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 three parts: pretreatment and on-treatment monitoring, posttreatment follow-up for persons in whom treatment has failed to clear virus, and posttreatment follow-up for those who achieved a sustained virologic response (SVR; virologic cure).

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 on 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 (albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels) • Calculated glomerular filtration rate (GFR) • Thyroid-stimulating hormone (TSH) if IFN is used **The following laboratory testing is 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 (paritaprevir, simeprevir, grazoprevir) should be assessed for a history of decompensated liver disease and for severity of liver disease using CTP score. Patients with current or prior history of decompensated liver disease or with a current CTP score of 7 or greater should NOT receive treatment with regimens that contain NS3 protease inhibitors due to increased area under the curve (AUC) 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 DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc.	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

Table: NS5A Resistance-Associated Substitutions (RASs) with Potential for Clinical Significance

Wild-type Amino Acid (sensitive)	Position	Substitution Amino Acid
M	28	A/G/T
Q	30	D/E/H/G/K/L/R
L	31	F/M/V
Y	93	C/H/N/S

The role of NS5A resistance-associated substitutions (RASs) is emerging. NS5A RASs appear to have impact on treatment response with regimens that include an NS5A inhibitor and this impact occurs primarily with genotype 1a and genotype 3 infections. However, the magnitude of the impact on treatment response varies with the specific combination of direct-acting antivirals. Recommendations on the need for NS5A testing, particularly at baseline prior to exposure to a NS5A inhibitor, will be made for individual regimens where there is sufficient data and it is felt the impact is great enough to be clinically significant and warrant testing. This is a rapidly evolving part of the field and will be updated regularly to reflect new and emerging data.

Pretreatment and On-Treatment Monitoring

The pretreatment testing described here 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 (eg, http://www.hep-druginteractions.org).

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*		X	X				X
Alfuzosin/tamsulosin			X				
Amiodarone	X	X	X	X	X		X
Anticonvulsants*	X	X	X	X	X	X	X
Antiretrovirals*	**See HIV section**						
Azole antifungals*	X**		X	X		X	
Buprenorphine/naloxone			X				
Calcineurin inhibitors*			X	X		X	
Calcium channel blockers*	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*	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)*	X	X	X	X		X	
Macrolide antimicrobials*	X**			X		X	
Other antiarrythmics*			X	X		X	
Phosphodiesterase inhibitors*			X	X		X	
Pimozide			X				
Rifamycin antimicrobials*	X	X	X	X	X	X	X
Salmeterol			X				
Sedatives*			X	X		X	

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

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
Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN. More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with 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 week 4 should prompt discontinuation of therapy. Any increase in ALT of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio, should also prompt discontinuation of therapy. Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. 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 at 12 weeks following 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
Patients with compensated cirrhosis‡ who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy) 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 patients develop ascites or encephalopathy or a significant increase in direct bilirubin or ALT or AST.	I, A
For HBsAg+ patients who are not already on HBV suppressive therapy, monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if treatment criteria for HBV are met.	IIa, B

‡ For decompensated cirrhosis, please refer to the appropriate section.

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 greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then 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 or week 8 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 ribavirin-containing antiviral regimens, and for up to 6 months after stopping.	I, C
Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving ribavirin-containing antiviral regimens, and for up to 6 months after stopping.	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

During treatment, individuals should be followed up 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. 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 III clinical trials, almost all patients who did not have cirrhosis had undetectable HCV RNA level at week 4; those with cirrhosis may require more than 4 weeks of treatment before HCV RNA level is undetectable. There are minimal data on how to use HCV RNA level during treatment to determine when to stop treatment for futility. The current recommendation to repeat quantitative HCV RNA testing at week 4 of treatment and to discontinue treatment if the quantitative HCV RNA level increases by more than 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 results at weeks 2, 3, or 4 of treatment, or that detectable HCV RNA level at these time points signifies medication nonadherence. Although HCV RNA testing is recommended at

week 4 of treatment, the absence of an HCV RNA level at week 4 is not a reason to discontinue treatment. Quantitative HCV RNA level testing at the end of treatment will help to differentiate viral breakthrough from relapse, if necessary. Some may choose to forego end-of-treatment viral load testing, given the high rates of viral response with the newer regimens, and to focus on the week 12 posttreatment viral load. Virologic relapse is rare at 12 or more weeks after completing treatment. Nevertheless, repeat quantitative HCV RNA testing can be considered at 24 or more weeks after discontinuing treatment for selected patients.

During clinical trials with ELB/GRZ with or without ribavirin, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), 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, Asians, and those 65 years or older. 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 (elbasvir and grazoprevir package insert). Patients who have compensated cirrhosis (Child's A) and are receiving paritaprevir/ritonavir-based regimens should be followed closely. (Please see above and statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.)

Patients who are being treated with amiodarone should not receive sofosbuvir-based regimens due to risk of life-threatening arrhythmias.

Pregnancy

Ribavirin causes fetal death and fetal abnormalities in animals and thus it is imperative for persons of childbearing potential who receive the drug to use at least two reliable forms of effective contraception during treatment and for a period of 6 months thereafter. Ethinyl estradiol-containing contraceptives should be avoided in those receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir due to risk of developing elevated transaminases. It is recommended that the healthcare practitioner document the discussion of potential teratogenic effects of ribavirin in the patient's medical record. Sofosbuvir, ledipasvir, paritaprevir, ombitasvir, and dasabuvir are pregnancy category B, although there are limited data on the use of these drugs in pregnancy. 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 many patients, the potential risks and benefits of delaying pregnancy until HCV antiviral treatment is completed should be considered. The education of patients and caregivers about potential adverse effects and their management is an integral component of treatment and is important for a successful outcome in all patient populations.

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 already on HBV suppressive therapy (Hayashi, 2016); (Takayama, 2016); (Ende, 2015); (Collins, 2015); (De Monte, 2016); (Sulkowski, 2016); (Wang, 2016). 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 testing for HBsAg, anti-HBs, and anti-HBc. 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. 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 (AASLD Guidelines for Treatment of Chronic Hepatitis B). Patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV DNA, and those patients with HBV DNA levels meeting treatment criteria should initiate HBV therapy (AASLD Guidelines for Treatment of Chronic Hepatitis B). There are insufficient data to provide clear recommendations for the monitoring of 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 groups in the event of unexplained increases in liver enzymes during and/or after completion of DAA therapy.

Monitoring Patients Who Have Completed Treatment

Patients who do not achieve an SVR, because of failure of the treatment to clear, or to maintain clearance of HCV infection with relapse after treatment completion, have ongoing HCV infection and the possibility of continued liver injury and transmission. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available. Patients who have undetectable HCV RNA in the serum, when assessed by a sensitive polymerase chain reaction (PCR) assay, 12 or more weeks after completing treatment, are deemed to have achieved an SVR. In these patients, HCV-related liver injury stops, although the patients remain at risk for non-HCV-related liver disease, such as fatty liver disease or alcoholic liver disease. Patients with cirrhosis remain at risk for developing hepatocellular carcinoma.

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

RECOMMENDED	RATING
Disease progression assessment every 6 months 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‡ is present.	I, A
Evaluation for retreatment is recommended as effective alternative treatments become available.	I, C

‡ 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 in whom treatment failed to achieve an SVR remain at risk for ongoing liver injury and progression of liver fibrosis (Dienstag, 2011). Thus, patients in whom treatment fails should be monitored for signs and symptoms of cirrhosis. There is currently no conclusive evidence to suggest that failure of antiviral treatment results in more severe liver injury or more rapidly progressive liver disease than would have occurred if the patient had not received treatment.

Patients in whom an initial antiviral treatment failed have achieved SVR when treated with the same drugs for a longer duration, or when treated with alternative antiviral regimens (Lawitz, 2014a). Thus, patients in whom treatment has failed to achieve an SVR should be considered for treatment when alternative antiviral regimens are available. Advice from a physician experienced in HCV treatment may be beneficial when considering retreatment after antiviral therapy failure.

Patients in whom antiviral therapy failed to achieve an SVR may harbor viruses that are resistant to one 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. The presence of baseline RASs in treatment-naive persons does not preclude achieving an SVR with a combination direct-acting antiviral regimen. Furthermore, RASs are often not detectable with routine (population sequencing) detection methods, nor with more sensitive tests of HCV substitutions, after patients are followed up for several months (Schneider, 2014). Subsequent retreatment with combination antivirals, particularly regimens containing antiviral drugs that have a high barrier to resistance, such as nonstructural protein 5B (NS5B) nucleotide polymerase inhibitors (eg, sofosbuvir), may overcome the presence of resistance to one or more antivirals.

There are three situations in which baseline testing for RASs is recommended in the treatment of HCV genotype 1 infection. First, for those patients whose prior treatment regimen containing an NS5A inhibitor failed and who have cirrhosis or require urgent retreatment, testing for RASs that confer decreased susceptibility to NS3 protease inhibitors (eg, Q80K) and to NS5A inhibitors should be performed using commercially available assays. In a pilot study of 41 patients with or without cirrhosis who did not achieve an SVR with 8 weeks or 12 weeks of therapy with the daily fixed-dose combination of ledipasvir (90 mg) and sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) who were retreated with 24 weeks of ledipasvir/sofosbuvir, rates of SVR at 12 weeks varied according to the presence or absence of certain NS5A inhibitor RASs. Among 11 patients in whom NS5A inhibitor RASs were not detected, SVR occurred in 11 of 11 (100%); in contrast, among 30 patients in whom certain NS5A inhibitor RASs were detected, SVR occurred in 18 of 30 (60%). Importantly, NS5B inhibitor RASs (eg, S282T) known to confer decreased activity of sofosbuvir were observed in 3 of 12 (25%) patients for whom the retreatment regimen was not successful. The additional finding of the Q80K substitution has implications for the retreatment regimen selected for these patients (see Retreatment of Persons in Whom Prior Therapy Has Failed).

Second, for those treatment-naive or PEGIFN/ribavirin-experienced persons with genotype 1a HCV who are being treated with elbasvir/grazoprevir, the presence of baseline NS5A RASs significantly reduces rates of SVR 12 using a 12-week elbasvir/grazoprevir regimen (Zeuzem, 2017). NS5A RASs were identified at baseline 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 a larger than 5-fold shift to elbasvir was associated with the most significant reductions in SVR 12 with only 22% (2/9) of genotype 1a patients with these high fold-change RASs achieving SVR12. The recommendation to extend duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial (Kwo, 2015). Based on known inferior response in patients with presence of baseline high fold-change NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir. If baseline high fold-change RASs are present, ie, substitutions at amino acid positions 28, 30, 31, or 93, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) is recommended to decrease relapse (see Initial Treatment of HCV Infection or Retreatment of Persons in Whom Prior Therapy Has Failed sections).

Third, for treatment-naive patients or those experienced with PEG-IFN/ribavirin who have HCV genotype 1a infection and cirrhosis, testing for the Q80K NS3 RAS is recommended when simeprevir and sofosbuvir are being considered as treatment. In the OPTIMIST-2 study, in which patients with cirrhosis were treated with simeprevir and sofosbuvir, the presence of NS3 RASs, specifically the Q80K substitution, was associated with a decreased SVR rate. SVR occurred in 25 of 34 (74%) patients with HCV genotype 1a infection and the Q80K RAS and in 35 of 38 (92%) patients with HCV genotype 1a infection without the Q80K RAS (see Initial Treatment of HCV Infection or Retreatment of Persons in Whom Prior Therapy Has Failed sections).

NS5A RAS testing is also recommended in persons with genotype 3 HCV who are considering treatment with sofosbuvir/velpatasvir or daclatasvir/sofosbuvir-based regimens. Baseline NS5A substitutions in genotype 3 impact DAA treatment response, with the Y93H substitution being most problematic. In the ALLY-3 study the Y93H was detected in 13 (9%) of patients with an SVR12 of 54% (7/13); including a 67% SVR12 in patients without cirrhosis. In the ASTRAL-3 study the Y93H was detected in 25 (9%) of patients with an SVR12 rate of 84% (21/25). Treatment-experienced cirrhotic patients are already recommended to have ribavirin added with or without extension of therapy depending on the specific regimen, thus baseline testing for NS5A RASs in genotype 3 is only recommended for treatment approaches for treatment-naive patients with cirrhosis or treatment-experienced patients without cirrhosis. Pending further data on optimal therapy in the setting of baseline Y93H substitution in these particular patient populations, the addition of ribavirin for patients with cirrhosis is recommended.

If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert in the treatment of HCV infection may be useful.

Recommended Follow-up for Patients Who Achieve a Sustained Virologic Response (SVR)

RECOMMENDED	RATING
For patients who do not have advanced fibrosis (ie, those with Metavir stage F0-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 assay rather than an anti-HCV serology test is recommended to test 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 an SVR.	I, C
A baseline endoscopy is recommended to screen for varices if cirrhosis‡ is present. Patients in whom varices are found should be treated and followed up as indicated.	I, C
Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR.	I, C

‡ For decompensated cirrhosis, please refer to the appropriate section.

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving an SVR among adherent, immunologically competent, treatment-naive patients with compensated liver disease generally exceeds 90%. Of patients who achieved an SVR with PEG-IFN/ribavirin treatment, more than 99% have remained free of HCV infection when followed up for 5 years after completing treatment (Manns, 2013). Thus, achieving an 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-F2) who achieve an 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 an SVR, decompensated liver disease (with the exception of hepatocellular carcinoma) rarely develops during follow-up, and overall survival is prolonged (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients who have advanced fibrosis or cirrhosis continue to be at risk for development of hepatocellular carcinoma after achieving an SVR, although the risk in these patients is lower than the risk in persistently viremic patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis who achieve SVR experience increased survival (compared with patients with cirrhosis who are untreated or in whom treatment fails), but still may be at some risk for hepatocellular carcinoma; thus, they should continue to undergo regular surveillance for hepatocellular carcinoma despite the lowered risk that results after viral eradication (Bruix, 2011). The risk of hepatocellular carcinoma 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 hepatocellular carcinoma and should be monitored at regular intervals for hepatocellular carcinoma. Alpha-fetoprotein (AFP) is considered an inadequate screening test for HCC (Bruix, 2011).

Liver fibrosis and liver function test results improve in most patients who achieve an SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Bleeding from esophageal varices is rare after an 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 and these should be treated or followed up as indicated (Garcia-Tsao, 2007).

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

Periodically testing patients with ongoing risk for HCV infection (eg, illicit drug use, high-risk sexual exposure) for HCV reinfection is recommended. Flares in liver enzyme test results should prompt evaluation of possible de novo reinfection with HCV through a new exposure (see Management of Acute HCV Infection). Antibody to HCV (anti-HCV) remains positive in most patients following an SVR. Thus, testing for reinfection with HCV is recommended and should be performed with an assay that detects HCV RNA (eg, a quantitative HCV RNA test).

Monitoring for HCV During Chemotherapy and Immunosuppression

NOT RECOMMENDED	RATING
Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who 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; thus, testing for hepatitis viruses should be included in the laboratory assessment of the cause of liver injury. However, while individuals with inactive (no detectable virus) or past hepatitis B virus infection may experience reactivation and clinically apparent hepatitis during immunosuppressive treatment or chemotherapy, this does not occur with hepatitis C infection. Although some patients with active HCV infection, primarily those with hematologic malignancy, may have a flare in their liver enzymes during chemotherapy, this is unusual (Mahale, 2012). Furthermore, reactivation of past HCV infection, such as after SVR or spontaneous clearance, is not anticipated since there is no residual reservoir for the virus. Thus, in this latter group, routine testing of HCV RNA during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

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