Monitoring During and After HCV Treatment

Background

The treatment of hepatitis C virus (HCV) should include a pretreatment baseline evaluation, consideration of drug interactions, evaluation of treatment response during and after therapy, and monitoring for safety during treatment. A typical schedule for clinic visits related to an 8- or 12-week treatment course with direct-acting antiviral (DAA) therapy would consist of a baseline visit just prior to starting therapy, a follow-up visit at week 4 of therapy, an end-of-treatment visit, and a post-treatment visit 12 weeks after completing therapy. For longer courses of treatment, such as a 16-week treatment course, most clinicians would add one or more on-treatment visits. Any patient with significant adverse effects or complications should be seen as needed. In addition, patients with cirrhosis or other complicating conditions may require more frequent follow-up. This topic review addresses the recommendations for monitoring for safety and efficacy during treatment, as well as considerations for monitoring patients after treatment.
Monitoring for Treatment Efficacy

Recommended Method for Monitoring of Treatment Efficacy

The optimal and standard approach to monitoring for treatment efficacy consists of repeated measurement of quantitative HCV RNA levels. Monitoring requires use of a highly sensitive quantitative HCV RNA assay, typically with a lower limit of quantification in the range of 12-25 IU/mL. In addition, to minimize interassay and interlaboratory variation, monitoring should utilize the same HCV RNA assay performed by the same laboratory. Three commercially available HCV RNA assays are widely used in the United States: Roche COBAS TaqMan Version 1.0, Roche COBAS TaqMan Version 2.0, and the Abbott RealTime HCV (ART) assay.

The following definitions related to HCV RNA assay results are used in clinical practice and in research studies (Figure 1):

- **Lower Limit of Quantification (LLOQ):** This is the lowest HCV RNA concentration that is within the validated range the assay can accurately quantify by the assay. If HCV RNA is not quantifiable, the result is either HCV RNA detected but below the LLOQ or HCV RNA not detected. Note that the lower limit of quantification is not the same as the lower limit of detection.
- **Limit of Detection (LOD):** This value is the concentration of HCV RNA detectable at a rate of at least 95%. The ability of the assay to detect HCV RNA gradually decreases as the actual amount of HCV RNA in the sample approaches 0 IU/mL. The result below the limit of detection is referred to as undetectable.
- **Target Detected (TD):** The HCV RNA is detected.
- **Target Not Detected (TND):** The HCV RNA is not detected.

Recommended Schedule for HCV RNA Monitoring

For patients receiving HCV therapy, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance recommends obtaining a quantitative HCV RNA level at baseline and at 12 weeks after completing therapy (Figure 2). The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines recommend obtaining an HCV RNA level at week 2 as an early evaluation of adherence.

On-Treatment HCV RNA Monitoring

The role of HCV RNA testing at week 4 of DAA-based therapy is not clear at this time. Phase 3 trials with DAAs have demonstrated that nearly all patients without cirrhosis had an HCV RNA level at week 4 that was undetectable (or less than the LLOQ); in contrast, a significant proportion of patients with compensated cirrhosis will have a detectable HCV RNA level at week 4. Observational data from the Veterans Administration suggest that detectable HCV RNA (15 IU/mL or greater) at week 4 may be associated with lower odds of sustained virologic response (SVR) at 12 weeks after completion of therapy. Nevertheless, SVR has been well documented among individuals who have a higher-than-expected or detectable HCV RNA level at week 4 of treatment. The AASLD-IDSA HCV Guidance now advises against routine testing for HCV RNA level during treatment unless: (1) ALT fails to decline from baseline, or (2) there is concern regarding patient adherence with DAA therapy. The panel also notes there are no data to support HCV treatment cessation or modification based on a detectable level at week 4 of treatment. It is also not clear that a detectable HCV RNA anytime during therapy reflects non-adherence.

On-Treatment Persistent Low-Level Viremia

The significance of on-treatment persistent low-level viremia (that does not increase) is not known and there is no clear indication this represents lack of adherence or likelihood of virologic relapse. Indeed, recent data involving patients receiving DAA sofosbuvir-containing therapy has shown that low-level quantifiable HCV RNA levels at week 4 were not clinically useful in predicting SVR12; these findings contrast sharply with prior...
studies using interferon-based regimens. The AASLD-IDSA guidelines do not provide a recommendation regarding stopping or extending therapy in the setting of stable low-level viremia. In contrast to the AASLD-IDSA recommended strategy, some experts do not routinely recheck the HCV RNA after a low detectable level (less than 25 IU/mL) at week 4 in patients believed to have good adherence, since the vast majority of these patients go on to clear HCV. If, however, adherence is a concern, it is advised to recheck the HCV RNA in 2 weeks, and if there is a greater than 10-fold increase, then obtain expert consultation and consider stopping therapy.

**Determining Sustained Virologic Response**

The recommended testing to determine whether the patient has achieved an SVR is a quantitative HCV RNA level 12 weeks after completing therapy (Figure 3). An undetectable HCV RNA level 12 weeks after completing therapy is referred to as SVR12 and this generally translates into a long-term cure of HCV infection. Some experts will obtain an HCV RNA level 24 weeks after completing treatment in selected patients, such as those with cirrhosis. Research studies have utilized HCV RNA levels 4 weeks after completing therapy (SVR4), but the SVR4 is not considered as robust a marker for treatment response as an SVR12.
Monitoring for Safety During Treatment

Baseline Safety Laboratory Studies

The optimal and standard approach to monitoring for treatment safety depends on whether ribavirin is a component of the regimen. The following baseline laboratory studies are recommended in the AASLD-IDSA HCV Guidance:[7]

- Complete blood count (CBC)
- International normalized ratio (INR)
- Hepatic function panel: albumin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase
- Serum creatinine level (and calculated glomerular filtration rate)
- Serum pregnancy testing for women of childbearing age, especially if the HCV treatment regimen includes ribavirin
- HCV genotype and subtype should be obtained if the planned treatment regimen is not a pan-genotypic regimen

Safety Issues with Ribavirin

The use of ribavirin for the treatment of HCV has markedly declined in recent years, but ribavirin may occasionally be indicated as an adjunct to DAA therapy in treatment-experienced individuals. Ribavirin can cause severe hemolytic anemia, especially at higher doses. For persons taking ribavirin, regular monitoring of hemoglobin is recommended. Ribavirin is a teratogenic drug in rodents and may cause birth defects and fetal harm when administered to women who are pregnant. It is therefore contraindicated in pregnant women and in men whose female partners are pregnant. In addition, extreme care must be taken to prevent pregnancy in females taking ribavirin and in female partners of male patients taking ribavirin. Accordingly, ribavirin should not be started unless there is a documented report of a negative pregnancy test immediately prior to planned initiation of ribavirin. Women taking ribavirin (and women who have a male partner taking ribavirin) should be instructed to use at least two forms of effective contraception during treatment that includes ribavirin and for 6 months after treatment has been stopped. Women receiving ribavirin (and women who have a male partner taking ribavirin) should have monthly pregnancy tests during ribavirin treatment and for 6 months after treatment has been completed.

Safety Laboratory Studies at Week 4 of Therapy

For patients receiving hepatitis C therapy, the AASLD-IDSA HCV Guidance recommends obtaining the following safety laboratory studies 4 weeks after starting therapy:[7]

- Serum creatinine level (and calculated glomerular filtration rate)
- Hepatic function panel: albumin, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase
- CBC if the patient is taking ribavirin

Management of Abnormal ALT During Therapy

Clinically significant hepatotoxicity has been reported with DAA therapy, specifically NS3 protease inhibitors, particularly for patients with advanced liver disease. The AASLD-IDSA HCV Guidance advises against the use of NS3 protease inhibitors in patients with a Child-Turcotte-Pugh score of 7 or greater. Elevations in ALT to greater than 5 times the upper limit of normal occurs in up to 1% of all persons taking elbasvir-grazoprevir; therefore, hepatic panel monitoring for persons taking elbasvir-grazoprevir has been recommended by the manufacturer at week 8 and as clinically indicated during therapy (some experts recommend monitoring of ALT every 4 weeks while on elbasvir-grazoprevir). Due to increased risk of hepatotoxicity, coadministration of ethinyl estradiol with glecaprevir-pibrentasvir is not recommended. For individuals who have on-treatment
increases in ALT levels at week 4, the AASLD-IDSA HCV Guidance provides the following recommendations based on the severity of the ALT elevation and whether symptoms are present.

- **A 10-fold or Greater Increase in ALT Levels**: If a patient receiving treatment for HCV develops a 10-fold or greater increase in ALT levels, regardless of the presence of clinical symptoms, they should immediately stop HCV therapy and undergo close clinical and laboratory monitoring for liver toxicity.

- **Clinical Symptoms and Increase in ALT Levels of Less than 10-Fold**: If a patient receiving treatment for HCV has elevated ALT levels that are less than a 10-fold increase they should immediately stop therapy if they have either of the following: (a) symptoms suggestive of acute hepatitis (weakness, nausea, vomiting, or jaundice) or (b) a significant increase in other hepatic function panel labs (bilirubin, alkaline phosphatase, or international normalized ratio). After stopping therapy the patient should have close clinical and laboratory monitoring for liver toxicity. The AASLD-IDSA HCV Guidance does not specify what degree of change in bilirubin, alkaline phosphatase, or international normalized ratio should be considered as “significant”. Most experts would use clinical judgment with this recommendation and not discontinue therapy with a low level increase in ALT accompanied by a low-level increase in bilirubin or alkaline phosphatase.

- **Asymptomatic and Increases in ALT Levels Less than 10-Fold**: Patients with an increase in ALT levels less than 10-fold, but without symptoms suggestive of acute hepatitis, should have close monitoring and repeat ALT levels checked at treatment weeks 6 and 8. If the ALT levels remain consistently elevated, discontinuation of therapy should be considered. Most experts in this situation would follow this general AASLD-IDSA recommendation, but decide on a case-by-case basis, taking into account the degree of ALT elevation, the trend in ALT levels, and the presence or absence of underlying cirrhosis or symptoms of hepatic injury.
Hepatitis B Reactivation Associated with HCV DAA Therapy

Background

Hepatitis B virus (HBV) reactivation associated with severe hepatitis flare has been increasingly recognized as a potential adverse event associated with HCV DAA therapy. Previous reports have described HBV reactivation after interferon-based therapy, but in these prior cases, clinically significant hepatitis was rare. Chronic HCV has been known to suppress HBV replication in persons coinfected with HCV and a reciprocal interaction between these viruses has long been postulated. The elimination of HCV can result in a potential loss of immunologic control of HBV infection and HBV reactivation.

Food and Drug Administration Warning and Adverse Event Reporting Data

The U.S. Food and Drug Administration (FDA) issued a drug safety warning on October 4, 2016 in which they identified 24 cases of confirmed reactivation of HBV infection in persons receiving DAA medications for treatment of HCV.[18] The FDA warning was based on a number of cases reported to the FDA and from published literature.[19,20,21,22,23,24] The FDA has published findings that summarized a total of 29 patients (5 from the United States) with confirmed HBV reactivation during DAA therapy; their summary was based on published reports and cases detected via their Adverse Event Reporting System database between November 2013 and October 2016.[25] The following summarizes key findings from this report:

- Unexpected ALT and AST elevations after starting DAAs were a common feature in all these cases, occurring typically 4 to 8 weeks (mean 53 days) from treatment initiation and, in approximately one-third of the cases, the initial suspected diagnosis was an adverse drug reaction caused by DAA hepatotoxicity.
- The DAA regimens used in treatment of these patients were heterogeneous and included sofosbuvir, simeprevir, daclatasvir with asunaprevir (investigational), and ledipasvir-sofosbuvir; note that simeprevir and daclatasvir are no longer manufactured in the United States. Hospitalization occurred in at least 6 patients.
- Severe clinical decompensation occurred in 3 cases, resulting in 2 deaths and 1 liver transplantation.
- Among the 29 cases of HBV reactivation, 13 (45%) occurred in chronic HBV carriers with positive hepatitis B surface antigen (HBsAg). There were notably some patients who had absent HBsAg and anti-HBs and an isolated anti-HB core profile among these cases. In many of the cases, some serologic data were missing.
- Although the anti-HB core and anti-HB surface antibody status were not known in a majority of cases (Figure 4), none of the patients with surface antibody (anti-HBs) were among the patients with HBV reactivation.
- Antiviral treatment of HBV was initiated in 15 patients, and in most cases resulted in improvement of the liver enzymes as well as symptoms of fatigue and malaise.

Additional Data on HBV Reactivation During Therapy

A prospective study from China evaluated 327 patients in an HBV-endemic area who were scheduled to receive DAA therapy for chronic HCV infection.[26] At baseline, 10 were HBsAg-positive. After starting DAA therapy for HCV, 30% (3 of 10) HBsAg-positive patients experienced a hepatitis flare with HBV reactivation versus none of the 317 who were HBsAg-negative, including 124 with occult HBV infection.[26] For the three patients who developed a hepatitis flare, the median time for onset of the flare was 8 weeks. Two retrospective studies, both based on national data from the U.S. Department of Veterans Affairs, suggested that HBV reactivation is a rare event and most likely to occur in HBsAg-positive patients.[27,28]

AASLD-IDSA HCV Guidance Related to HBV Reactivation

The AASLD-IDSA HCV Guidance provides specific recommendations that address the risk of HBV reactivation
following initiation of DAA treatment for HCV.[7] The following summarizes these AASLD-IDSA HCV Guidance recommendations.

- All persons about to initiate HCV DAA therapy should undergo assessment for coinfection with HBV with HBsAg, anti-HB core, and anti-HBs.
- If the HBV serologic testing indicates the patient is susceptible to HBV infection, they should receive the hepatitis B vaccine series.
- For patients who test positive for HBsAg, follow-up HBV DNA testing should be performed. If the HBsAg-positive individual is not receiving HBV suppressive therapy, treatment for HBV should be given if treatment criteria is met based on HBV DNA levels.[29]
- If treatment of HBV is indicated, it should occur at the same time (or before) starting HCV DAA therapy.
- For patients who are HBsAg-positive and do not have an indication for HBV therapy (based on low or undetectable HBV DNA levels), options include either (1) prophylactic HBV therapy, or (2) monitoring HBV DNA levels at regular intervals (but generally not more often than every 4 weeks) during HCV DAA therapy.
- If an individual who did not meet criteria for HBV therapy is undergoing HBV DNA monitoring during HCV DAA therapy and has a 10-fold increase in HBV DNA levels, or a single HBV DNA level greater than 1,000 IU/mL, then treatment for HBV should be started.
- There are not adequate data on the outcomes of persons with isolated anti-HBc to provide specific recommendations. It is possible that persons with isolated anti-HBc could reactivate HBV during HCV DAA therapy.

**Author's Recommendations**

We recommend obtaining baseline HBsAg, anti-HB core, and anti-HBs prior to starting HCV DAA therapy to evaluate for risk of HBV reactivation during DAA therapy for HCV. Individuals with a positive baseline HBsAg should have a baseline HBV DNA level ordered. Based on results from this baseline evaluation, we recommend the following:

- Individuals with a positive HBsAg should receive therapy for HBV to prevent reactivation during HCV DAA therapy. Our recommendation is based on the significant risk of HBV reactivation in persons with positive HBsAg and the potential severity of the hepatitis flares associated with this resurgence.[25,26] The treatment for HBV should begin prior or concomitant with initiation of HCV DAA therapy, preferably 2 to 4 weeks in advance of starting HCV therapy. Assuming the patient has not previously received HBV therapy, we recommend treatment of HBV with entecavir 0.5 mg orally once daily or tenofovir disoproxil fumarate 300 mg orally once daily; the treatment of HBV should continue for at least 3 months following completion of HCV DAA therapy, with possible discontinuation of HBV treatment if the patient did not have an indication for chronic HBV therapy at baseline; preferably this decision is made along with expert consultation.
- Individuals who are anti-HB core positive, but HBsAg and anti-HBs negative may have risk of HBV reactivation during HCV DAA therapy, but the risk is likely significantly lower than in persons who are HBsAg positive.[25,26,30] For patients with an isolated anti-HB core positive test, we recommend monitoring ALT and AST levels every 4 weeks during HCV DAA therapy; if these levels increase greater than two-fold from baseline, then obtain a quantitative HBV DNA level. Consider initiating HBV therapy (with a regimen outlined above) if the HBV DNA is detectable.
- For individuals who are anti-HBs positive, HBsAg negative, and anti-HB core positive, we do not recommend HBV DNA testing or treatment to prevent HBV reactivation. In addition, we do not recommend monitoring for HBV reactivation in persons who have a positive anti-HBs and negative anti-HB core (i.e. individuals who received hepatitis B vaccine but have never been exposed to HBV infection naturally).
Monitoring After Receiving HCV Therapy

Approach to Monitoring After Receiving HCV Therapy

The approach to monitoring patients following completion of a course of HCV therapy depends entirely on the patient's response to therapy. Three main scenarios exist: (1) the patient achieved an SVR12, (2) the patient completed therapy but did not achieve an SVR12, or (3) the patient had an inadequate treatment course because of adherence problems, intolerance, or laboratory toxicity necessitating premature discontinuation of the treatment regimen.

Monitoring Patients Who Achieved an SVR

Individuals who have an undetectable HCV RNA at week 12 after completing HCV therapy (or later than 12 weeks) are considered to have achieved an SVR and this is associated with long-term reduced liver-related morbidity and mortality.\[13,31,32\] In a review of 44 studies involving more than 4,228 patients who achieved an SVR with an interferon-based regimen, 97% of patients maintained the SVR during the long-term follow-up period.\[33\] Some experts will obtain an HCV RNA level 24 weeks after completing treatment in selected patients. In a review by Manns, more than 99.2% of 1002 patients who achieved an SVR12 with interferon- or peginterferon-based therapy maintained undetectable HCV RNA levels for 5 years.\[15\] Available long-term data for durability of treatment response with all-oral DAA therapy suggest SVR12 responses translate into sustained HCV clearance.\[34\] All patients who achieve an SVR should clearly understand they are not immune to HCV and can become reinfected with HCV.\[16,34,35,36\] The AASLD-IDSA HCV Guidance stratifies the follow-up for persons who achieve an SVR based on the degree of hepatic fibrosis and the risk of reinfection.\[7\]

- **Patients with Minimal to Moderate Fibrosis (F0-F2):** These patients do not need special monitoring or follow-up specifically for hepatitis C or liver care. This recommendation is based on data that show patients with SVR following hepatitis C treatment generally do not have further progression of HCV-related liver fibrosis.

- **Individuals with Advanced Fibrosis (F3-F4):** Although fibrosis may improve in these patients, they are considered to have persistent risk for developing hepatocellular carcinoma (HCC). Accordingly, these patients should have continued surveillance for HCC with an abdominal ultrasound (with or without alpha fetoprotein) every 6 months.\[37\] In addition, patients with cirrhosis (F4 fibrosis) should have a baseline upper endoscopy to screen for varices, unless this has previously been done. Patients identified with varices should receive appropriate management and follow-up.\[38\]

- **Patients with Persistently Abnormal Liver Tests:** Any person who has achieved an SVR12, but who has persistently elevated hepatic aminotransferase levels should undergo evaluation for possible other causes of liver disease, such as alcohol use, iron overload, or fatty liver disease.

- **Persons with Ongoing Risk of HCV Reinfection:** All persons with ongoing risk for acquiring HCV should have periodic assessment for HCV reinfection and counseling on prevention of reinfection. At least annual HCV RNA screening is recommended for persons who inject drugs and for men with HIV who have condomless sex with men, given the significant risk of HCV reinfection in these individuals. Obtaining HCV antibody does not provide useful information in persons with known prior HCV infection since they are likely to remain antibody positive. Thus, HCV screening for reinfection should consist of a quantitative HCV RNA level. In addition, for these individuals, any elevation in hepatic aminotransferase levels should prompt evaluation for reinfection with a quantitative HCV RNA level.

Monitoring of Persons Who Do Not Achieve SVR

The AASLD-IDSA HCV Guidance recommends the following for patients who did not achieve an SVR with HCV therapy:\[7\]

- **All Patients:** For all patients who did not achieve an SVR and are awaiting or deferring retreatment,
follow-up laboratory testing should occur every 6-12 months with a hepatic function panel, complete blood count, and international normalized ratio. It is important these patients receive counseling for alcohol abstinence and avoidance of hepatotoxic medications.

- **Patients with Advanced Fibrosis (F3-F4):** These patients should have surveillance for hepatocellular carcinoma with abdominal ultrasound, with or without serum alpha fetoprotein, every 6 months.[37] In addition, patients with cirrhosis (F4 fibrosis) should have a baseline upper endoscopy to screen for varices, unless this has previously been done.[38] Patients identified with varices should receive appropriate management and follow-up.[38]
Summary Points

- All persons undergoing treatment for hepatitis C need monitoring before, during, and in those with stage 4 fibrosis or those at risk for reinfection, after therapy.
- Quantitative HCV RNA is the preferred test for monitoring response to therapy, ideally with a lower limit of quantification in the range of 12 to 25 IU/mL. Patients should have a quantitative HCV RNA level obtained at baseline prior to starting therapy and 12 weeks after completion of treatment.
- An undetectable HCV RNA at 12 weeks after treatment is considered a sustained virologic response and effectively a cure for nearly all patients.
- Safety laboratory studies should be obtained at baseline and after 4 weeks of treatment. Further safety laboratory monitoring may be required in circumstances with abnormal results.
- All women of childbearing potential should be advised of the teratogenic potential of ribavirin. If its use is necessary, patients should be instructed to use at least two forms of effective contraception during any treatment that includes ribavirin and for 6 months after treatment has been stopped. A pregnancy test is required at baseline, monthly during ribavirin treatment, and for 6 months after completing ribavirin treatment. These same precautions and recommendations exist for women with male partners taking ribavirin.
- All persons with a 10-fold or greater increase in ALT levels at treatment week 4 should have therapy promptly discontinued with close follow-up. In most circumstances, individuals with symptoms suggestive of acute hepatic injury and increases in ALT that are less than 10-fold should discontinue therapy.
- Hepatitis B (HBV) reactivation associated with severe hepatitis flare has been increasingly recognized as a potential adverse event associated with HCV DAA therapy. The highest risk has been observed with HBsAg-positive patients, but HBV reactivation has been reported in persons with isolated anti-HB core.
- Monitoring of patients after treatment depends on whether the patient achieved an SVR12 and whether they have advanced fibrosis (Metavir stage 3 or 4).
- Patients with an SVR12 should receive education and counseling on the risk of becoming reinfected with HCV. At least annual quantitative HCV RNA testing for reinfection is recommended for persons who inject drugs and for men with HIV who have condomless sex with other men.
- Individuals with advanced fibrosis require long-term surveillance for HCC, regardless of whether they achieve an SVR12.
- Persons who do not achieve an SVR12 should continue to have regular follow-up and periodic reassessment for retreatment.
Citations


7. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Monitoring patients who are starting HCV treatment, are on treatment, or have completed therapy. [AASLD-IDSA HCV Guidance]


12. Childs-Kean LM, Hong J. Detectable Viremia at the End of Treatment With Direct-Acting Antivirals Can


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Figures

Figure 1 HCV RNA Assay Reports

This graphic illustrates sample cutoffs for lower limit of quantification (LLOQ) and limit of detection (LOD) for HCV RNA values. In this example, the HCV RNA assay has an LLOQ of 25 IU/mL and an LOD of 10 IU/mL.
Figure 2 Monitoring of Quantitative HCV RNA Levels in Persons Receiving 12 Weeks HCV Antiviral Therapy

This graphic shows the AASLD/IDSA HCV Guidance recommendations for obtaining HCV RNA levels in persons treated with HCV antiviral therapy. The recommended time points are noted with solid red circles and time points to consider for HCV RNA levels are noted as dashed gray circles.
Figure 3 Measurement of Sustained Virologic Response Following HCV Treatment

This graphic shows common time points for measurement of HCV RNA levels after completion of therapy. The preferred measurement for evaluation of SVR is an HCV RNA level 12 weeks after completing therapy (SVR12). The SVR4 is often obtained in research trials. Some experts evaluate certain patients for SVR24.
Figure 4 Baseline HBV Parameter in Patients Who Developed HBV Flare During HCV DAA Therapy


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*Timing of HBV DNA testing not given