HCV Testing and Linkage to Care

Recommendations for One-Time Hepatitis C Testing

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

Other persons should be screened for HCV infection risk factors. One-time testing should be performed for all persons with behaviors, exposures, and conditions or circumstances associated with an increased risk of HCV infection.
 	
Risk Behaviors
 	
• Injection-drug use (current or ever, including those who injected only once)
• Intranasal illicit drug use
 	
Risk Exposures
 	
• Persons on long-term hemodialysis (ever)
• Persons with percutaneous/parenteral exposures in an unregulated setting
• Healthcare, emergency medical, and public safety workers after needle-stick, sharps, or mucosal exposures to HCV-infected blood
• Children born to HCV-infected women
• Prior recipients of transfusions or organ transplants, including persons who:
  ◦ Were notified that they received blood from a donor who later tested positive for HCV
  ◦ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
  ◦ Received clotting factor concentrates produced before 1987
• Persons who were ever incarcerated
 	
Other Conditions and Circumstances
 	
• HIV infection
• Sexually-active persons about to start pre-exposure prophylaxis (PreP) for HIV
• Unexplained chronic liver disease and/or chronic hepatitis, including elevated alanine aminotransferase (ALT) levels
• Solid organ donors (deceased and living)
	I, B

[a] Regardless of country of birth

HCV Testing for Persons With Ongoing Risk Factors

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

Initial HCV Testing and Follow-Up

Recommendations for Initial HCV Testing and Follow-Up	
RECOMMENDED	RATING
An HCV-antibody test is recommended for initial HCV testing. If the result is positive, current infection should be confirmed by a sensitive HCV-RNA test.	I, A
Among persons with a negative HCV-antibody test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered for persons who are immunocompromised.	I, C
Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an HCV-antibody test is expected to be positive.	I, C
Quantitative HCV-RNA testing is recommended prior to initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).	I, A
HCV genotype testing is recommended to guide selection of the most appropriate antiviral regimen.	I, A
Persons found to have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have evidence of current (active) HCV infection.	I, A

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

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

Linkage to Care

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

Last update: May 24, 2018

When and in Whom to Initiate HCV Therapy

Goal of Treatment

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

Recommendation for When and in Whom to Initiate Treatment

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

Pretreatment Assessment

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

Recommendation for Repeat Liver Disease Assessment	
RECOMMENDED	RATING
Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.	I, C

Last update: September 21, 2017

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

Pretreatment and On-Treatment Monitoring

Recommended Assessments Prior to Starting Antiviral Therapy

RECOMMENDED	RATING
Staging of hepatic fibrosis is essential prior to HCV treatment (see Testing and Linkage to Care and see When and in Whom to Treat). Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy. • Patients should also be educated about the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment. **The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:** • Complete blood count (CBC) • International normalized ratio (INR) • Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels) • Calculated glomerular filtration rate (eGFR) **The following laboratory tests are recommended at any time prior to starting antiviral therapy:** • HCV genotype and subtype • Quantitative HCV RNA (HCV viral load)	I, C
Patients scheduled to receive an HCV NS3 protease inhibitor (ie, paritaprevir, simeprevir, grazoprevir, voxilaprevir, glecaprevir) should be assessed for a history of decompensated liver disease and for liver disease severity using the Child-Turcotte-Pugh (CTP) score (see third-party calculator). • Patients with current or prior history of decompensated liver disease or with a current CTP score ≥7 should **not** receive treatment with regimens that contain NS3 protease inhibitors due to increased blood levels and/or lack of safety data. • Similarly, patients with a CTP score of 5 or 6 who cannot be closely monitored for laboratory or clinical symptoms during treatment should **not** receive treatment with a regimen that contains paritaprevir/ritonavir.	I, A
All patients initiating HCV direct-acting antiviral (DAA) therapy should be assessed for HBV coinfection with HBsAg testing, and for evidence of prior infection with anti-HBs and anti-HBc testing.	IIa, B

Recommended Assessments Prior to Starting Antiviral Therapy	
Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the Initial Treatment and the Retreatment sections.	IIb, B

Recommended Monitoring During Antiviral Therapy	
RECOMMENDED	RATING
Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence, and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications.	I, B
Creatinine level, calculated glomerular filtration rate (eGFR), and a hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. More frequent assessment for drug-related adverse effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with a hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).	I, B
A 10-fold increase in alanine aminotransferase (ALT) activity at any time during treatment should prompt discontinuation of therapy. An increase in ALT <10-fold that is accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio (INR) should also prompt discontinuation of therapy. Asymptomatic increases in ALT <10-fold should be closely monitored with repeat testing at 2-week intervals. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.	I, B
Quantitative HCV viral load testing is recommended after 4 weeks of therapy and 12 weeks after completion of therapy. Antiviral drug therapy should **not** be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.	I, B
Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.	I, B
For HBsAg-positive patients who are not already on HBV suppressive therapy, the following are recommended:	IIa, B

Recommended Monitoring During Antiviral Therapy

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

Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

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

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

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

Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response	
RECOMMENDED	RATING
Disease progression assessment every 6 to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended.	I, C
Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).	I, C
Endoscopic screening for esophageal varices is recommended if cirrhosis[a] is present.	I, A
Evaluation for retreatment is recommended as effective alternative treatments become available.	I, C
[a] For decompensated cirrhosis, please refer to the appropriate section.	

The Following Monitoring Is Not Recommended During or After Therapy	
NOT RECOMMENDED	RATING
Monitoring for HCV drug resistance-associated substitutions during or after therapy is not recommended.	IIb, C

The Following Monitoring Is Not Recommended During or After Therapy

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

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

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

Last update: May 24, 2018

HCV Resistance Primer

Resistance Testing in Clinical Practice

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

Regimen-Specific Clinical Practice Situations in Which RAS Testing Is Not Recommended

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

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

DAA	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N
Ledipasvir	20x	>100x	>100x /	>1000x /	>100x/	>100x / --

			>100x	>10,000	>50x	
Ombitasvir	>1000x	>100x	<3x >100x	>10,000x / >10,000x	<10x	20x / 50x
Daclatasvir	>100x	>1000x	>100x / >1000x	>1000x / >10,000x	<10x	20x / 50x
Elbasvir	20x	>100x	>10x >100x	>1000x / >1000x	<10x	>100x / --
Velpatasvir	<10x	<3x	20x / 50x	>100x/ >1000x	<3x	<3x / --

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

Table 2. Clinically Important RASs by DAA Regimen and Genotype

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

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

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

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

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