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

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

Pretreatment and On-Treatment Monitoring

Recommended Assessments Prior to Starting Antiviral Therapy

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

Recommended Assessments Prior to Starting Antiviral Therapy

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

Recommended Monitoring During Antiviral Therapy

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

Recommended Monitoring During Antiviral Therapy

Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.	I, B
For HBsAg-positive patients who are not already on HBV suppressive therapy, the following are recommended: • For patients whose HBV DNA level meets AASLD criteria for treatment, antiviral therapy for HBV should be initiated. • For patients whose baseline HBV DNA level does not meet criteria for treatment, one of two approaches may be taken: ◦ Initiate prophylactic antiviral therapy for those with low or undetectable HBV DNA levels. If this course is elected, pending further data, prophylaxis should be continued until 12 weeks after completion of DAA therapy. ◦ Monitor HBV DNA levels during and immediately after DAA therapy for HCV. Antiviral treatment for HBV should be given in the event of a rise in HBV DNA >10-fold above baseline or to >1000 IU/mL in those with a previously undetectable or unquantifiable HBV DNA level.	IIa, B

Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

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

Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy

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

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

Reactivation of HBV

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

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

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

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

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

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

The Following Monitoring Is Not Recommended During or After Therapy

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

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

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

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

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

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

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

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

SVR typically aborts progression of liver injury with regression of liver fibrosis in most, but not all, treated patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0, F1, or F2) who achieve SVR should receive standard medical care that is recommended for patients who were never infected with HCV.

Among patients with advanced liver fibrosis (ie, Metavir stage F3 or F4) who achieve SVR, decompensated liver disease (with the exception of HCC) rarely develops during follow-up, and overall survival is prolonged (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Liver fibrosis and liver function test results improve in most patients who achieve SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Bleeding from esophageal varices is rare after SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis should receive routine surveillance endoscopy for detection of esophageal varices if not previously done; if varices are found, they should be treated or followed as indicated (Garcia-Tsao, 2007).

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

Patients with cirrhosis who achieve SVR remain at risk for HCC. Thus, they should continue to undergo regular surveillance for HCC despite the lowered risk that results after viral eradication (Bruix, 2011). The risk of HCC among patients with advanced fibrosis prior to treatment but who have regression to minimal fibrosis after treatment is not known. In the absence of data to the contrary, such patients remain at some risk for HCC and should be monitored at regular intervals for HCC. Alpha-fetoprotein (AFP) alone is considered an inadequate screening test for HCC (Bruix, 2011).

Patients in whom SVR is achieved but who have another potential cause of liver disease (eg, excessive alcohol use, metabolic syndrome with or without proven fatty liver disease, or iron overload) remain at risk for fibrosis progression. It is recommended that such patients be educated about the risk of liver disease and monitored for liver disease progression with periodic physical examination, blood tests, and potentially, tests for liver fibrosis by a liver disease specialist.

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

Monitoring for HCV During Chemotherapy and Immunosuppression

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

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

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

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