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 people chronically infected with HCV. When the US Food and Drug Administration (FDA) approved the first interferon-sparing treatment for HCV infection, many persons with HCV infection who had previously been "warehoused" sought treatment. The infrastructure (ie, experienced practitioners, budgeted health care dollars, etc) did not yet exist to immediately treat all people living with HCV infection. 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 individuals 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 persons with chronic HCV infection, except for 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 persons with chronic HCV infection, pretreatment assessment of a person's understanding of treatment goals and provision of education about adherence and follow-up are essential. A well-established therapeutic relationship between the 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 persons with HCV infection. The descriptions of unique populations discussed in this section may help medical practitioners make more informed treatment decisions for these groups. For additional information, see unique and key patient populations: Persons With HIV/HCV Coinfection; Persons With Decompensated Cirrhosis; Persons With Hepatocellular Carcinoma; Persons Who Develop Recurrent HCV Infection Post Liver Transplantation; Treatment of HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors; Persons 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 persons with HCV infection 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 persons with acute or chronic HCV infection, except for those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Persons with a short life expectancy owing to liver disease should be managed in consultation with an expert.	I, A

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of people followed for ≥5 years (Manns, 2013); (Swain, 2010). While follow-up studies after cure using DAAs are limited, durability of SVR appears to be just as high (Huang, 2021); (Reddy, 2018); (Sarrazin, 2017). Persons in whom SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology (Coppola, 2013); (Garcia-Bengoechea, 1999) (Marcellin, 1997). Assessment of viral response, including documentation of SVR, requires use of an FDA-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of ≤25 IU/mL.

Persons who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase levels (ie, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and a reduction in the rate of liver fibrosis progression (Poynard, 2002b). Among 3,010 treatment-naive persons from 4 randomized trials who had pretreatment and post-treatment liver biopsies (separated by a mean of 20 months) and were treated with 10 different interferon-based regimens, 39% to 73% of participants who achieved SVR had improvement in liver fibrosis and necrosis (Poynard, 2002b). Additionally, cirrhosis resolved in 49% of the cases. Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons, SVR is associated with a >70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]), and a 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan, 2013); (van der Meer, 2012); (Veldt, 2007).

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of persons with HCV infection (Sise, 2016); (Fabrizi, 2013); (Landau, 2010). Persons with HCV infection and non-Hodgkin lymphoma and another lymphoproliferative disorder achieve complete or partial remission in up to 75% of cases following successful HCV therapy (Takahashi, 2012); (Gisbert, 2005); (Svoboda, 2005); (Hermine, 2002); (Mazzaro, 2002). These reductions in disease severity contribute to dramatic reductions in all-cause mortality (van der Meer, 2012); (Backus, 2011). Furthermore, people who attain SVR have a substantially improved quality of life, which spans their physical, emotional, and social health (Gerber, 2016); (Boscarino, 2015); (Younossi, 2014b); (Neary, 1999). Conversely, persons who do not achieve SVR after treatment have a continued worsening in health-related quality of life (Younossi, 2019).

Despite convincing data from observational studies demonstrating the benefit of SVR on all-cause and liver-related mortality, the lack of randomized, placebo-controlled trials of HCV DAA treatment focusing on clinical endpoints (eg, mortality, HCC, liver decompensation, etc) and reliance on surrogate endpoints (eg, HCV RNA) have led some to question the benefits of HCV treatment. In further support of the dramatic benefit of HCV

cure, a French cohort study that prospectively followed almost 10,000 people with chronic HCV infection (including 2,500 who remained untreated for HCV) for a median of 33 months demonstrated a 52% reduction in all-cause mortality and a 34% reduction in HCC (Carrat, 2019). More recently, a cohort study of 245,596 adults with chronic HCV infection using data from the Optum Clinformatics Data Mart database (2010–2021) found that DAA treatment (compared with no treatment) was independently associated with a lower risk of mortality, adverse hepatic outcomes (ie, HCC and decompensation), and nonhepatic complications (ie, diabetes, chronic kidney disease, cardiovascular disease, and nonliver cancer) (Ogawa, 2023).

Because of the many benefits associated with successful HCV treatment, clinicians should treat persons living with chronic HCV infection with antiviral therapy with the goal of achieving SVR, preferably early in the course of chronic hepatitis C before the development of severe liver disease and other complications.

Benefits of Treatment at Early Fibrosis Stages (Metavir Stage Less Than F2)

Initiating therapy in persons with lower-stage fibrosis augments the benefits of SVR. In a long-term follow-up study, 820 individuals with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed for up to 20 years (Jezequel, 2015). The 15-year survival rate was significantly better for those who experienced SVR than for those whose treatment failed or those who remained untreated (93%, 82%, and 88%, respectively). The study results support an argument for consideration of early initiation of HCV treatment. Several modeling studies also suggest a greater mortality benefit if treatment is initiated at fibrosis stages prior to F3 (Matsuda, 2016); (Zahnd, 2015); (Øvrehus, 2015).

Treatment delay may decrease the benefit of SVR. In a report from France, 820 participants with HCV infection and biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed for as long as 20 years (Jezequel, 2015). The investigators noted rapid progression of fibrosis in 15% of participants during follow-up; among participants who were treated successfully, long-term survival was improved. Specifically, at 15 years, the survival rate was 92% for those with SVR compared with 82% for persons in whom HCV treatment failed and 88% for those who were 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 the investigators note that in their situation of low HCV prevalence (0.4%) with approximately 50% undiagnosed, a policy that restricts HCV 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 HCV disease is lower if all eligible persons with HCV infection 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-times and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2 (Zahnd, 2016). 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 HCV therapy (at a FIB-4 score <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 a single life by almost 50% (Matsuda, 2016).

Considerations in Specific Populations

Despite the recommendation for treatment of nearly all persons with HCV infection, it remains important for clinicians to understand patient-related and disease-related factors that place individuals at risk for HCV-related complications (hepatic and extrahepatic) as well as for HCV transmission. Although these population groups are no longer singled out for high prioritization for treatment, it is nonetheless important for clinicians to 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 HCV treatment when necessary.

Persons With Advanced Liver Disease

For persons with advanced liver disease (Metavir stage F3 or F4), the risk of developing liver disease complications, such as hepatic decompensation (Child-Turcotte-Pugh [CTP] class B or C[Methods Table 4]) or HCC, is substantial and may occur in a relatively short time frame. A large prospective study of persons 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 US National Institutes of Health (NIH)-sponsored HALT–C study included a group of 220 participants 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). Persons 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, participants with advanced fibrosis secondary to HCV infection who achieved 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 incident HCC (HR 0.19; 95% CI 0.04–0.80) compared with participants with similarly advanced liver fibrosis who did not achieve SVR (Dienstag, 2011). Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see Monitoring Persons Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy).

Given the clinical complexity and need for close monitoring, persons with advanced liver disease that has already decompensated (CTP class B or C [Methods Table 4]) should be treated by physicians with experience treating HCV in conjunction with a liver transplantation center, if possible (see Persons with Decompensated Cirrhosis).

Persons Who Have Undergone Liver Transplantation

Among persons living with chronic HCV infection, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients within the first 6 months following liver transplantation (Neumann, 2004). By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis (Neumann, 2004); (Charlton, 1998). A small proportion of people (4% to 7%) develop an accelerated course of liver injury (cholestatic hepatitis C associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection post transplantation is associated with decreased graft survival for recipients with HCV infection compared with recipients who undergo liver transplantation for other indications (Forman, 2002).

Effective HCV therapy prior to transplantation resulting in SVR (virologic cure) prevents HCV recurrence post transplantation (Everson, 2003). In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases (Everson, 2005); (Forns, 2004). Preliminary data from a study of persons with complications of cirrhosis secondary to HCV infection who were wait-listed for liver transplantation (included individuals with MELD scores up to 14 and CTP scores up to 8) indicate that treatment with sofosbuvir and weight-based ribavirin for up to 48 weeks was well tolerated and associated with an overall SVR rate of 70% post transplantation (Curry, 2015). Posttransplant SVR was nearly universal among persons who had undetectable HCV RNA for 28 days or longer prior to transplantation.

Treatment of established HCV infection post transplantation also yields substantial improvements in patient and graft survival (Berenguer, 2008); (Picciotto, 2007). The availability of effective, interferon-free antiviral therapy has addressed the major hurdles to treating HCV recurrence post transplantation—poor tolerability and efficacy. A multicenter, open-label study evaluated the efficacy of sofosbuvir plus ribavirin to induce virologic suppression in 40 persons after liver transplantation with compensated recurrence of HCV infection. Daily

sofosbuvir plus ribavirin for 24 weeks resulted in SVR12 in 70% of these persons (Charlton, 2015a). No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to the study treatment. There were no drug-drug interactions reported between sofosbuvir and any of the concomitant immunosuppressive agents. In contrast, treatment with sofosbuvir plus ribavirin, with or without peginterferon, in 64 individuals with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 of 59% and a mortality rate of 13% (Forns, 2015). On an intent-to-treat basis, treatment was associated with clinical improvement in 57% and stable disease in 22% of participants. Given the clinical complexity (including drug-drug interactions and the need for close monitoring), patients with a liver transplant should be treated by physicians with experience in treating this population (see Persons Who Develop Recurrent HCV Infection Post Liver Transplantation).

Persons at Increased Risk for Rapidly Progressive Fibrosis and Cirrhosis

Fibrosis progression is variable across different patient populations as well as within the same individual over time. Many of the components that determine fibrosis progression and development of cirrhosis in an individual are unknown. However, certain factors, such as coinfection with HIV and/or the hepatitis B virus (HBV) and prevalent coexistent liver diseases (eg, metabolic dysfunction-associated steatohepatitis [MASH]), are well recognized contributors to accelerated fibrosis progression (see Table below).

HIV/HCV Coinfection

HIV coinfection accelerates fibrosis progression among persons with chronic HCV infection (Konerman, 2014); (Macías, 2009); (Benhamou, 1999). Although control of HIV replication and restoration of the CD4 cell count may mitigate this to some extent, the effect is not completely reversed (Lo Re, 2014); (Bräu, 2006); (Benhamou, 2001). Thus, HIV antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfected persons with 435 paired biopsies were prospectively evaluated (Konerman, 2014). Thirty-four percent of participants showed fibrosis progression of at least 1 Metavir stage at a median of 2.5 years. Importantly, 45% of participants with no fibrosis on initial biopsy had progression. Finally, a more rapid progression to death following decompensation combined with lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for HCV treatment in this population regardless of current fibrosis stage (Terrault, 2012); (Merchante, 2006); (Pineda, 2005) (see Persons with HIV/HCV Coinfection).

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 regimens as are recommended for HCV monoinfection (see Initial Treatment of HCV Infection). HBV infection in such cases should be treated as recommended for HBV monoinfection (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 persons 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 affected persons (Mazzaro, 2021);(Comarmond, 2017); (Emery, 2017). Despite this, persons 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 persons with chronic HCV infection, 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). Persons with type 2 diabetes and insulin resistance are also at increased risk for HCC (Hung, 2010).

Successful HCV 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 among persons with HCV infection (Arase, 2009). 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 persons with HCV infection and diabetes who received antiviral therapy compared to untreated, matched controls (Hsu, 2014). Therefore, antiviral therapy may prevent progression to diabetes in HCV-infected individuals with prediabetes (Butt, 2020b) and may reduce renal and cardiovascular complications in persons with HCV infection and established diabetes.

Fatigue

Fatigue is the most frequently reported symptom in persons with chronic hepatitis C and has a major effect on quality of life and activity level as evidenced by numerous measures of impaired quality of life (Foster, 1998). The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in individuals with HCV infection and cirrhosis (Poynard, 2002a). Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection (Bonkovsky, 2007). In the Virahep-C study, 401 participants with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and severity of fatigue (Sarkar, 2012). At baseline, 52% of participants reported having fatigue, which was more frequent and severe in those with cirrhosis compared with participants without cirrhosis. Achieving SVR was associated with a substantial decrease in the frequency and severity of fatigue.

An analysis of 413 participants from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and achieved SVR12 demonstrated improvement in fatigue (present in 12%) from the pretreatment level (Younossi, 2014). After achieving SVR12, participants had marked improvements in fatigue over their pretreatment scores, measured by 3 separate validated questionnaires. Additional studies support

and extend these findings beyond fatigue, with improvements in overall health-related quality of life and work productivity observed following successful HCV therapy (Gerber, 2016); (Younossi, 2016a); (Younossi, 2015b); (Younossi, 2015c); (Younossi, 2015d); (Younossi, 2015e).

Dermatologic Manifestations

The reported prevalence of HCV infection among individuals with porphyria cutanea tarda approximates 50% and occurs disproportionately in those with cirrhosis (Gisbert, 2003). The treatment of choice for active porphyria cutanea tarda is iron reduction by phlebotomy and maintenance of a mildly iron-reduced state without anemia. Although improvement of porphyria cutanea tarda during HCV treatment with interferon has frequently been described (Takikawa, 1995), there are currently insufficient data to determine whether HCV DAA therapy and achievement of SVR results in porphyria cutanea tarda improvement.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. HCV antibodies are present in 10% to 40% of persons with lichen planus but a causal link with chronic HCV infection is not established. Resolution of lichen planus has been reported with interferon-based regimens, but there have also been reports of exacerbation with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with interferon-free regimens would appear to be a more advisable approach to addressing this disorder (Gumber, 1995); (Sayiner, 2017).

Benefit of Treatment to Reduce HCV Transmission

People who have successfully achieved SVR (virologic cure) no longer transmit HCV to others. As such, successful treatment of HCV infection benefits public health. Several models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs (PWID) can decrease hepatitis C prevalence and incidence (Harris, 2016); (Martin, 2013a); (Martin, 2013b); (Durier, 2012); (Hellard, 2012). Models developed to estimate the impact of HCV testing and treatment on the burden of hepatitis C at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated (Baumann, 2024); (Wedemeyer, 2014).

There are also benefits to eradicating HCV infection between couples and among families, thus eliminating the perception that an individual might be contagious. In addition, mother-to-child transmission of HCV does not occur if the woman is not viremic, providing an additional benefit of curing a woman before she becomes pregnant (Thomas, 1998). The safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus, however, have not yet been established. Thus, HCV treatment is not currently recommended for pregnant persons.

The Society for Healthcare Epidemiology of America (SHEA) advises that health care workers who have substantial HCV viral replication (threshold 2,000 IU/mL) be restricted from performing procedures exposure-prone procedures (Henderson, 2022) and that all health care workers with confirmed HCV infection should be treated. For reasons already stated, the achievement of SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission (Henderson, 2022), the availability of effective, all-oral DAA regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

Successful treatment of persons with HCV at greatest risk for transmission represents a formidable tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. To guide implementation of hepatitis C treatment as a prevention strategy, studies are needed to: define the best candidates for treatment to stop transmission; determine additional interventions needed to maximize the benefits of HCV treatment (eg, preventing reinfection); and explore the cost-effectiveness of the strategies when used in target populations.

Persons Who Inject Drugs

Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence rate of 10% to 70% (Amon, 2008); (Nelson, 2011). IDU also accounts for the majority of new HCV infections (approximately 70%) and is the key driving force in the perpetuation of the epidemic. Given these facts and the absence of an effective vaccine against HCV, testing and linkage to care combined with treatment of HCV infection with potent DAAs has the potential to dramatically decrease HCV incidence and prevalence (Martin, 2013b). However, treatment-based strategies to prevent HCV transmission have yet to be studied, including how to integrate hepatitis C treatment with other risk-reduction strategies (eg, opiate substitution therapy, and needle and syringe exchange programs) (Martin, 2013a).

In studies of interferon-based treatments among PWID, adherence and efficacy rates are comparable to those of persons who do not use injected drugs. A meta-analysis of treatment with peginterferon, with or without ribavirin, in active or recent injection drug users showed SVR rates of 37% and 67% for genotype 1 or 4, and 2 or 3, respectively (Aspinall, 2013). With the introduction of shorter, better-tolerated, and more efficacious interferon-free therapies, these SVR rates are expected to improve. Importantly, the rate of reinfection in this population is lower (2.4/100 person-years of observation) than that of incident infection in the general population of injection drug users (6.1 to 27.2/100 person-years), although reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited (Aspinall, 2013); (Grady, 2013).

Ideally, treatment of PWID with HCV infection should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population (Dore, 2016); (Matheï, 2016); (Midgard 2016); (Murphy 2015). Regardless of the treatment setting, recent or active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which PWID have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit treatment access in this patient population (Hellard, 2014); (Aspinall, 2013); (Grebely, 2011). Indeed, combining HCV treatment with needle exchange and opioid agonist therapy programs in this population with a high prevalence of HCV has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate high return on the modest investment of addressing this often-ignored segment of the population with HCV infection (Martin, 2013b). These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from HCV therapy. Scaling up HCV treatment among PWID is necessary to positively impact the HCV epidemic in the US and globally.

Men With HIV Infection Who Have Sex With Men

Since 2000, a dramatic increase in incident HCV infections among men with HIV who have sex with men (MSM) who did not report IDU as a risk factor has been demonstrated in several US cities (Samandari, 2017); (van de Laar, 2010). Recognition and treatment of HCV infection (including acute infection) in this population may represent an important step in preventing subsequent infections (Martin, 2016). As with PWID, MSM living with HIV/HCV coinfection who engage in ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education about risk-reduction strategies. In particular, safer-sex strategies should be emphasized given the high rate of reinfection after SVR, which may approach 30% over 2 years among MSM living with HIV with acute HCV infection (Lambers, 2011).

Some of the best examples of HCV treatment as prevention of transmission have come from well characterized cohorts of MSM who are living with HIV/HCV coinfection. In the Dutch acute HCV in HIV study cohort, a 51% decrease in HCV incident infections among MSM living with HIV was realized in just 2 years after implementing a comprehensive HCV screening and immediate treatment program (Boerekamps, 2018).

Similarly, in the Swiss HIV cohort study, an 84% reduction in HCV infection prevalence and 57% decrease in incident HCV infections was realized within 2 years of implementing universal screening and treatment within a cohort of MSM living with HIV (Braun, 2021).

Incarcerated Persons

A systematic review and meta-analysis of HCV seroprevalence in US carceral facilities between 2013–2021 estimated that the HCV seroprevalence among incarcerated populations ranges from 3.0% to 34.6% (Busschots, 2022). A separate systematic review and meta-analysis demonstrated the rate of acute infection among global populations in carceral settings 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 incarceration has been cited as a major limitation to widespread, effective HCV treatment in incarceration facilities (Post, 2013); (Chew, 2009). Shorter HCV treatment duration with DAA regimens reduces stay-related barriers to HCV treatment in correctional facilities. 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. The pooled prevalence of HCV infection among persons on hemodialysis was 20.7% (range 3.6% to 28.0% by world zone) according to a large, multinational, meta-analysis involving 407 studies and 1,285,389 participants (Greeviroj, 2022). 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 individuals (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.

Persons with HCV 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 Persons with Renal Impairment).

Persons Unlikely to Benefit From HCV Treatment

People with limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment. Individuals 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 the initiation of HCV treatment in persons with a limited life expectancy (<12 months) owing to nonliver-related comorbid conditions. For these persons, 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 (Hoefs, 2011);(Everhart, 2010). Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function (Singal, 2023); (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 persons 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 (VCTE). 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).

VCTE is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in persons 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 VCTE (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 person 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 VCTE 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 among people for whom therapy has been deferred. In line with evidence-driven recommendations for the treatment of nearly all persons with HCV infection, 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 persons with HCV infection who receive treatment, regardless of baseline fibrosis. Additionally, successful HCV treatment may improve or prevent extraheptatic 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 HCV 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 people 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 persons with HCV infection have concomitant metabolic dysfunction-associated steatotic liver disease (MASLD). 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); (Macías, 2009). Therefore, immunocompromised persons should be treated even if they have mild liver fibrosis at presentation.

HCV RNA level does not correlate with the stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in persons with HCV genotype 3 infection (Kanwal, 2014); (Bochud, 2009). Aside from coinfection with HBV and/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.

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 • Metabolic dysfunction-associated steatotic liver disease • Obesity • Insulin resistance	• Genotype 3 • Coinfection with hepatitis B virus and/or HIV

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