Introduction

NOTICE: Guidance for hepatitis C treatment in adults is changing constantly with the advent of new therapies and other developments. A static version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this. We urge you to review this guidance on this website (www.hcvguidelines.org) for the latest recommendations.

The landscape of treatment for hepatitis C virus (HCV) infection has evolved substantially since the introduction of highly effective HCV protease inhibitor therapies in 2011. The pace of change is expected to increase rapidly, as numerous new drugs with different mechanisms of action will likely become available over the next few years. To provide healthcare professionals with timely guidance as new therapies are available and integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD), in collaboration with the International Antiviral Society–USA (IAS–USA), developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management. The IAS–USA provided the structure and assistance to sustain the process that represents the work of leading authorities in hepatitis C prevention, diagnosis, and treatment in adults, from 2013 to 2015.

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 based on evidence and are rapidly updated as new data from peer-reviewed evidence become available. For each treatment option, recommendations reflect the best possible management for a given patient and a given point of disease progression. Recommendations are 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 Boards of Directors of AASLD and IDSA have appointed an oversight committee of 5 co-chairs and have selected panel members from the 2 societies.

This Guidance should be considered a "living document" in that the Guidance will be updated frequently as new information and treatments become available. This continually evolving report provides guidance on FDA-approved regimens. At times, it may also recommend off-label use of certain drugs or tests or provide guidance for regimens not yet approved by FDA. Readers should consult prescribing information and other resources for further information. Of note, the choice of treatment may, in the future, be further guided by data from cost-effectiveness studies.

Last update: January 14, 2016. Reviewed June 2016

Methods

The Guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases, using an evidence-based review of information that is largely available to healthcare practitioners. The process and detailed methods for developing the Guidance are detailed in Methods Table 1. Recommendations were rated according to the strength of the recommendation and quality of the supporting evidence (see Methods Table 2). Commonly used abbreviations are expanded in Methods Table 3.

The Panel regularly reviews available data and decides whether a regimen should be classified as Recommended, Alternative, or Not Recommended for a particular subgroup of patients. Recommended regimens are those that are favored for most patients in that subgroup, based on optimal efficacy, favorable tolerability and toxicity profiles, duration, and pill burden. Alternative regimens are those that are effective but have, relative to Recommended regimens, 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 a specific patient situation. Not Recommended regimens are clearly inferior compared to Recommended or Alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection.

Last update: February 24, 2016. Reviewed June 2016

Methods: Table 1 - Summary of the Process and Methods for the Guidance Development

Topic	Description
Statement of need	Increased awareness of the rising number of complications of hepatitis C virus (HCV) infection, the recent screening initiatives by the Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force (USPSTF), and the rapid evolution of highly effective antiviral therapy for HCV infection have driven a need for timely guidance on how new developments change practice for 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 adults with HCV infection in the United States, considering the best available evidence. The Guidance is updated regularly, as new data, information, and tools and treatments become available.
Panel members	Panel members are chosen based on their expertise in the diagnosis, management, and treatment of HCV infection. Members from the fields of hepatology and infectious diseases are included, as well as HCV community representatives. Members were appointed by the respective Sponsor Societies after vetting by an appointed Sponsor Society committee. The Panel chairs are appointed by the Society boards, 2 each from the Sponsor Societies. All Panel chairs and members serve as volunteers (not compensated) for defined terms (2-3 years), which may be renewed based on panel needs.
Conflict of interest management	The panel was established with the goal of having no personal (ie, direct payment to the individual) financial conflicts of interest among its chairs and among fewer than half of its panel members. All potential panel members are asked to disclose any personal relationship with a pharmaceutical, biotechnology, medical device, or health-related company or venture that may result in financial benefit. Disclosures are obtained prior to the panel member appointments and for 1 year prior to the initiation of 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.

Topic	Description
	The following relationships are prohibited during membership on the guidance panel and are grounds for exclusion from the panel: • Employment with any commercial company with products in the field of hepatitis C. • An ownership interest in a commercial entity that produces hepatitis C products. • Participation in/payment for promotional or marketing activities sponsored by companies with HCV-related products including non-CME educational activities or speakers bureaus for audiences outside of the company. • Participation in any single-funder CME activity. • Participation on a marketing or medical affairs advisory board. The following relationships or activities are reportable but were not deemed to merit exclusion: • Commercial support of research that is paid to an organization or practice group. Due to the rapidly evolving nature of the subject matter, having individuals with expertise in the particular clinical topic is crucial to developing the highest-quality and most-informed recommendations. To that end, research support from commercial entities is not considered grounds for panel exclusion (an unresolvable conflict) if the funding of the research was paid to the institution or practice group, as opposed to the individual. In the instance of someone conducting clinical research in a community practice, research funds to the group practice were acceptable. • Participation on commercial company scientific advisory boards. Participation in advisory boards, data safety monitoring boards, or in consultancies sponsored by the research arm of a company (eg, study design or data safety monitoring board) is considered a potential personal conflict 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.

Topic	Description
Sponsors, funding, and collaborating partner	The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) are the sponsors of the Guidance and provide ongoing financial support. Grant support was sought and obtained from the Centers for Disease Control and Prevention (CDC) for the initial gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings.
Evidence identification and collection	The Guidance is developed using an evidence-based review of information that is largely available to 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 new products under FDA review. Press releases, unpublished reports, and personal communications are generally not considered. Literature searches are conducted regularly and before each major revision to ensure that the Panel addresses all relevant published data. Medical subject headings and free text terms are combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases. To be considered for inclusion, articles were required to have been published in English from 2010 to the present. Data from abstracts presented at national or international scientific conferences are also considered
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 in the Guidance are indicated by highlighted text on the online site and a notice of update is posted on the Home Page.
Abbreviations	Commonly used abbreviations in the text with their expansions are listed in Methods Table 3.
Opportunity for comments	Evidence-based comments may be submitted to the Panel by email to 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 summary, but should not be

Topic	Description
	contacted for individual patient management questions.

Last update: November 28, 2016

Methods: Table 2 - Rating System Used to Rate the Level of the Evidence and Strength of the Recommendation for Each Recommendation

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

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 IFN-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practicably be conducted. The US Food and Drug Administration (FDA) has suggested alternative study designs, including historical controls or immediate versus deferred, placebo-controlled trials. For additional examples and definitions see FDA link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf. In those instances for which there was a single pre-determined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B.

Last update: June 2016

Methods: Table 3 - Commonly Used Abbreviations and Their Expansions

Abbreviation	Expansion or Notes
These terms are not expanded in text	
HCV	hepatitis C virus. In this Guidance "hepatitis C virus" and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the resulting disease.
IFN	interferon alfa
PEG	peginterferon alfa
These terms are expanded at first mention in text	
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BOC	boceprevir
CBC	complete blood cell (eg, complete blood cell count)
CrCl	creatinine clearance
CTP	Child Turcotte Pugh (see below)
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
IDU	injection drug use or user

Abbreviation	Expansion or Notes
INR	international normalized ratio
MELD	model for end-stage liver disease

Abbreviation	Expansion or Notes
MSM	men who have sex with men
NAT	nucleic acid testing
NIH	National Institutes of Health
OATP	organic anion-transporting polypeptide
P-gp	p-glycoprotein
PrOD	paritaprevir/ritonavir/ombitasvir plus dasabuvir
RAS	resistance-associated substitution
RBC	red blood cell (eg, red blood cell count)
RBV	ribavirin
RGT	response-guided therapy
RVR	rapid virologic response
sAg	surface antigen
SMV	simeprevir; used for the treatment of those with genotype 1 of hepatitis C virus (HCV) who have compensated liver disease, including cirrhosis
SOF	sofosbuvir; a nucleoside analogue used in combination with other drugs for the treatment of HCV infection
SVR12 (or 24 or 48, etc)	sustained virologic response at 12 weeks (or at 24 weeks, or at 48 weeks, etc)
TSH	thyroid-stimulating hormone
TVR	telaprevir; an antiviral agent to treat hepatitis C

Definition of Terms: 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)

Term	Definition of Terms
IFN ineligible	IFN ineligible is defined as one or more of the below: • Intolerance to IFN • Autoimmune hepatitis and other autoimmune disorders • Hypersensitivity to PEG or any of its components • Decompensated hepatic disease • Major uncontrolled depressive illness • A baseline neutrophil count below 1500/µL, a baseline platelet count below 90,000/µL, or baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease
Relapser	a person who has achieved an undetectable level of virus during a prior treatment course of PEG/RBV and relapsed after treatment was stopped

Last update: September 16, 2016