

# Monitoring During and After HCV Treatment

This is a PDF version of the following document:

Section 5: [Treatment of Chronic Hepatitis C Infection](#)

Topic 6: [Monitoring During and After HCV Treatment](#)

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## Background

The treatment of hepatitis C 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.

## 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 to 25 IU/mL.[1] 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.[2,3,4,5,6] The following definitions related to HCV RNA assay results are used in clinical practice and in research studies (Figure 1):[4]

- **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 hepatitis C therapy, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) guidance recommends obtaining a quantitative HCV RNA level at baseline, at 4 weeks after starting therapy, and at 12 weeks after completing therapy; in addition, providers may consider obtaining HCV RNA levels at the end of treatment and 24 weeks after completing therapy (Figure 2).[7] The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines recommends obtaining a week 2 HCV RNA level as an early evaluation of adherence.[8]

### Approach When HCV RNA Detectable at Treatment Week 4

The role of week 4 HCV RNA testing with the use of DAA-based therapy is not completely clear at this time. Phase 3 trials with direct-acting antivirals have demonstrated that nearly all patients without cirrhosis had a week 4 HCV RNA level 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.[9,10] For patients who have low-level detectable HCV RNA at treatment week 4, the AASLD-IDSA guidance recommends performing a repeat quantitative HCV RNA level 2 weeks later (at treatment week 6) and if the HCV RNA has increased by more than 10-fold ( $1 \log_{10}$  IU/mL) then HCV therapy should be stopped.[7]

### 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 was not clinically useful in predicting SVR12; these findings contrast sharply with prior studies using interferon-based regimens.[9] The AASLD-IDSA guidelines do not provide a recommendation regarding stopping or extending therapy in the setting

of stable low-level viremia.[7] 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 (SVR)**

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](#)).[11,12] 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.[11,13,14] 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.[15]

## 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 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)

### Safety Laboratory Studies at Week 4 of Therapy

For patients receiving hepatitis C therapy, the AASLD-IDSA guidance recommends obtaining the following safety laboratory studies 4 weeks after starting therapy:[\[7\]](#)

- Complete blood count (CBC)
- Serum creatinine level (and calculated glomerular filtration rate)
- Hepatic function panel: albumin, total bilirubin, direct bilirubin, ALT, AST, and alkaline phosphatase

### Management of Abnormal ALT at Week 4 of Therapy

On October 22, 2015 the US FDA issued a Drug Safety Warning that treatment with ombitasvir-paritaprevir-ritonavir, with or without dasabuvir, can cause serious liver injury, mostly in patients with underlying advanced liver disease.[\[16\]](#) In most of the reported cases, the liver injury occurred within 1 to 4 weeks of starting treatment. Elevations in ALT to greater than 5 times the upper limit of normal have also been reported to occur in up to 1% of patients 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 have advised every 4 week monitoring of ALT in patients on elbasvir-grazoprevir. Patients taking ethinyl estradiol may also be at excess risk for hepatotoxicity on DAA therapy with ombitasvir-paritaprevir-ritonavir (with or without dasabuvir) or glecaprevir-pibrentasvir and thus coadministration is not advised. For individuals on any treatment regimen who have 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.[\[7\]](#)

- **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.
- **Symptomatic 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 ionized 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 ionized ratio should be considered as "significant". Most experts would use clinical judgment with this recommendation and not discontinue therapy with a very low level increase in ALT accompanied by a low level

increase in bilirubin or alkaline phosphatase.

- **Asymptomatic 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 week 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 make a decision 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 acute hepatitis symptoms.

# Hepatitis B Reactivation Associated with HCV DAA Therapy

## Background

Hepatitis B (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 coinfecting 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.

## FDA Warning and Adverse Event Reporting Data

The Food and Drug Administration 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.[17] The FDA warning was based on a number of cases reported to the FDA and from published literature.[18,19,20,21,22,23] 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 database between November 2013 and October 2016.[24] The following summarizes key findings from this report:

- Unexpected ALT and AST elevations after starting DAAs was 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. 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.
- 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.[25] At baseline, 10 were HBsAg-positive. After starting DAA therapy for HCV, 30% (3 of 10) HBsAg-positive patients experienced a hepatitis flare due to HBV reactivation compared to none of the 317 who were HBsAg-negative, including 124 with occult HBV infection.[25] 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.[26,27]

## 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 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 serology 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.[28]
- 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.
- If an individual who did not meet criteria for HBV therapy is undergoing HBV DNA monitoring during HCV 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 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:

- Patients 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.[24,25] 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 does not have an indication for chronic HBV therapy; 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 therapy, but the risk is likely significantly lower than in persons who are HBsAg positive.[24,25,29] 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 an HBV DNA level. Consider initiating HBV therapy (with a regimen outlined above) if the HBV DNA test is positive.
- 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

Patients who have an undetectable HCV RNA at week 12 (or later) after completing HCV therapy are considered to have achieved an SVR and this is associated with long-term reduced liver-related morbidity and mortality.[11,30,31] 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.[32] Some experts will obtain an HCV RNA level 24 weeks after completing treatment in selected patients. In a more recent 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.[13] Available long-term durability of treatment response with all-oral DAA therapy suggest SVR12 responses translate into sustained HCV clearance.[33] All patients who achieve an SVR should clearly understand they are not immune to HCV and can become reinfected with HCV.[14,33,34,35] The AASLD-IDSA Guidance stratifies the follow-up for persons who achieve an SVR based on the degree of hepatic fibrosis and the risk of developing 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.
- **Patients 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 surveillance for HCC with hepatic ultrasound every 6 months. 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.[36]
- **Patients with Ongoing Risk of HCV Reinfection:** Regardless of the degree of hepatic fibrosis, all patients with ongoing risk for acquiring HCV should have periodic assessment for HCV reinfection and counseling on prevention of reinfection. Obtaining HCV antibody does not provide useful information in these individuals with known prior HCV infection since they are highly likely to remain antibody positive. Thus, reassessment should consist of a quantitative HCV RNA level. In addition, for these patients, any flare in liver enzyme tests should prompt evaluation for reinfection with a quantitative HCV RNA level.
- **Patients with Persistently Abnormal Liver Tests:** Any patient that develops persistently elevated liver tests should undergo evaluation for possible other causes of liver disease, such as alcohol use, iron overload, or fatty liver disease.

### Monitoring for Patients who do not Achieve SVR

The AASLD-IDSA 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, follow-up laboratory testing should occur every 6 to 12 months with a hepatic function panel, complete blood count, and



international normalized ratio. In addition, these patients should have periodic reevaluation for retreatment, especially as new options become available. 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 hepatic ultrasound every 6 months. In addition, patients with cirrhosis (F4 fibrosis) should have a baseline upper endoscopy to screen for varices, unless this has previously been done.[36] Patients identified with varices should receive appropriate management and follow-up.[36]

## Summary Points

- All persons undergoing treatment for hepatitis C need systematic monitoring before, during, and 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, 4 weeks after starting treatment, and 12 weeks after completion of treatment.
- The significance of low-level detectable HCV RNA values at treatment week 4 remains unclear; additional follow-up HCV RNA testing at treatment week 6 should be considered, especially if adherence or virologic breakthrough is a concern.
- 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 safety laboratory studies.
- 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 hepatitis 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 patients 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.
- Patients with advanced fibrosis require long-term surveillance for HCC, regardless of whether they achieve an SVR12.
- Patients who do not achieve an SVR12 should continue to have regular follow-up and periodic reassessment for retreatment, especially when additional new DAA medications become available.

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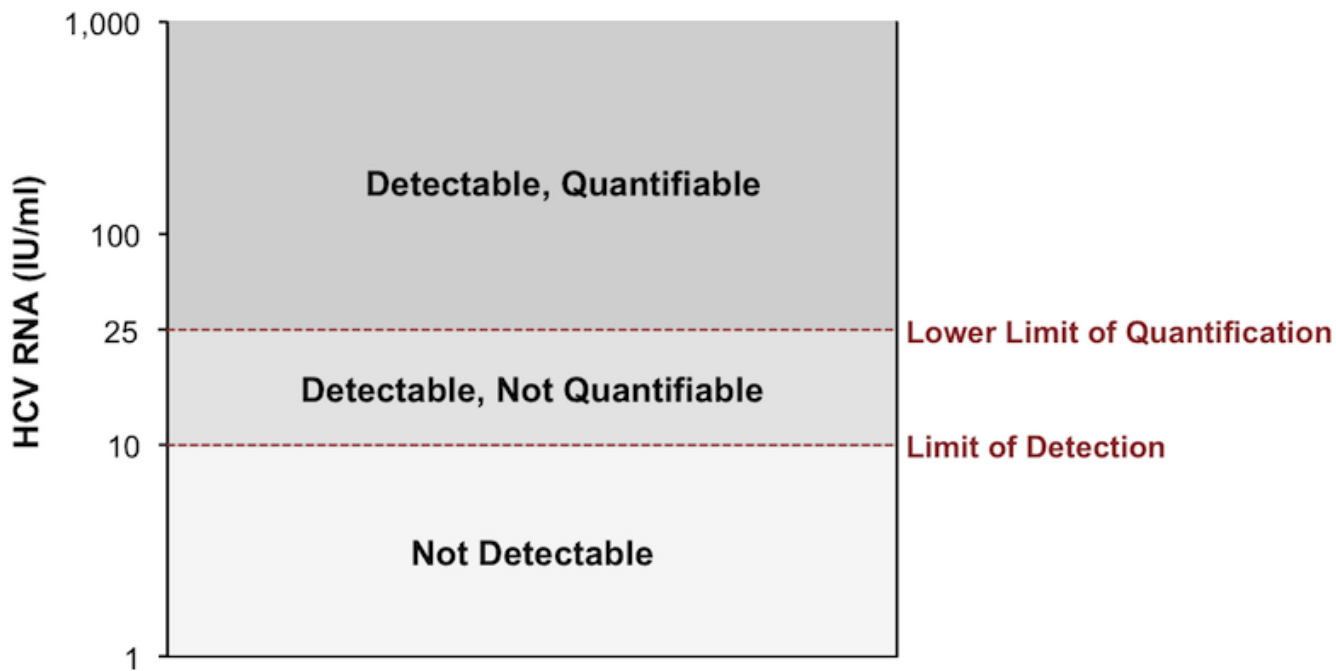
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## Figures

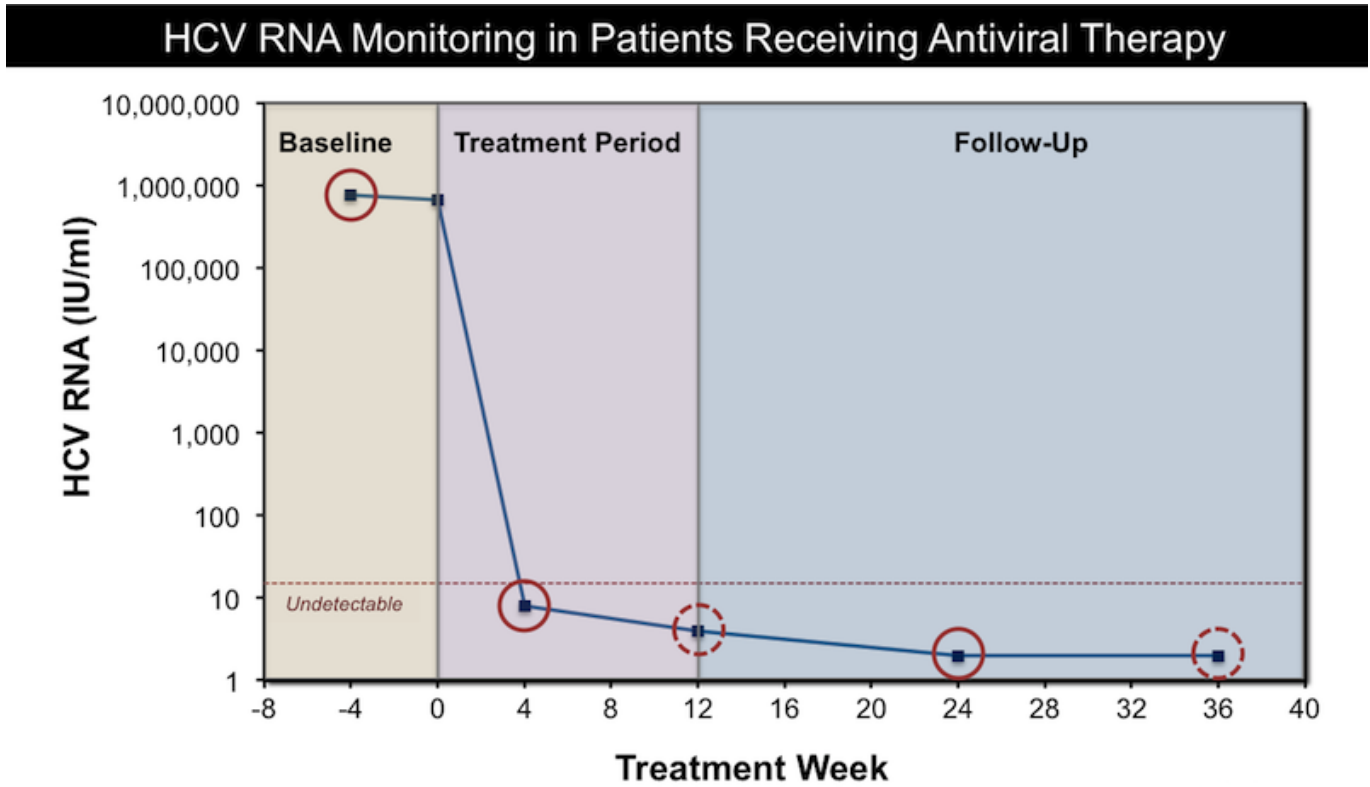
**Figure 1 HCV RNA Assay Reports**

This graphic illustrates sample cut-offs 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 HCV Antiviral Therapy

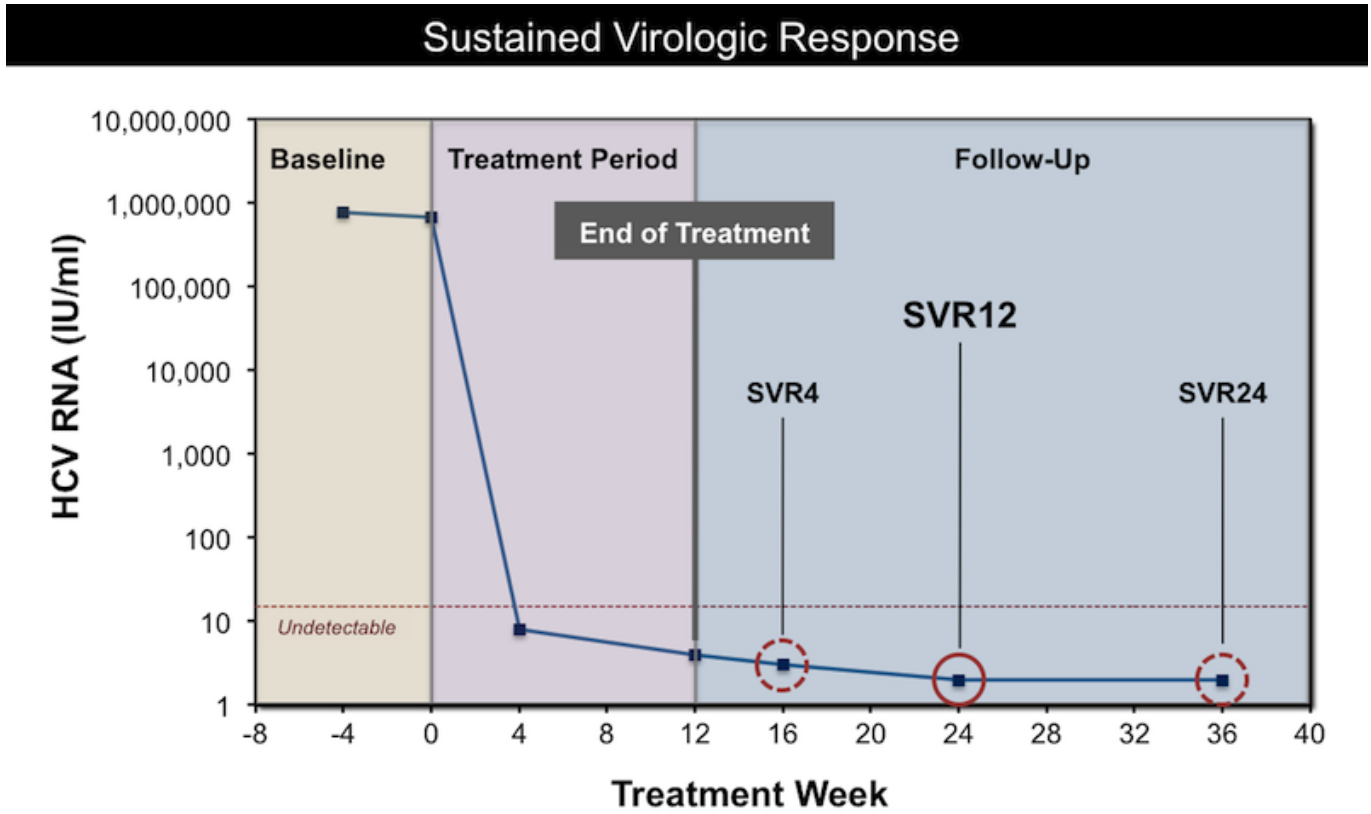
This graphic shows the AASLD/IDSA guidance for obtaining HCV RNA levels in persons treated with HCV antiviral therapy. The recommended time points are noted with solid red circles and time points to consider for HCV RNA levels are noted as dashed red circles.





**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**

Source: Bersoff-Matcha SJ, Cao KY, Jason M, et al. Hepatitis B reactivation associated with direct acting antiviral therapy for hepatitis C: a review of spontaneous post-marketing cases. Program and abstracts of the 2016 AASLD Meeting; November 11-15, 2016; Boston, Massachusetts. Abstract LB-17.

<b>Baseline HBV Parameters in Persons with HBV Flare During DAA Therapy</b>			
<b>Laboratory Study</b>	<b>Positive</b>	<b>Negative</b>	<b>Unknown</b>
HBsAg	13	4	12
HBsAb	0	3	26
HBcAb	6	0	23
HBV DNA*	9	16	4

\*Timing of HBV DNA testing not given