recommendation for Patients With CKD Stage[a]	
RECOMMENDED	RATING
No dose adjustment in direct-acting antivirals is required when using recommended regimens.[b]	I, A or IIa, 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] A ribavirin dose reduction may be required for patients with CKD stage 3, 4, or 5; see prescribing information for details.
[c] The rating is I, A for patients with CKD stage 1, 2, or 3 and IIa, B for those with CKD stage 4 or 5.

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 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. 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 patients with baseline NS5A resistance-associated substitutions (RASs) experienced viral relapse. The only reported relapse occurred in a patient with genotype 1b. The basis for the lack of impact of NS5A RASs on SVR rates in this population is unclear but may relate to the moderately increased area under the curve (AUC) with grazoprevir and elbasvir observed in patients with stage 4/5 CKD (Zepatier prescribing information, 2019). Among 99 patients assigned to deferred treatment 97 (98%) achieved SVR (Bruchfeld, 2017). In patients with genotype 1a, SVR12 was 85% (11/13) among patients with detectable baseline NS5A RASs and 100% (98/98) among those patients without RASs. One serious adverse event occurred during the deferred treatment (interstitial nephritis) that was considered study drug related. Overall, the efficacy of this regimen among patients assigned to deferred treatment

reflected the findings of the immediate treatment group, and the overall efficacy remained high in all subgroups including cirrhosis, diabetes, and hemodialysis. These data support no modification of elbasvir plus grazoprevir dosing for patients on hemodialysis. Of the 3 patients who relapsed in both the immediate and deferred treatment groups, 2 had genotype 1a infection with baseline NS5AA RASs, underscoring the importance of baseline NS5A RASs affecting treatment outcome with this regimen (Bruchfeld, 2017).

Based on these data, daily fixed-dose elbasvir/grazoprevir is recommended for the treatment of genotype 1 in patients with severely compromised renal function. While C-SURFER did not evaluate patients with genotype 4, 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 persons with genotype 4 and 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).

Several real-world studies demonstrated the effectiveness of elbasvir/grazoprevir in persons with genotype 1 or 4 infection. In a retrospective cohort analysis from the TRIO network, 99% (113/114) of patients with stage 4/5 CKD achieved SVR12 (Flamm, 2018). A nationwide retrospective observational cohort study of patients in the US Veterans Health Administration system identified 5961 patients (42.5% genotype 1a, 55.0% genotype 1b) who completed elbasvir/grazoprevir therapy, including 860 patients with stage 3 CKD, 740 patients with stage 4/5 CKD, and 4361 controls (eGFR ≥60). The SVR rates were 97% overall, 96% for those with an eGFR ≥60, 98% for patients with stage 3 CKD, and 97% for participants with stage 4/5 CKD. No statistically significant differences were found in the SVR rates in persons with or without dialysis among the stage 4/5 CKD patients (adjusted OR 0.91; 95% CI 0.56-1.47 and OR 1.74; 95% CI 0.63-4.81) compared with those with an eGFR ≥60 (Choi, 2020).

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 4/5, including those with 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. 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, including ESRD. The recommended duration of therapy is the same as for patients without CKD.

EXPEDITION-5 evaluated the efficacy and safety of fixed-dose glecaprevir/pibrentasvir for chronic HCV infection in adults without cirrhosis or with compensated cirrhosis and stage 3b, 4, or 5 CKD. Among the 101 study participants, 76% (n=77) were on dialysis and 24% (n=24) had predialysis CKD. Fifty-five percent of patients had genotype 1, 27% had genotype 2, 15% had genotype 3, and 4% had genotype 4; no patients had genotype 5 or 6 infection. Eighty-four patients were treated for 8 weeks, 13 patients for 12 weeks, and 4 patients for 16 weeks. The overall SVR12 was 97% (98/101) with no reported virologic failures (Lawitz, 2020).

An integrated analysis of the efficacy and safety of glecaprevir/pibrentasvir in persons with genotypes 1 through 6 and CKD stage 3b, 4, or 5 was performed based on the EXPEDITION-4 and EXPEDITION-5 clinical trials. This analysis included 205 patients with compensated liver disease (with and without cirrhosis) and an eGFR <30 mL/min (EXPEDITION-4) or <45 mL/min (EXPEDITION-5). The majority of patients were treatment naive (69%), with genotype 1 (54%), and on dialysis (79%). In this integrated analysis, 100% SVR12 (mITT) was found with glecaprevir/pibrentasvir

therapy in patients with chronic hepatitis C and severe renal impairment regardless of treatment duration (Lawitz, 2018).

Colchicine-induced rhabdomyolysis due to interaction with glecaprevir/pibrentasvir has been reported in a patient receiving this medicine for treatment of gout. Despite a 50% dose reduction of colchicine before initiation of HCV therapy, the patient experienced rhabdomyolysis. This potential interaction with colchicine has the potential for increased risk for muscle toxicity and should prompt consideration of discontinuation of colchicine during therapy, especially in patients with any renal insufficiency (Harrison, 2020).

Sofosbuvir-Based Regimens

Despite higher concentrations of the primary sofosbuvir metabolite GS-331007 in persons with renal impairment, several studies demonstrate the safety of sofosbuvir-based regimens in those with an eGFR <30 mL/min (Desnoyer, 2016); (Nazario, 2016); (Saxena, 2016). A phase 2, open-label study examined the safety and efficacy of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks in patients with genotype 1 or 4 with a creatinine clearance ≤30 mL/min not undergoing dialysis. SVR was 100% in 18 patients with severe renal insufficiency. Treatment was well tolerated without any significant treatment-related cardiac adverse effects (Lawitz, 2017b).

A real-world case series of treatment-naive and -experienced patients demonstrated that 12 weeks of sofosbuvir/velpatasvir administered in persons with any genotype and on dialysis resulted in a 95% (56/59) SVR12. There were no treatment-related discontinuations or serious adverse events. There were 2 virologic relapses; 1 was associated with nonadherence (Borgia, 2019).

A retrospective analysis of 31 treatment-naive patients on hemodialysis demonstrated that 12 weeks of sofosbuvir/velpatasvir administered in persons with any genotype (68% with genotype 1) resulted in a 95% (30/31) SVR12. There was a single virologic relapse among the 3 persons with cirrhosis (Gaur, 2020).

A recent systematic review and meta-analysis of 717 patients with chronic kidney disease stage 4/5 (58.4% on dialysis) treated with sofosbuvir regimens across 21 studies demonstrated a pooled SVR 12/24 of 97% and a serious adverse event rate of 4.8%. Cirrhotic and noncirrhotic patients achieved comparable SVR rates (Li, 2019a).

In November 2019, the FDA amended the package inserts for sofosbuvir-containing regimens to allow use in patients with renal disease, including those with an eGFR ≤30 mL/min and those on dialysis.

Colchicine-induced rhabdomyolysis has been reported in a patient with renal dysfunction being treated with ledipasvir/sofosbuvir while continuing atorvastatin (Patel, 2016).

Elbasvir, Grazoprevir, and Ledipasvir Metabolism

Elbasvir, grazoprevir, and ledipasvir 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—dose adjustments are not required 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.

Last update: August 27, 2020

Kidney Transplant Patients

Post Kidney Transplantation: Genotype 1-6

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

Treatment-Naive and Non-DAA-Experienced Kidney Transplant Patients With Genotype 1-6 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]
Genotype 1, 4, 5, or 6 only: 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	IIa, C
ALTERNATIVE	**DURATION**	**RATING**
Genotype 1 or 4 only: Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg) for patients without baseline NS5A RASs[e] for elbasvir	12 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] Based on evidence for patients without cirrhosis.
[d] Based on evidence for patients with compensated cirrhosis.
[e] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Recommended regimen for:

DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg), with or without ribavirin[b]	12 weeks	IIa, C

[a] Excludes CTP class B and class C patients. For decompensated cirrhosis, please refer to the appropriate section.
[b] For patients with cirrhosis and multiple negative baseline characteristic, consideration should be given to adding ribavirin. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d for patients who weigh <75 kg and 1200 mg/d for those who weigh ≥75 kg.

For additional information on treatment of DAA failures post transplant, treatment of decompensated cirrhosis following transplantation, treatment of transplant recipients from HCV-positive donors, and post-transplant drug-drug interactions, please see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation.

Recommended Regimens

Glecaprevir/Pibrentasvir

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 with genotypes 1-6 infection who were at least 3 months post transplant. Cirrhotic patients were excluded. SVR12 was achieved in 98% of patients; a single patient experienced virologic failure (Reau 2018). The safety profile was excellent with 1 treatment discontinuation for an adverse event not considered to be therapy related. One rejection episode occurred in a liver transplant recipient. While glecaprevir/pibrentasvir is an effective pangenotypic regimen as demonstrated in the nontransplant population, there were no genotype 5 transplant recipients in the study.

There are potential drug-drug interactions with cyclosporine. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Ledipasvir/Sofosbuvir

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%); a single participant discontinued treatment because of an adverse event. Four patients with an eGFR >40 mL/min at baseline experienced a decrease to <30 mL/min during therapy. The eGFR increased to >30 mL/min at the last visit recorded in 3 of these patients; 1 patient who had interrupted study treatment had a final eGFR 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 (Saxena, 2017); (Sawinski, 2016). One study evaluated treatment safety and efficacy among 20 HCV-infected kidney transplant recipients (88% genotype 1; 50% with advanced fibrosis; 60% treatment-experienced with an interferon-based regimen) who received 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.

Real-world 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 and 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%). SVR12 was 95% in those with kidney transplant and 91% in dual liver and kidney transplant recipients.

No change in calcineurin inhibitor dose is needed for patients receiving ledipasvir/sofosbuvir. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Sofosbuvir/Velpatasvir

There are no published clinical trials regarding the use of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in kidney transplant recipients. There are, however, significant data addressing the efficacy and safety of this regimen in the nontransplant and liver transplant settings.

In liver transplant recipients (discussed in Patients who Develop Recurrent HCV Infection Post Liver Transplantation), the safety and efficacy of sofosbuvir/velpatasvir for 12 weeks was evaluated in 79 patients (n=5 with cirrhosis; n=4 DAA experienced) with genotype 1-4 infection (Agarwal, 2018). Treatment was well-tolerated with 99% of patients completing treatment. SVR12 rates by genotype were 93% genotype 1a (n=15); 96% genotype 1b (n=22); 100% genotype 2 (n=3); 97% genotype 3 (n=35); and 100% genotype 4 (n=4).

In the nontransplant setting (discussed in detail in the Initial and Retreatment sections), the phase 3, double-blind, placebo-controlled ASTRAL-1 study demonstrated an overall SVR of 99% among 742 treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection (Feld, 2015). In the phase 3, open-label ASTRAL-3 study, 552 treatment-naive or -experienced patients with genotype 3 (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. SVR12 was 95% for the sofosbuvir/velpatasvir treatment arm, which was superior to the SVR12 80% among patients receiving sofosbuvir plus ribavirin for 24 weeks (Foster, 2015a).

No change in calcineurin inhibitor dose is needed for patients receiving sofosbuvir/velpatasvir. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Sofosbuvir/Velpatasvir/Voxilaprevir

To date, there are no published clinical trials evaluating use of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in kidney transplant recipients. There are, however, significant data addressing the efficacy and safety of this regimen in the nontransplant setting (Degasperi, 2019); (Llaneras, 2019); (Bourliere, 2017); (Jacobson, 2017); (Soriano, 2017); (Saxena, 2016).

Two phase 3, open label, randomized clinical trials were conducted to determine the safety and efficacy of

sofosbuvir/velpatasvir/voxilaprevir in nontransplant patients previously treated with a DAA regimen. The POLARIS-1 study included nontransplant patients who had previously received a regimen containing and NS5A inhibitor. Patients were randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir or placebo. SVR for patients on active treatment was 96%. POLARIS-4 compared 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced nontransplant patients (Bourliere, 2017). Overall, 69% of participants 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 were 98% with sofosbuvir/velpatasvir/voxilaprevir and 90% with sofosbuvir/velpatasvir.

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). Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Alternative Regimen

Elbasvir/Grazoprevir

The use of elbasvir/grazoprevir has also been studied in kidney transplant recipients including two small studies of HCV-negative recipients of HCV-viremic donor kidneys. Among 20 anti-HCV negative kidney transplant recipients who received organs from genotype 1 HCV-RNA positive donors and were treated with 12 weeks of elbasvir/grazoprevir (16 weeks with the addition of ribavirin for patients with genotype 1a and baseline NS5A RASs), 100% achieved SVR. In a 1-year follow-up study, kidney function in those who received kidneys from HCV-RNA positive donors was better than matched controls who had HCV-negative donors (Reese, 2018); (Goldberg, 2017). In a similar trial of HCV-negative kidney transplant recipients who received organs from HCV-RNA positive donors (all genotypes), elbasvir/grazoprevir was started immediately prior to transplantation and continued for 12 weeks, with the addition of sofosbuvir for patients whose donors had genotype 2 or 3 infection. SVR12 was 100% (Durand, 2018).

Data from small, real-world studies evaluating elbasvir/grazoprevir are also available. One such study evaluated 11 kidney transplant recipients with significant kidney function impairment (GFR <40 mL/min) treated with elbasvir/grazoprevir for 12 to 16 weeks. SVR12 was 100% (Eisenberger, 2019).

There are significant drug-drug interactions with cyclosporine. Review the DAA interactions with calcineurin inhibitors table in the post liver transplantation section before prescribing HCV DAA therapy to a renal transplant recipient.

Last update: August 27, 2020

Management of Acute HCV Infection

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 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). 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 a positive HCV RNA test in the setting of a negative HCV antibody test (identification during the seronegative window period) (Cox, 2005), or 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).

No Discrete Exposure

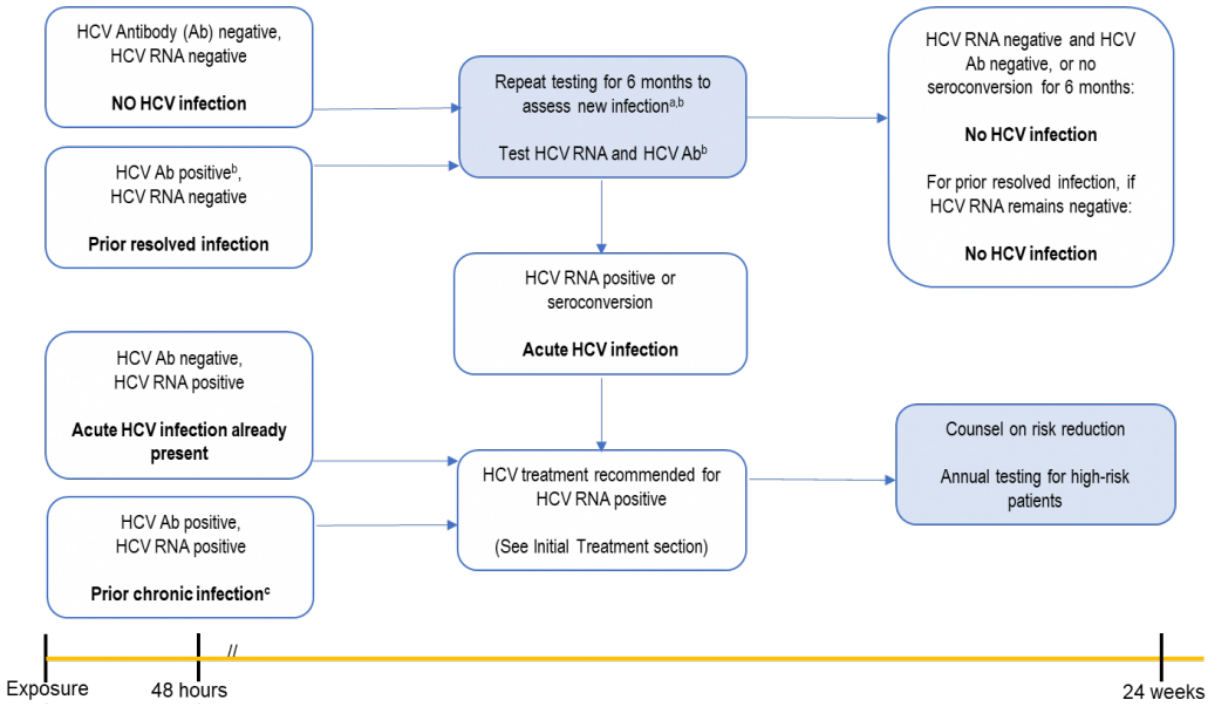
Individuals suspected of having acute HCV infection often do not have a discrete exposure or have no prior baseline testing, making a diagnosis of acute infection more difficult (see Blood Test Interpretation Table). Acute infection should be suspected if there is a new rise in the ALT level without an alternate cause (Blackard, 2008); (Kim, 2013). Acute infection should also be suspected when there are low (especially <104 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).

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.
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 1. Testing Algorithm for Discrete Recognized Hepatitis C Virus (HCV) Exposure[a]



[a] Often there is no discrete exposure or the entry to healthcare occurs with jaundice or elevated liver enzymes. In those instances, baseline testing cannot be performed and the diagnosis of acute infection is more challenging (see text).

[b] Repeat HCV Ab is not needed if the test is positive at baseline. Frequency of testing can be tailored based on risk of exposure.

[c] 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 distinguish acute from chronic HCV.

[d] Baseline testing should be done within 48 hours of exposure to determine existing infection status, including 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

There are no data on the efficacy or cost-effectiveness of antiviral therapy for pre-exposure or post-exposure prophylaxis of HCV infection.

Medical Management and Monitoring of Acute HCV Infection

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING
After the initial diagnosis of acute HCV with viremia (defined as quantifiable RNA), HCV treatment should be initiated without awaiting spontaneous resolution.	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 treated upon initial diagnosis without awaiting spontaneous resolution, using a “test and treat” strategy. Real-world data have demonstrated a reduction in HCV viremia prevalence and incidence with unrestricted access to HCV therapy (Boerekamps, 2018). In addition, mathematical modeling suggests that DAA treatment scale-up, especially among those at highest risk of transmission, can reduce HCV incidence and prevalence (Martin, 2013); (Martin, 2016). Moreover, delay introduced by waiting for spontaneous clearance may be associated with loss to follow up.

Individuals with acute HCV 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 Testing and Linkage to Care). For individuals with acute HCV infection who have a history of recent injection drug use, referral to harm reduction services and 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). With treatment, a rapid improvement of laboratory parameters is expected.

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. 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.

HCV infection spontaneously clears in 20% to 50% of patients (Kamal, 2008). Clearance of acute HCV infection occurs within 6 months of the estimated time of infection (median, 16.5 weeks) in at least 2/3 of patients who spontaneously clear HCV. Only 11% of those who remain viremic at 6 months will spontaneously clear the infection at a later time (Grebely, 2014). Patients who have spontaneously cleared 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 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 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).

Antiviral Therapy

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

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 (Deterding, 2017); (Naggie, 2017); (Rockstroh, 2017b). As yet, there are insufficient data to support a particular regimen or treatment duration. Until more definitive data are available, treatment as described for chronic hepatitis C is recommended (see Initial Treatment of HCV Infection). Pangenotypic regimens are recommended if HCV genotyping is unavailable or if concern of exposure to more than 1 genotype exists.

Referral to an addiction specialist and harm reduction counseling should be provided if relevant.

Last update: November 6, 2019

HCV in Pregnancy

Testing

Recommendation for Universal Hepatitis C Screening in Pregnancy	
RECOMMENDED	RATING
As part of prenatal care, all pregnant women should be tested for HCV infection with each pregnancy, ideally at the initial visit. (See Recommendations for Initial HCV Testing and Follow-Up.)	IIb, C

It has been estimated that up to 29,000 HCV-infected women gave birth each year from 2011 to 2014 (Ly, 2017). Additionally, there has been an increase in HCV among young adults, including women of childbearing age (Watts, 2017); (Koneru, 2016); (Kuncio, 2016). Identifying HCV infection 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 exposed children. Risk factor-based HCV screening 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). Consequently, both the US Preventative Task Force (Owens, 2020) and the US Centers for Disease Control (Schillie, 2020) have published recommendations for universal HCV screening of all adults, including screening during prenatal care. 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 HCV 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 Testing and Linkage to Care section). Recent modeling studies demonstrate that universal HCV screening in pregnancy is cost-effective and would reduce long-term morbidity with linkage to care and treatment (Tasillo, 2019). Infants of HCV-infected women should be tested and followed as described in the HCV in Children section.

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).

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

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). Women who become pregnant while on DAA therapy (with or without ribavirin) should discuss the risks versus benefits of continuing treatment with their physicians. 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. If exposed to ribavirin, they should also have their maternal and fetal outcomes reported to the ribavirin pregnancy registry (also see Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin).

There are no large-scale clinical trials evaluating the safety of direct-acting antivirals (DAAs) in pregnancy. A small study evaluating the pharmacokinetics of sofosbuvir in pregnancy demonstrated 100% SVR12 and no safety concerns (Chappell, 2019). Similarly, an international case series of 15 pregnant women treated with ledipasvir/sofosbuvir reported 100% SVR12 and no early safety concerns in the women or their infants (Yattoo, 2018). Currently, there are no available data on the use of pangenotypic regimens during pregnancy.

Despite the lack of a recommendation, treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits.

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 severity 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 and increased maternal plasma volume. HCV-infected pregnant women have a higher incidence of intrahepatic cholestasis of pregnancy (ICP) (pooled OR 20.40 [95% CI, 9.39-44.33, I^2=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% (Jhaveri, 2015); (Shebl, 2009); (Mast, 2005); (Ceci, 2001), 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 HCV 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 formally studied as a way to interrupt MTCT. DAAs 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, it is recommended that HCV-infected women who breastfeed abstain from doing so while their nipples are cracked, damaged, or bleeding, and 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 to 4 $\log_{10}$) in the postpartum period (Lin, 2000). This is most likely due to the release of tolerance in HCV-specific T lymphocyte responses that develop 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 (Honegger, 2013); (Hattori, 2003); (Lin, 2000). 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 re-evaluated 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: August 27, 2020

HCV in Children

Testing

Recommendations for HCV Testing of Perinatally Exposed Children and Siblings of Children With HCV Infection	
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 testing is unknown.	IIa, C
Testing with an HCV-RNA assay can be considered as early as 2 months of age.	IIa, B
Repetitive HCV RNA testing prior to 18 months of age 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 hepatitis C is lower in children than adults, an estimated 3.5 to 5 million children worldwide have chronic HCV infection (Indolphi, 2019); (Gower, 2014). Data from the National Health and Nutrition Examination Survey (NHANES) indicate 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 HCV antibody positive (Alter, 1999).

As birth to a woman with chronic hepatitis C is a known risk for infection, children born to these women 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, (>6 log10 IU/mL) (Benova, 2014); (Delotte, 2014); (Cottrell, 2013); (Shebl, 2009). Identifying, following, and treating exposed children is recommended. The preferred assay for evaluation of HCV infection early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months (Aniszewska, 2012); (England, 2005). About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 4 years of age (Indolfi, 2019); (Garazzino, 2014); (Farmand, 2012); (Yeung, 2007); (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. Proponents also want to seize opportunity to test in a patient group that is often lost to follow-up. 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. One large single center study demonstrated that HCV-RNA testing done in exposed infants aged 2 months to 6 months led to reliable positive and negative results that correlated with ultimate testing at 18 months (Honegger, 2018). 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 Children with HCV Infection	
RECOMMENDED	RATING
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, children with HCV infection 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 public misunderstanding regarding hepatitis C transmission. 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 is generally inefficient except among HIV-infected men who have unprotected sex with men (see HCV Testing and Linkage to Care) (Tieu, 2018); (Vaux, 2019); (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 Children With HCV Infection	
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 children with chronic HCV infection who are not immune to hepatitis B virus and/or hepatitis A virus to prevent these infections.	I, C

Recommendations for Monitoring and Medical Management of Children With HCV Infection	
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 infection.	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 infection after assessment of potential risks versus benefits of treatment. Use of corticosteroids, cytotoxic chemotherapy, and/or therapeutic doses of acetaminophen are not contraindicated in children with chronic HCV infection.	II, C
Solid organ transplantation and bone marrow transplantation are not contraindicated in children with chronic HCV infection.	II, C
Anticipatory guidance about the potential risks of ethanol for progression of liver disease is recommended for adolescents with chronic HCV infection and their families. Abstinence from alcohol and interventions to facilitate cessation of alcohol consumption, when appropriate, are advised for all persons with chronic HCV infection.	I, C

Liver disease due to chronic HCV infection generally progresses slowly in children, and cirrhosis and liver cancer occur infrequently. Although elevated serum aminotransferase levels are often noted, HCV-infected children younger than 3 years virtually never develop 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. 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 nonimmune children who may not have received routine childhood HAV and HBV vaccines.

Disease staging in children can be accomplished via physical examination and assessment of routine laboratory parameters including albumin, serum hepatic 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 (Nielsen, 2019); (Pokorska-Spiewak, 2017); (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 those with cirrhosis. There are reports that children with chronic HCV infection 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 (Marrero, 2018). A baseline endoscopy is advisable to detect esophageal varices in children with cirrhosis and every 3 years thereafter in the absence of viral clearance. After successful antiviral therapy, the risk for cirrhosis complications decreases substantially.

In children with advanced fibrosis from chronic HCV infection, 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 infection and should be prescribed for appropriate indications based on overall risks versus benefits. Of note, icteric flares of HCV—as reported in children and adults with chronic HBV—have not been reported in children receiving an organ transplant 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 (Kukla, 2015); (Petta, 2011); (Cua, 2008); (Moucari, 2008). Commonly used medications, such as antimicrobial agents, antiepileptics, and cardiovascular agents, should be dosed per standard recommendations. However, nonsteroidal anti-inflammatory drugs 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.

Whom and When to Treat Among Children and Adolescents With HCV Infection

Recommendations for Whom and When to Treat Among Children and Adolescents With HCV Infection	
RECOMMENDED	RATING
Direct-acting antiviral (DAA) treatment with an approved regimen is recommended for all children and adolescents with HCV infection aged ≥3 years as they will benefit from antiviral therapy, regardless of disease severity.	I, B
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

HCV-related, advanced liver disease is uncommon during childhood. However, liver disease progresses over time with increasing fibrosis severity (Indolfi, 2019); (Mizuochi, 2018); (Bortolotti, 2008); (EPHCVN, 2005); (Resti, 2003). Although uncommon, cirrhosis occurs occasionally in children and adolescents (aged <18 years) with HCV infection. Children have a long life expectancy during which HCV complications may develop. Children and adolescents with HCV infection may also transmit the virus to others.

The high success rates with DAA regimens in adults with chronic HCV infection are increasingly being replicated in the pediatric population. Interferon and ribavirin exert general and pediatric-specific toxicities (eg, temporary growth impairment) that do not occur with DAA regimens. Additionally, interferon-based regimens have limited success in children and adolescents with genotype 1 or 4. Promising early and emerging clinical trial data evaluating DAA regimens in children and adolescents usher in the opportunity to expand use of these safe, well-tolerated, efficacious HCV therapies in the pediatric population. Treatment of children as young as 12 years is predicted to be very cost-effective with currently approved DAA regimens as well as those in clinical trials (Nguyen, 2019b). Another cost-utility analysis compared DAA treatment at age 6 versus delaying treatment until age 18. The researchers reported the incremental cost-utility ratio for early vs delayed DAA therapy was <$12,000 per QALY gained. They concluded that treatment during early childhood is cost-effective and delaying therapy until early adulthood may result in increased lifetime risk of complications of late-stage liver disease (Greenway, 2019). FDA-approved DAA regimens are available for children aged 3 to <18 years with genotype 1, 4, 5 or 6 infection and for children aged 6 to <18 years with any HCV genotype.

HCV Antiviral Therapy for Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommended regimens listed by age:

Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children aged ≥3 years with genotype 1, 4, 5, or 6	12 weeks	I, B
Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) for children aged ≥6 years or weighing ≥17 kg with any genotype	12 weeks	I, B
Combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with any genotype	8 weeks	I, B

[a] Child-Pugh A

Recommended regimens listed by age:

DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Genotype 1: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, without cirrhosis	12 weeks	I, C
Genotype 1: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, with compensated cirrhosis[a]	24 weeks	I, C

Recommended regimens listed by age:

DAA-Experienced Children and Adolescents, Without Cirrhosis or With Compensated Cirrhosis[a]

Genotype 4, 5, or 6: Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children and adolescents aged ≥3 years with prior exposure to an interferon (± ribavirin) plus an HCV protease inhibitor regimen, without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, C
Genotype 1, 2, 4, 5, or 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis	8 weeks	I, C
Genotype 1, 2, 4, 5, or 6: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, with compensated cirrhosis[a]	12 weeks	I, C
Genotype 3: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an interferon-based regimen (± ribavirin) and/or sofosbuvir but no exposure to NS3/4A or NS5A protease inhibitors, without cirrhosis or with compensated cirrhosis[a]	16 weeks	I, C
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to NS3/4A protease inhibitors but no NS5A inhibitor exposure, without cirrhosis or with compensated cirrhosis[a]	12 weeks	I, C
Genotype 1: Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with prior exposure to an NS5A inhibitor but no NS3/4A protease inhibitor exposure, without cirrhosis or with compensated cirrhosis[a]	16 weeks	I, C

[a] Child-Pugh A

Table 1. Weight-Based Dosing of Ledipasvir/Sofosbuvir for Children Aged ≥3 Years

Body Weight	Once Daily Dose of Ledipasvir/Sofosbuvir
<17 kg	33.75 mg/150 mg
17 to <35 kg	45 mg/200 mg
≥35 kg	90 mg/400 mg per day

Table 2. Weight-Based Dosing of Sofosbuvir/Velpatasvir for Children Aged ≥6 Years or Weighing ≥17 kg

Body Weight	Once Daily Dose of Sofosbuvir/Velpatasvir
17 kg to <30 kg	200 mg/50 mg
≥30 kg	400 mg/100 mg

Ledipasvir/Sofosbuvir

Ledipasvir/sofosbuvir is approved for use in children aged 3 through 17 years with genotype 1, 4, 5, or 6 infection. In a phase 2, multicenter, open-label study of 100 adolescents with genotype 1 treated for 12 weeks with the adult formulation of ledipasvir/sofosbuvir, SVR12 was documented in 98% of participants (Balistreri, 2017). The 2 patients who did not achieve SVR12 were lost to follow-up during or after treatment. Eighty percent of the patients were treatment naive. 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. Two clinical trials supporting the approval of ledipasvir/sofosbuvir in the pediatric population aged 3 through 11 years demonstrated high SVR12 rates comparable to those seen in adults (Schwarz, 2019); (Murray, 2018). Among children <12 years of age, dosing is weight based (see Table 1). Twelve weeks of ledipasvir/sofosbuvir is recommended for treatment-naive children and adolescents aged ≥3 years without cirrhosis or with compensated cirrhosis (Child-Pugh A). This regimen is also recommended for interferon-experienced (± ribavirin, with or without an HCV protease inhibitor) children and adolescents aged ≥3 years with genotype 1 or 4. A 12-week course is recommended for patients without cirrhosis; 24 weeks is recommended for those with compensated cirrhosis.

The combination of ledipasvir/sofosbuvir is the only treatment option for children with genotype 1, 4, 5, or 6 infection who are 3 to <6 years of age. It is also a good option for older children and adolescents with these genotypes.

Sofosbuvir/Velpatasvir

The efficacy of sofosbuvir/velpatasvir once daily for 12 weeks was evaluated in an open-label trial among 173 pediatric participants aged ≥6 years with genotype 1, 2, 3, 4, or 6 infection, without cirrhosis or with compensated cirrhosis. Eighty-five percent of participants (147/173) were treatment naive and 15% (26/173) were treatment experienced. Overall SVR12 was ≥92% across genotypes (Jonas, 2019a).

Among 102 adolescents aged 12 to <18 years, 78% (n=80) were treatment naive and 22% (n=22) were treatment experienced. The median age was 15 years (range 12 to 17 years); 51% were female. The genotype distribution among the participants was 74% genotype 1, 6% genotype 2, 12% genotype 3, 2% genotype 4, and 6% genotype 6. No adolescents had known cirrhosis. The majority (89%; 91/102) had been infected through vertical transmission. SVR12 rates were 93% in adolescents with genotype 1, 91% in those with genotype 3, and 100% in participants with genotype 2, 4, or 6. One participant discontinued treatment at week 4 and subsequently relapsed. The other 4 participants who did not achieve SVR12 did not meet virologic failure criteria (lost to follow-up).

Among 71 children aged 6 to <12 years, the genotype distribution was 76% genotype 1, 3% genotype 2, 15% genotype 3, and 6% genotype 4. None of the participants had known cirrhosis. Ninety-four percent (n=67) were treatment naive and 6% (n=4) 4 were treatment experienced. The median age was 8 years (range 6 to 11 years); 54% were female. The majority of children (94%; 67/71) had been infected through vertical transmission. SVR12 rates were 93% (50/54) in children with genotype 1, 91% (10/11) in those with genotype 3, and 100% in participants with genotype 2 (2/2) or genotype 4 (4/4). One participant had on-treatment virologic failure; the other 4 participants who did not achieve SVR12 did not meet virologic failure criteria (lost to follow-up).

Sofosbuvir/velpatasvir was approved by the FDA for pediatric patients aged ≥6 years in March 2020. Given its pangenotypic activity, safety, and efficacy, sofosbuvir/velpatasvir is recommended as a first choice for HCV treatment in children and adolescents at least 6 years of age. Due to reports from experience among adults, coadministration of sofosbuvir/velpatasvir with amiodarone is not recommended due to the risk for symptomatic bradycardia.

Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) was approved for adolescents aged 12 through 17 years in April 2019. In the registration trial, 47 adolescents were treated with the adult-approved coformulated preparation; the duration of treatment was based on viral genotype, prior treatment, and cirrhosis status (Jonas, 2019). Genotypes 1 through 4 were represented in the trial. Two participants were HIV coinfected, none had cirrhosis, and 11 had a prior treatment failure with peginterferon/ribavirin. SVR12 was 100%. The study drugs were well tolerated with no serious adverse events and no drug discontinuations.

Although there are no data from the adolescent population, EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 343 treatment-naive adults with genotype 1, 2, 3, 4, 5, or 6 and compensated cirrhosis. Overall SVR12 rates were 99.7% (334/335) in the per-protocol population and 97.7% (335/343) in the intention-to-treat population (Brown, 2019). Similarly, FDA approval and HCV guidance panel HCV treatment recommendations for DAA-experienced adolescents are based on clinical trial data from adults (Asselah, 2018b); (Puoti, 2018); (Wyles, 2018); (Zeuzem, 2018); (Forns, 2017).

Given its pangenotypic activity, safety, and efficacy record in adult patients, glecaprevir/pibrentasvir is recommended as a first choice for adolescent HCV treatment. As in adults, coadministration of carbamazepine, efavirenz-containing regimens, and St. John's wort is not recommended since these compounds may decrease concentrations of glecaprevir and pibrentasvir.

Sofosbuvir Plus Ribavirin

In September 2019, the FDA approved weight-based sofosbuvir plus ribavirin (see Table 3) for treatment-naive or interferon-experienced (± ribavirin) children aged ≥3 years with genotype 2 or 3, without cirrhosis or with compensated cirrhosis (Child-Pugh A). A 12-week course is recommended for patients with genotype 2; 24 weeks is recommended for those with genotype 3. The registration trial conducted in children aged 3 to <11 years demonstrated an SVR12 of 98% (Rosenthal, 2020). The use of sofosbuvir plus ribavirin is further supported from clinical trials conducted among adolescents (Wirth, 2017) and adults with genotype 2 or 3 infection (Sulkowski, 2014); (Zeuzem, 2014a); (Jacobson, 2013); (Lawitz, 2013).

Currently, sofosbuvir plus ribavirin remains the only FDA-approved DAA for children 3 through 5 years with genotype 2 or 3 infection. However, recent clinical trials evaluating weight-based dosing of sofosbuvir/velpatasvir (Jonas, 2019a) and glecaprevir/pibrentasvir (Jonas, 2019b) are expected to lead to FDA approval for children beginning at 3 years of age. The HCV guidance panel recommends delaying treatment pending approval of a pangenotypic regimen unless there is a compelling need for immediate antiviral treatment of children aged 3 through 5 years with genotype 2 or 3 infection.

Table 3. Weight-Based Dosing of Ribavirin for Children Aged ≥3 Years

Body Weight	Daily Dose of Ribavirin (divided AM and PM)
<47 kg	15 mg/kg
47 to 49 kg	600 mg
50 to 65 kg	800 mg
66 to 80 kg	1000 mg
>80 kg	1200 mg

Last update: August 27, 2020

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.

Last update: November 6, 2019

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 during 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 (Jones, 2015). 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 antiviral treatment have the potential to 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 including intranasal naloxone, needle/syringe service programs, medications for opioid use disorder, and other 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 previously used injection drugs 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 or dried blood spot collection for a confirmatory HCV-RNA test may be implemented.

Among persons at risk for 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 substance use disorder treatment programs, needle/syringe service 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

Treatment of HCV-infected PWID should ideally 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 are not absolute contraindications 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). Modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population (Martin, 2013b); (Fraser, 2018b); (Zelenev, 2018). 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.

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); (Coyle, 2016); (Ramirez, 2016); (Ford, 2017); (Coyle, 2019). 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 essential 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); (Grebely, 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 medications for opioid use disorder (MOUDs); no active drug use with MOUDs; active drug use without MOUDs; and active drug use MOUDs. The study found that regardless of active drug or MOUD use, patients who received direct-acting antiviral (DAA) therapy at this urban primary care clinic achieved high HCV cure rates (SVR ≥95%) (Norton, 2017).

Furthermore, MOUDs do not compromise HCV treatment outcomes. Similar SVR12 rates are achieved by PWID engaged in MOUD use compared to individuals not engaged with such medications in clinical trials involving various DAA regimens (Feld, 2014); (Lalezari, 2015); (Grebely, 2016); (Zeuzem, 2015); (Dore, 2016). HCV-infected patients receiving MOUDs 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 MOUDs (Lalezari, 2015). Further, an analysis of a clinical trial evaluating outcomes of sofosbuvir/velpatasvir treatment in patients receiving MOUDs (n=51) compared to those not receiving these medications (n=984) demonstrated that MOUD use 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 provided 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 MOUDs and mental health services, have been associated with reduced 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 MOUDs for ≥3 months had a reinfection rate of 2.3/100 person-years, with a persistent reinfection rate of 1.6/100 person-years due to spontaneous HCV clearance in several instances. A reinfection rate of 4.2/100 person-years was found 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 injection equipment; utilization of MOUDs (such as methadone, buprenorphine and naltrexone); safe injection spaces; and overdose education and naloxone distribution. Heroin overdose deaths in the US increased 286% from 2002 to 2013 (Jones, 2015). Broad implementation of harm reduction strategies has the potential to significantly impact the HCV epidemic.

Medications for Opioid Use Disorder

Methadone, buprenorphine, and naltrexone are FDA-approved treatments for opioid use disorder with evidence from randomized controlled trials and real-world cohorts to support their effectiveness in reducing opioid use, improving mortality, decreasing criminal activity, and improving social functioning and retention in care (Volkow, 2014); (Kampman 2015); (Tasillo, 2017). Methadone is a long-acting opioid agonist that has the longest history in clinical use and is proven to reduce illicit drug use and improve social functioning (Mattick, 2009). Although methadone is effective, concern about diversion leads to methadone maintenance being highly regulated in the US, typically requiring daily visits to a dedicated dispensing clinic (Mattick, 2014). Buprenorphine-naloxone is a partial opioid agonist that also relieves withdrawal, and quells opioid craving. Multiple randomized trials support its effectiveness in reducing drug use and improving retention in care (Tasillo, 2017); (Volkow, 2017); (Kampman, 2015); (Volkow, 2014); (Mattick, 2014); (Moore, 2012); (Weiss, 2011); (Comer, 2010); (Jones, 2010); (Ling, 2010); (Lucas, 2010); (Mattick, 2009); (Kakko, 2007); (Fischer, 2006); (Jones, 2005); (Fudala, 2003); (Kakko, 2003); (Johnson, 2000); (Ling, 1998); (O'Connor, 1998); (Ling, 1996); (Johnson,1995). Buprenorphine-naloxone's major benefits include that it is a partial agonist which limits its overdose risk; coformulation with naloxone provides a deterrent from injecting; and it can be successfully prescribed in routine primary care settings (Korthuis, 2017); (LaBelle, 2016); (Fudala, 2003). Prescribing buprenorphine-naloxone requires 8 hours of training and registration with the US Drug Enforcement Agency and receiving a waiver from the Substance Abuse Mental Health Services Administration, which limits the number of providers (Stein, 2015). Naltrexone is an opioid antagonist that prevents the euphoric and respiratory effects of opioids, reducing cravings (SAMHSA, 2019). Naltrexone has low diversion potential and requires no special licensing for prescribers (Rudd, 2016). Further, it is available as a monthly injection. Naltrexone precipitates opioid withdrawal, however, and is therefore only initiated in opioid-abstinent patients.

Several reviews have identified MOUDs 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 shown 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).

Overdose Education and Naloxone Distribution (OEND)

HCV treatment is a touchpoint with the care delivery system and should be used as an opportunity to mitigate the harms of drug use, especially overdose risk. Naloxone is a powerful opioid antagonist that reverses the respiratory depressive effects of opioids and is lifesaving to those experiencing opioid overdose (Wermeling, 2015). Expanding access to intranasal naloxone significantly decreases mortality at the community level (Walley, 2013). Many states have standing orders for intranasal naloxone, which allow providers to dispense naloxone directly to patients. When no standing order exists or when it is not feasible to provide naloxone directly, providers should offer patients a prescription for naloxone to fill at a local pharmacy. Importantly, naloxone is not an opioid and carries no overdose risk, no dependency risk, and no risk of diversion. Naloxone is safe and effective and can be prescribed with confidence by HCV providers who do not treat addictions more generally.

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).

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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 (Wandeler, 2012); (van de Laar, 2010); (Urbanus, 2009); (Matthews, 2007). 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 and receptive fisting) and rectal bleeding are associated with HCV transmission among HIV-infected MSM (Daskalopoulou, 2017); (Page, 2016); (Apers, 2015); (Vanhommerig, 2015); (Witt, 2013); (Wandeler, 2012); (CDC, 2011); (Schmidt, 2011); (Danta, 2007).

The recent proliferation of chemsex (also known as party and play [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 (Pufall, 2018); (Hegazi, 2017); (NHS, 2014). 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); (van de Laar, 2007); (Gambotti, 2005); (Gotz, 2005); (Browne, 2004); (Ghosn, 2004).

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 US 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 (Pufall, 2018); (Daskalopoulou, 2017); (Page, 2016); (Apers, 2015); (CDC, 2015); (Vanhommerig, 2015); (NHS, 2014); (Witt, 2013); (Wandeler, 2012); (CDC, 2011); (Schmidt, 2011); (Bottieau, 2010); (Danta, 2007); (van de Laar, 2007); (Gambotti, 2005); (Gotz, 2005); (Browne, 2004); (Ghosn, 2004).

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, 2017); (Ingiliz, 2014); (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

Because 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 successful treatment or spontaneous clearance of 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); (Martin, 2015b); (Lambers, 2011). 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 antiviral 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 lower 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 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 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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