

When and in Whom to Initiate HCV Therapy

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure and, as such, is expected to benefit nearly all chronically infected persons. When the US Food and Drug Administration (FDA) approved the first interferon-sparing treatment for HCV infection, many patients who had previously been “warehoused” sought treatment. The infrastructure (ie, experienced practitioners, budgeted healthcare dollars, etc) did not yet exist to treat all patients immediately. Thus, the panel offered guidance for prioritizing treatment first for those with the greatest need.

Since that time, there have been opportunities to treat many of the highest-risk patients and accumulate real-world experience regarding the tolerability and safety of interferon-free HCV regimens. More importantly, from a medical standpoint, data continue to accumulate that demonstrate the many benefits, both intrahepatic and extrahepatic, that accompany HCV eradication. Therefore, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy. Accordingly, prioritization tables have been removed from this section.

Despite the strong recommendation for treatment of nearly all HCV-infected patients, pretreatment assessment of a patient’s understanding of treatment goals and provision of education about adherence and follow-up are essential. A well-established therapeutic relationship between clinician and patient remains crucial for optimal outcomes with direct-acting antiviral (DAA) therapies. Additionally, in certain settings there remain factors that impact access to medications and the ability to deliver them to patients. The descriptions of unique populations discussed in this section may help physicians make more informed treatment decisions for these groups. For additional information, see unique patient populations: [Patients With HIV/HCV Coinfection](#); [Patients With Decompensated Cirrhosis](#); [Patients Who Develop Recurrent HCV Infection Post Liver Transplantation](#); [Treatment of HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors](#); [Patients With Renal Impairment](#); [HCV During Pregnancy](#); [HCV in Children](#); [Acute HCV Infection](#); and [HCV Post Kidney Transplant](#).

Goal of Treatment

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

Recommendation for When and in Whom to Initiate Treatment

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

Treatment delay may decrease the benefit of SVR. In a report from France, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed for as long as 20 years ([Jezequel, 2015](#)). The authors noted rapid progression of fibrosis in 15% of patients during follow-up, and in patients treated successfully, long-term survival was better. Specifically, at 15 years, survival rate was 92% for those with SVR versus 82% for treatment failures and 88% for those not treated. In a Danish regional registry study, investigators modeled treatment approaches with the aim of evaluating the benefit to the region in terms of reductions in morbidity and mortality and HCV prevalence ([Øvrehus, 2015](#)). Although they note that in their situation of low HCV prevalence (0.4%) with approximately 50% undiagnosed, a policy that restricts treatment to those with Metavir fibrosis stage F3 or higher would decrease mortality from HCC and cirrhosis, the number needed to treat to halve the prevalence of the disease is lower if all eligible patients receive treatment at diagnosis.

A modeling study based on the Swiss HIV cohort study also demonstrated that waiting to treat HCV infection until Metavir fibrosis stages F3 and F4 resulted in 2- and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2 ([Zahnd, 2015](#)). A US Veterans Administration dataset analysis that used very limited endpoints of virologic response dating from the interferon-treatment era suggested that early initiation of therapy (at a fibrosis-4 [FIB-4] score of <3.25) increased the benefit attained with respect to likelihood of treatment success and mortality reduction, and ultimately decreased the number of patients needed to treat to preserve 1 life by almost 50% ([Matsuda, 2016](#)).

Considerations in Specific Populations

Despite the recommendation for treatment of nearly all patients with HCV infection, it remains important for clinicians to understand patient- and disease-related factors that place individuals at risk for HCV-related complications (liver and extrahepatic) as well as for HCV transmission. Although these groups are no longer singled out for high prioritization for treatment, it is nonetheless important that clinicians recognize the unique dimensions of HCV disease and its natural history in these populations. The discussions offered below may assist clinicians in making compelling cases for insurance coverage of treatment when necessary.

Persons With Advanced Liver Disease

For persons with advanced liver disease (Metavir stage F3 or F4), the risk of developing complications of liver disease, such as hepatic decompensation (Child-Turcotte-Pugh [CTP] class B or C [Methods Table 3] ⓘ) or HCC, is substantial and may occur in a relatively short timeframe. A large prospective study of patients with cirrhosis resulting from HCV infection examined the risk of decompensation—including HCC, ascites, jaundice, bleeding, and encephalopathy—and found that the overall annual incidence rate was 3.9% ([Sangiovanni, 2006](#)). The National Institutes of Health (NIH)-sponsored HALT-C study included a group of 220 patients with HCV-related cirrhosis who were observed for approximately 8 years. A primary outcome of death, hepatic decompensation, HCC, or an increase in CTP score ≥ 2 occurred at a rate of 7.5% per year ([Di Bisceglie, 2008](#)); ([Everson, 2006](#)). Patients with a CTP score of ≥ 7 experienced a death rate of 10% per year.

Numerous studies have demonstrated that hepatitis C therapy and the achievement of SVR in this population results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality ([Mira, 2013](#)); ([Morgan, 2013](#)); ([van der Meer, 2012](#)); ([Backus, 2011](#)); ([Dienstag, 2011](#)); ([Berenguer, 2009](#)). In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved SVR, compared with patients with similarly advanced liver fibrosis who did not achieve SVR, had a decreased need for liver transplantation (HR, 0.17; 95% CI, 0.06-0.46), decreased development of liver-related morbidity and mortality (HR, 0.15; 95% CI, 0.06-0.38), and decreased HCC (HR, 0.19; 95% CI, 0.04-0.80) ([Dienstag, 2011](#)). Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see [Monitoring Patients Who Are Starting Hepatitis C Treatment. Are on Treatment, or Have Completed Therapy](#)).

Given the clinical complexity and need for close monitoring, patients with advanced liver disease that has already decompensated (CTP class B or C [Methods Table 3] ⓘ) should be treated by physicians with experience treating HCV in conjunction with a liver transplantation center, if possible (see [Patients with Decompensated Cirrhosis](#)).

HBV/HCV Coinfection

The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally ([Tyson, 2013](#)); ([Chu, 2008](#)). Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC. HBV/HCV-coinfected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus. Thus, when treating one or both viruses with antiviral drugs, periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. Treatment of HCV infection in such cases utilizes the same genotype-specific regimens as are recommended for HCV mono-infection (see [Initial Treatment of HCV Infection](#)). HBV infection in such cases should be treated as recommended for HBV mono-infection ([Lok, 2009](#)).

Other Coexistent Liver Diseases

Persons with other chronic liver diseases who have coincident chronic HCV infection should be considered for HCV therapy given the potential for rapid liver disease progression. An interferon-free regimen is preferred for immune-mediated liver diseases, such as autoimmune hepatitis, because of the potential for interferon-related exacerbation.

Persons With Extrahepatic Manifestations of Chronic HCV Infection

Cryoglobulinemia

Chronic hepatitis C is associated with a syndrome of cryoglobulinemia, an immune complex and lymphoproliferative disorder that leads to arthralgia, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels ([Agnello, 1992](#)). Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli ([Johnson, 1993](#)). Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (>50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. Limited data with DAA therapy in the setting of vasculitis end-organ disease related to cryoglobulinemia have demonstrated responses in 20% to 90% of patients ([Comarmond, 2017](#)); ([Emery, 2017](#)). Despite this, patients with severe end-organ disease may still require treatment with plasmapheresis or rituximab ([Emery, 2017](#)).

Diabetes

The relationship between chronic hepatitis C and diabetes (most notably type 2 diabetes and insulin resistance) is complex and incompletely understood. The prevalence and incidence of diabetes is increased in the context of hepatitis C ([White, 2008](#)). In the United States, type 2 diabetes occurs more frequently in HCV-infected patients, with a >3-fold greater risk in persons older than 40 years ([Mehta, 2000](#)). The positive correlation between plasma HCV RNA load and established markers of insulin resistance confirms this relationship ([Yoneda, 2007](#)). Insulin resistance and type 2 diabetes are independent predictors of accelerated liver fibrosis progression ([Petta, 2008](#)). Patients with type 2 diabetes and insulin resistance are also at increased risk for HCC ([Hung, 2010](#)).

Successful antiviral treatment has been associated with improved markers of insulin resistance and a greatly reduced incidence of new-onset type 2 diabetes and insulin resistance in HCV-infected patients ([Arase, 2009](#)). Most recently, HCV antiviral therapy has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence rates of end-stage renal disease, ischemic stroke, and acute coronary syndrome were greatly reduced in HCV-infected patients with diabetes who received antiviral therapy compared to untreated, matched controls ([Hsu, 2014](#)). Therefore, antiviral therapy may prevent progression to diabetes in HCV-infected patients with prediabetes, and may reduce renal and cardiovascular complications in HCV-infected patients with established diabetes.

Fatigue

Fatigue is the most frequently reported symptom in patients with chronic hepatitis C, and has a major effect on quality of

Some of the best examples of HCV treatment as prevention of transmission have come from well characterized cohorts of HIV/HCV coinfecting MSM. In the Dutch acute HCV in HIV study (DAHHS) cohort, a 51% decrease in HCV incidence among MSM living with HIV was realized in just 2 years after implementing a comprehensive HCV screening and immediate treatment program ([Boerekamps, 2017](#)). Similarly, in the Swiss HIV cohort study (SHCS), a 92.5% reduction in HCV prevalence and 51% decrease in incident HCV infections was realized shortly after implementing universal screening and treatment within an MSM cohort living with HIV ([Braun, 2018](#)).

Incarcerated Persons

Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% ([Post, 2013](#)) and the rate of acute infection is approximately 1% ([Larney, 2013](#)). Screening for HCV infection is relatively uncommon in state prison systems. Treatment uptake has historically been limited, in part because of the toxic effects and long treatment duration of older interferon-based therapies as well as cost concerns ([Spaulding, 2006](#)). In particular, truncation of HCV treatment owing to release from prison has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities ([Post, 2013](#)); ([Chew, 2009](#)). Shorter HCV treatment duration with DAA regimens reduces stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of DAA regimens diminishes concerns about toxic effects. Coordinated treatment efforts within prison systems would likely rapidly decrease HCV prevalence in this at-risk population ([He, 2016](#)), although research is needed in this area.

Persons on Hemodialysis

HCV prevalence is markedly elevated in persons on hemodialysis, ranging from 2.6% to 22.9% in a large multinational study ([Fissell, 2004](#)). US studies found a similarly elevated prevalence of 7.8% to 8.9% ([Finelli, 2005](#)); ([CDC, 2001](#)). Importantly, the seroprevalence of HCV was found to increase with time on dialysis, suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients ([Fissell, 2004](#)). Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risk for persons on hemodialysis ([Jadoul, 1998](#)), but clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared to those who are uninfected ([Fabrizi, 2009](#)); ([Fabrizi, 2007](#)); ([Fabrizi, 2002](#)). HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival ([Fabrizi, 2014](#)). The increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments for HCV therapy as effective antiviral regimens that can be used in persons with advanced renal failure are now available (see [Patients with Renal Impairment](#)).

Patients Unlikely to Benefit From HCV Treatment

Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Chronic hepatitis C is associated with a wide range of comorbid conditions ([Louie, 2012](#)); ([Butt, 2011](#)). Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (<12 months) owing to nonliver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence ([Maddison, 2011](#)); ([Holmes, 2006](#)).

Pretreatment Assessment

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

An accurate assessment of fibrosis remains vital as the degree of hepatic fibrosis is one of the most robust prognostic factors used to predict HCV disease progression and clinical outcomes ([Everhart, 2010](#)). Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function ([Bruix, 2011](#)); ([Garcia-Tsao, 2007](#)). In some instances, the recommended duration of treatment is also longer.

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to 1/3 of bilobar biopsies had a difference of at least 1 stage between the lobes ([Bedossa, 2003](#)). In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Although rare, serious complications such as bleeding are well recognized.

Noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone, and each test must be interpreted carefully. A publication from the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis ([Selph, 2014](#)).

Vibration-controlled transient liver elastography is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. The measurement range, however, overlaps between stages ([Afdhal, 2015](#)); ([Castera, 2005](#)); ([Ziol, 2005](#)).

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography ([European Association for the Study of the Liver and Asociacion Latinoamericana para el Estudio del Higado, 2015](#)); ([Boursier, 2012](#)). A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making (eg, one shows cirrhosis and the other does not). The need for liver biopsy with this approach is markedly reduced.

Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can prove helpful—although neither is sensitive enough to rule out substantial fibrosis ([Chou, 2013](#)); ([Castera, 2010](#)); ([Sebastiani, 2009](#)). Biopsy should be considered for those in whom more accurate fibrosis staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).

Recommendation for Repeat Liver Disease Assessment

RECOMMENDED	RATING 
Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.	I, C

Ongoing assessment of liver disease is especially important in patients for whom therapy has been deferred. In line with evidence-driven recommendations for treatment of nearly all HCV-infected patients, several factors must be taken into consideration if treatment deferral is entertained or mandated by lack of medication access. As noted, strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Additionally, successful HCV treatment may improve or prevent extrahepatic complications, including diabetes mellitus, cardiovascular disease, renal disease, and B-cell non-Hodgkin lymphoma ([Torres, 2015](#)); ([Hsu, 2015](#)); ([Conjeevaram, 2011](#)), which are not tied to fibrosis stage ([Petta, 2016](#)); ([Allison, 2015](#)). Deferral practices based on fibrosis stage alone are inadequate and shortsighted.

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (Table 1); ([Feld, 2006](#)). Fibrosis may not progress linearly. Some individuals (often those aged >50 years) may progress slowly for many years followed by accelerated fibrosis progression. Others may never develop substantial liver fibrosis despite longstanding infection. The presence of existing fibrosis is a strong risk factor for future fibrosis progression. Fibrosis results from chronic hepatic necroinflammation; thus, a higher activity grade on liver biopsy and higher serum transaminase levels are associated with more rapid fibrosis progression ([Ghany, 2003](#)). However, even patients with a normal ALT level may develop substantial liver fibrosis over time ([Pradat, 2002](#)); ([Nutt, 2000](#)). The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

Host factors associated with more rapid fibrosis progression include male sex, longer duration of infection, and older age at the time of infection ([Poynard, 2001](#)). Many patients have concomitant nonalcoholic fatty liver disease. The presence of hepatic steatosis (with or without steatohepatitis) on liver biopsy, elevated body mass index, insulin resistance, and iron overload are associated with fibrosis progression ([Konerman, 2014](#)); ([Everhart, 2009](#)). Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression ([Feld, 2006](#)). A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression. For more counseling recommendations, see [Testing and Linkage to Care](#).

Immunosuppression leads to more rapid fibrosis progression, particularly in the settings of HIV/HCV coinfection and solid organ transplantation ([Konerman, 2014](#)); ([Berenguer, 2013](#)); ([Macias, 2009](#)). Therefore, immunocompromised patients should be treated even if they have mild liver fibrosis at presentation.

HCV RNA level does not correlate with stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with genotype 3 ([Kanwal, 2014](#)); ([Bochud, 2009](#)). Aside from coinfection with HBV or HIV, no other viral factors are consistently associated with disease progression.

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and update testing for hepatic function and markers of disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of evaluation every 6 months.

Table. Factors Associated With Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable • Fibrosis stage • Inflammation grade • Older age at time of infection • Male sex • Organ transplant Modifiable • Alcohol consumption • Nonalcoholic fatty liver disease • Obesity • Insulin resistance	• Genotype 3 • Coinfection with hepatitis B virus or HIV

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