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WHEN AND IN WHOM TO INITIATE HCV THERAPY

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure; virologic cure is expected to benefit chronically infected persons. Limitations of workforce and societal resources may limit the feasibility of treating all patients within a short period of time. Therefore, when such limitations exist, initiation of therapy should be prioritized first to those specific populations that will derive the most benefit or have the greatest impact on further HCV transmission. Others should be treated as resources allow.

Expansions and notes for abbreviations used in this section can be found in Methods Table 3 [1].

A summary of recommendations for When and in Whom to Initiate HCV Therapy is found in theBOX[2].

Goal of treatment

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 an SVR.

Rating: Class I, Level A

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of

detectable HCV RNA 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 patients followed up for 5 years or more. (Swain, 2010 [3]); (Manns, 2013 [4]) Patients in whom an SVR is achieved have HCV antibodies, but no longer have detectable HCV RNA serum, liver tissue, or mononuclear cells, and achieve substantial liver histology improvement. (Marcellin, 1997 [5]); (Coppola, 2013 [6]); (Garcia-Bengoechea, 1999 [7]) 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 or lower.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase (ie, alanine aminotransferase, aspartate aminotransferase) levels and a reduction in the rate of progression of liver fibrosis. (Poynard, 2002b [8]) Of 3010 treatment-naive HCV-infected patients with pretreatment and posttreatment biopsies from 4 randomized trials of 10 different IFN-based regimens (biopsies separated by a mean of 20 months), 39% to 73% of patients achieving an SVR had improvement in liver fibrosis and necrosis (Poynard, 2002b [8]) and cirrhosis resolved in half 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 more than 70% reduction in the risk of liver cancer (hepatocellular carcinoma) and a 90% reduction in the risk of liver-related mortality and liver transplantation. (Morgan, 2013 [9]); (van der Meer, 2012 [10]); (Veldt, 2007 [11])

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients. (Fabrizi, 2013 [12]); (Landau, 2010 [13]) HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful antiviral therapy for HCV infection. (Gisbert, 2005 [14]); (Takahashi, 2012 [15]); (Svoboda, 2005 [16]); (Mazzaro, 2002 [17]); (Hermine, 2002 [18]) These reductions in disease severity contribute to dramatic reductions in all-cause mortality. (van der Meer, 2012 [10]); (Backus, 2011 [19]) Lastly, patients achieving SVR have substantially improved quality of life, which includes physical, emotional, and social health. (Neary, 1999 [20]); (Younossi, 2013 [21]) Because of the myriad benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving an SVR, preferably early in the course of their chronic HCV infection before the development of severe liver disease and other complications.

Recommendations for when and in whom to initiate treatment

Treatment is recommended for patients with chronic HCV infection.

Rating: Class I, Level A

Treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C (Table 1[22]).

Based on available resources, treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority (Table 1[22]).

Ratings: See tables

The most immediate and high-impact benefits of SVR will be realized by populations that are at the highest risk for liver-related complications due to progressive liver disease (Metavir F3 or F4) and transplant recipients or those with clinically severe extrahepatic manifestations **(Table 1 [22])**.

Other populations at high risk for liver disease progression (Metavir F2) or with substantial extrahepatic manifestations **(Table 1 [22])** are also expected to garner appreciable benefits, although the time course for realizing these benefits may be more protracted.

SVR will also remove the risk of further transmission. Treatment of individuals at high risk to transmit HCV to others **(Table 2 [23])** may yield long-term future benefits from decreased transmission and a potential decrease in HCV disease prevalence.

When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)

Rating: Class I, Level A

Organ transplant

Rating: Class I, Level B

Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)

Rating: Class I, Level B

Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

Rating: Class IIa, Level B

High Priority for Treatment Owing to High Risk for Complications

Fibrosis (Metavir F2)

Rating: Class I, level B

HIV-1 coinfection

Rating: Class I, Level B

HBV coinfection

Rating: Class IIa, Level C

Other coexistent liver disease (eg, NASH)

Rating: Class IIa, Level C

Debilitating fatigue

Rating: Class IIa, Level B

Type 2 Diabetes mellitus (insulin resistant)

Rating: Class IIa, Level B

Porphyria cutanea tarda

Rating: Class IIb, Level C

Ratings refer to the strength and level of evidence with regard to benefits of treatment in these settings.

When and in Whom to Initiate HCV Therapy Table 2. Persons Whose Risk of HCV Transmission is High and in Whom HCV Treatment May Yield Transmission Reduction Benefits

High HCV Transmission Risk*
MSM with high-risk sexual practices
Active injection drug users
Incarcerated persons
Persons on long-term hemodialysis
Rating: Class IIa, Level C

*Patients at high risk of transmitting HCV should be counseled on ways to decrease transmission and minimize the risk of reinfection.

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 (CTP Class B or C [24] [**Methods Table 3** [1]]) or hepatocellular carcinoma 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 hepatocellular carcinoma, ascites, jaundice, bleeding, and encephalopathy, and found that the overall annual incidence rate was 3.9%. (Sangiovanni, 2006 [25]) The National Institutes of Health (NIH)-sponsored HALT–C study included a group of 220 patients with cirrhosis resulting from HCV infection who were observed for approximately 8 years. A primary outcome of death, hepatic decompensation, hepatocellular carcinoma, or advance in CTP score of 2 or higher occurred at a rate of 7.5% per year. (Everson, 2006 [26]); (Di Bisceglie, 2008 [27]) Patients with a CTP score of 7 or higher experienced a death rate of 10% per year.

Numerous studies have demonstrated that hepatitis C therapy and the achievement of an SVR in this population results in dramatic decreases in hepatic decompensation events, hepatocellular carcinoma, and liver-related mortality. (Morgan, 2013 [9]); (van der Meer, 2012 [10]); (Backus, 2011 [19]); (Dienstag, 2011 [28]); (Berenguer, 2009 [29]); (Mira, 2013 [30]) In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved an SVR, compared with patients with similarly advanced liver fibrosis who did not achieve an SVR, had a decreased need for liver transplantation (hazard ratio [HR], .17, 95% confidence interval [CI], .06–.46),

development of liver-related morbidity and mortality (HR, .15, 95% CI, .06–.38) and hepatocellular carcinoma (HR, .19, 95% CI, .04–.80). (Dienstag, 2011 [28]) Based on these considerations, prompt HCV treatment is recommended for persons with advanced liver disease unless contraindicated (eg, hypersensitivity) or substantial nonhepatic life-limiting comorbidities are present. Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see **Monitoring Section** [31]).

Given the clinical complexity and the need for close monitoring, patients with advanced liver disease that has already decompensated (CTP Class B or C [24] [**Methods Table 3** [1]]) should, in general, be treated by physicians with experience in treating HCV in conjunction with a liver transplantation center if possible.

Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the allograft occurs universally in patients in whom viral replication is ongoing at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients in the first 6 months following liver transplantation. (Neumann, 2004 [32]) By the fifth postoperative year, untreated, up to 30% have progressed to cirrhosis. (Neumann, 2004 [32]); (Charlton, 1998 [33]) A small proportion of patients (4%-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 has led to shorter period of graft survival for recipients with HCV infection than for recipients who undergo liver transplantation for other indications. (Forman, 2002 [34])

Effective antiviral therapy pre-transplantation resulting in a SVR (virologic cure) prevents HCV recurrence post-transplantation. (Everson, 2003 [35]) In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases. (Forns, 2004 [36]); (Everson, 2005 [37]) Preliminary data from a study of patients with complications of cirrhosis secondary to HCV infection who are wait-listed for liver transplantation that included patients with MELD scores up to 14 and CPT scores up to 8 found that treatment with sofosbuvir and weight-based RBV for up to 48 weeks was well tolerated and was associated with an overall post-transplant SVR of 69%. (Curry, 2013b [38]) Post-transplant SVR was near ubiquitous among patients 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 [39]); (Picciotto, 2007 [40]) The availability of effective IFN-free HCV treatment regimens has addressed the major hurdles to treating HCV recurrence post-transplantation: poor tolerability and efficacy. In a multicenter, open-label study evaluating the ability of sofosbuvir plus RBV to induce virologic suppression in 40 post–liver-transplant patients with compensated recurrence of HCV infection, daily sofosbuvir and RBV for 24 weeks achieved an SVR12 in 70%. (Charlton, 2013 [41]) No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to study treatment. There were no drug interactions with sofosbuvir and any of the concomitant immunosuppressive agents reported. In contrast, treatment with sofosbuvir plus RBV with or without PEG in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 of 57% and a mortality rate of 25%. (Forns, 2013c [42]) On an intent-to-treat basis, treatment was associated

with clinical improvement in 64% and stable disease in 11% of patients.

Persons at Greater Risk of 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 or HBV and prevalent coexistent liver diseases (eg, nonalcoholic steatohepatitis [NASH]), are well-recognized contributors to accelerated fibrosis progression. Patients with these conditions should be prioritized for hepatitis C therapy.

HIV coinfection. HIV coinfection accelerates fibrosis progression among HCV-infected persons, (Benhamou, 1999 [43]); (Macias, 2009 [44]); (Konerman, 2014 [45]) although control of HIV replication and restoration of CD4+ cell counts may mitigate this to some extent. (Benhamou, 2001 [46]); (Bräu, 2006 [47]) In the largest paired biopsy study, 282 HIV/HCV-coinfected patients with 435 paired biopsies were prospectively evaluated; (Konerman, 2014 [45]) one-third of patients showed fibrosis progression of at least 1 Metavir stage at a median of 2.5 years. Importantly, 45% of patients with no fibrosis on initial biopsy had progression. Finally, a more rapid progression to death following decompensation, combined with a lack of widespread access to liver transplantation and poor outcomes following transplantation, argue for treatment prioritization in this population, regardless of the current fibrosis stage. (Pineda, 2005 [48]); (Merchante, 2006 [49]); (Terrault, 2012 [50])

HBV coinfection and other coexistent liver diseases. The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally. (Tyson, 2013 [51]); (Chu, 2008 [52]) 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 hepatocellular carcinoma.

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, it is prudent to periodically retest HBV DNA and HCV RNA levels during and after therapy, particularly if only one of the viruses is being treated at a time. Treatment of HCV in such cases utilizes the same genotype-specific regimens as are recommended for HCV monoinfection **(see Treatment Section [53])**. HBV infections in such cases should be treated as recommended for HBV monoinfection. (Lok, 2009 [54])

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

Persons with Severe Extrahepatic Manifestations of Chronic HCV Infection

Chronic hepatitis C is associated with a syndrome of cryoglobulinemia and an immune complex and lymphoproliferative disorder that produces arthralgias, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, CNS vasculitis), and reduced complement levels. (Agnello, 1992 [55]) Because

patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (more than 50% in some series), antiviral treatment should be prioritized for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. IFN-based regimens can produce clinical remission; however, the adverse effects of IFN may mimic manifestations of cryoglobulinemia. (Saadoun, 2014 [56]) Although clinical data are not yet available, the use of IFN-free DAA regimens is an attractive alternative for these patients. Organ-threatening disease (eg, severe neuropathy, renal failure, digital ischemia), in addition to the antiviral HCV therapy, should also be treated more acutely with immunosuppressive agents or plasmapheresis to clear immune complexes.

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli. (Johnson, 1993 [57]) Successful treatment of HCV using IFN-based regimens can reverse proteinuria and the nephrotic syndrome, but usually does not fully ameliorate azotemia. (Johnson, 1994 [58]) No clinical trial data are yet available using IFN-free regimens, but the high rates of SVR (virologic cure) using antiviral therapy support their use in management of hepatitis C-related renal disease and cryoglobulinemia.

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 [59]) In the United States, type 2 diabetes occurs more frequently in HCV-infected patients with a more than 3-fold greater risk in persons over 40 years of age. (Mehta, 2000 [60]) The positive correlation between quantity of plasma HCV RNA and established markers of insulin resistance confirms this relationship. (Yoneda, 2007 [61]) Insulin resistance and type 2 diabetes are independent predictors of a more rapid progression of liver fibrosis and impaired response to IFN-based therapy. (Petta, 2008 [62]) Patients with type 2 diabetes and insulin resistance also are at increased risk for hepatocellular carcinoma. (Hung, 2010 [63])

Successful antiviral treatment has been associated with improved markers of insulin resistance and greatly reduced incidence of new onset of type 2 diabetes and insulin resistance in HCV-infected patients. (Arase, 2009 [64]) Most recently, antiviral therapy for HCV infection has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence of ESRD, ischemic stroke, and acute coronary syndrome were greatly reduced in HCV-infected patients with diabetes who received antiviral therapy compared with untreated, matched controls. (Hsu, 2014 [65]) Therefore, antiviral therapy in patients with pre-diabetes who have hepatitis C may prevent progression to diabetes and reduce renal and cardiovascular complications in hepatitis C patients with established diabetes.

Persons with Other ExtrahepaticManifestations of HCV Infection

In patients with chronic hepatitis C, fatigue is the most frequently reported symptom and has a major effect on quality of life and activity level evidenced by numerous measures of impaired quality of life. (Foster, 1998 [66]) The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis. (Poynard, 2002a [67]) 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. (Bonkovsky, 2007 [68])

In the Virahep-C study, 401 HCV patients were evaluated for fatigue prior to treatment and after therapy using validated scales assessing presence and severity of fatigue. (Sarkar, 2012 [69]) At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving an SVR was associated with a substantial decrease in frequency and severity of fatigue. A recent analysis of 413 patients who achieved an SVR12 from the NEUTRINO and FUSION trials treated with a sofosbuvir-containing regimen demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level. (Younossi, 2014 [70]) After achieving an SVR12, participants had marked improvement in fatigue over their pretreatment scores using 3 separate validated questionnaires.

The reported prevalence of HCV infection in patients with porphyria cutanea tarda approximates 50% and occurs disproportionately in those with cirrhosis. (Gisbert, 2003 [71]) The treatment of choice for active porphyria cutanea tarda is iron reduction by phlebotomy and maintenance of a mildly iron-reduced state without anemia. However, although improvement of porphyria cutanea tarda during HCV treatment with IFN has frequently been described (Takikawa, 1995 [72]), there are currently insufficient data to determine whether treating HCV infection with DAAs and achieving an SVR improves porphyria cutanea tarda.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. Antibodies to HCV are present in 10% to 40% of patients with lichen planus, but the causal link with chronic infection is not established. Resolution of lichen planus has been reported with IFN-based regimens, but there have also been reports of exacerbation of lichen planus with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with IFN-free regimens would appear to be a more advisable approach to addressing this disorder. (Gumber, 1995 [73])

Persons at High Risk of Transmitting HCV

Persons who have successfully achieved an SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence. (Martin, 2013a [74]); (Durier, 2012 [75]); (Martin, 2013b [76]); (Hellard, 2012 [77]) 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. (Wedemeyer, 2014 [78]) There are also benefits between couples and among families to eradicating HCV infection and thus eliminating the perception that an individual might be contagious. The safety and efficacy of treating pregnant women to prevent transmission to the fetus have not yet been established.

Successful treatment of HCV-infected persons 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; the additional interventions needed to maximize the benefits of HCV treatment (eg, preventing reinfection), and the cost effectiveness of the strategies when used in the target populations.

Persons who inject drugs. Injection drug use is the most common risk factor for HCV infection

in the United States and Europe with an HCV seroprevalence from 10% to 70%; (Amon, 2008 [79]); (Nelson, 2011 [80]) injection drug use also accounts for the majority of new infections (approximately 70%) and is the key driving force in 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 using potent IFN-free regimens has the potential to dramatically decrease HCV incidence and prevalence. (Martin, 2013b [76]) 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 including opiate substitution therapy and needle and syringe exchange programs. (Martin, 2013a [74])

Studies of IFN-containing treatments in persons who inject drugs have shown comparable adherence and efficacy rates to patients who do not use injection drugs. A recent meta-analysis of treatment in active or recent injection drug users with PEG with or without RBV showed SVR rates of 37% and 67% for genotype 1 or 4 and 2 or 3, respectively. (Aspinall, 2013 [81]) As shorter, better-tolerated, more-efficacious IFN-free therapies are introduced, 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 incident infection in the injection drug user population in general (6.1-27.2/100 person years); though reinfection increases with active or ongoing injection drug use (6.44/100 person years) and available data are limited in follow-up duration. (Aspinall, 2013 [81]); (Grady, 2013 [82])

Ideally, treatment of HCV-infected persons who inject drugs 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. Regardless of the treatment setting, recent and active injection drug use should not be seen as an absolute contraindication to HCV therapy. Scale up of HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the United States and globally.

HIV-infected MSM with high-risk sexual practices. Over the past decade a dramatic increase in incident HCV infections has been demonstrated in several US cities among HIV-infected MSM who did not report injection drug use as a risk factor. (van de Laar, 2010 [83]) Recognition and treatment of HCV (including acute infection) in this population may represent an important step in preventing subsequent infections. As with persons who inject drugs, HIV-infected MSM with ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education on risk reduction strategies. In particular, safer sex strategies should be emphasized given the high rates of reinfection after SVR, which may approach 30% over 2 years, in HIV-infected MSM with acute HCV infection. (Lambers, 2011 [84])

Incarcerated persons. Among incarcerated individuals, the HCV seroprevalence ranges from 30% to 60% (Post, 2013 [85]) and an acute infection rate of about 1%. (Larney, 2013 [86]) Screening for HCV is relatively uncommon in state prison systems. Treatment uptake has been limited in part because of the toxic effects and long treatment duration of older IFN-based therapies as well as concerns about cost. (Spaulding, 2006 [87]) In particular, truncation of treatment owing to release from prison during therapy has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities. (Post, 2013 [85]); (Chew, 2009 [88]) Shorter (12-week to 24-week) HCV therapies reduce duration of stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of newer, all-oral regimens diminishes toxicity

concerns. Coordinated treatment efforts within prison systems would likely rapidly decrease the prevalence of HCV infection in this at-risk population, although research is needed in this area.

Persons on hemodialysis. The prevalence of HCV infection is markedly elevated in persons on hemodialysis and ranged from 2.6 to 22.9% in a large multinational study. (Fissell, 2004 [89]) Studies in the United States found a similarly elevated prevalence of 7.8% to 8.9%. (Centers for Disease Control and Prevention, 2001 [90]); (Finelli, 2005 [91]) 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 [89]) Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risks for persons on hemodialysis, (Jadoul, 1998 [92]) 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 with persons on hemodialysis without HCV infection. (Fabrizi, 2002 [93]); (Fabrizi, 2007 [94]); (Fabrizi, 2009 [95]) HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival. (Fabrizi, 2014 [96]) The increased risk for nosocomial transmission combined with the substantial clinical impact of HCV infection in those on hemodialysis suggest that this group should also be prioritized for HCV therapy as effective antiviral regimens that can be used in advanced renal failure become available.

For all these populations, the decision to treat should be based on a favorable risk-benefit ratio taking into account the anticipated reduction in transmission(s) versus the likelihood of reinfection.

Populations Unlikely to Benefit from HCV Treatment

Patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. (Butt, 2011 [97]); (Louie, 2012 [98]) Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence. (Holmes, 2006 [99]); (Maddison, 2011 [100])

Recommendations for pretreatment assessment

An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.

Rating: Class I, Level A

An accurate assessment of fibrosis is vital in assessing the urgency for treatment. The degree of hepatic fibrosis is one of the most robust prognostic factors used to predict disease progression

and clinical outcomes. (Everhart, 2010 [101]) Those with substantial fibrosis (defined as Metavir F2 or higher) should be given priority for therapy in an effort to decrease the risk of clinical consequences such as cirrhosis, liver failure, and hepatocellular cancer. However, those with severe fibrosis (Metavir stage F3 and F4) are most in need of immediate therapy. In addition to urgency for antiviral therapy, individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function. (Garcia-Tsao, 2007 [102]); (Bruix, 2011 [103])

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to one-third of bilobar biopsies had a difference of at least 1 stage between the lobes. (Bedossa, 2003 [104]) In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Serious complications such as bleeding, although rare, 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 recent publication of 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 [105])

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. A cutoff value of 8.7 kPa correlates with Metavir F2 or higher fibrosis stage; greater than 9.5 kPa with F3; and 14.5 or higher kPa with F4 or cirrhosis. The measurement range does overlap between stages. (Ziol, 2005 [106])

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography. (Boursier, 2012 [107]) A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making. For example, 1 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 aspartate aminotransferase-to-platelet ratio index (APRI) or fibrosis-4 index (FIB-4) can help identify those most likely to have F3 or F4 fibrosis stage. (Sebastiani, 2009 [108]); (Castera, 2010 [109]); (Chou, 2013b [110]) An APRI above 2.0 or FIB-4 above 3.25 has a high specificity for advanced fibrosis or cirrhosis, although neither test is sensitive enough to rule out substantial fibrosis if values are below these thresholds. (Chou, 2013b [110]) Biopsy should be considered in 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

Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.

Rating: Class I, Level C

When therapy is deferred, it is especially important to monitor liver disease in these patients. Among individuals with less-advanced stages of fibrosis, fibrosis progression over time will help determine the urgency of subsequent antiviral therapy. Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (**Table 3** [111]). (Feld, 2006 [112]) Fibrosis may not progress linearly. Some individuals (often those who are aged 50 years or older) may progress slowly for many years followed by an acceleration of 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 and thus a higher activity grade on liver biopsy and higher serum transaminase values is associated with more rapid fibrosis progression. (Ghany, 2003 [113]) However, even patients with normal ALT levels may develop substantial liver fibrosis over time. (Pradat, 2002 [114]); (Nutt, 2000 [115])

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 [116]) Many patients have concomitant nonalcoholic fatty liver disease, and the presence of hepatic steatosis with or without steatohepatitis on liver biopsy as well as elevated body mass index and insulin resistance are associated with fibrosis progression, as is iron overload. (Konerman, 2014 [45]); (Everhart, 2009 [117]) Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression. (Feld, 2006 [112]) A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression.

Immunosuppression leads to more rapid fibrosis progression, particularly HIV coinfection and solid organ transplantation. (Macias, 2009 [44]); (Konerman, 2014 [45]); (Berenguer, 2013 [118]) Therefore, immunocompromised patients should be prioritized for antiviral therapy even if they have mild liver fibrosis at presentation.

The level of virus in the serum (HCV RNA) is not highly correlated with the stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with genotype 3 HCV infection. (Kanwal, 2014 [119]) (Bochud, 2009 [120]) Aside from coinfections 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

for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of every 6 months evaluation.

When and in Whom to Initiate HCV Therapy Table 3. Factors Associated with Accelerated Fibrosis Progression

Host	Viral
Non-Modifiable 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 HBV or HIV

Links
[1] http://www.hcvguidelines.org/node/11
[2] http://hcvguidelines.org/node/145
[3] http://hcvguidelines.org/full-report/references#swain2010
[4] http://hcvguidelines.org/full-report/references#manns2013
[5] http://hcvguidelines.org/full-report/references#marcellin1997
[6] http://hcvguidelines.org/full-report/references#coppola2013
[7] http://hcvguidelines.org/full-report/references#garcia-bengoechea1999
[8] http://hcvguidelines.org/full-report/references#poynard2002b
[9] http://hcvguidelines.org/full-report/references#morgan2013
[10] http://hcvguidelines.org/full-report/references#vandermeer2012
[11] http://hcvguidelines.org/full-report/references#veldt2007
[12] http://hcvguidelines.org/full-report/references#fabrizi2013
[13] http://hcvguidelines.org/full-report/references#landau2010
[14] http://hcvguidelines.org/full-report/references#gisbert2005
[15] http://hcvguidelines.org/full-report/references#takahashi2012
[16] http://hcvguidelines.org/full-report/references#svoboda2005

[17] http://hcvguidelines.org/full-report/references#mazzaro2002
[18] http://hcvguidelines.org/full-report/references#hermine2002
[19] http://hcvguidelines.org/full-report/references#backus2011
[20] http://hcvguidelines.org/full-report/references#neary1999
[21] http://hcvguidelines.org/full-report/references#younossi2013
[22] http://hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy#table1
[23] http://hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy#table2
[24] http://hcvguidelines.org/node/11#ctpclass
[25] http://hcvguidelines.org/full-report/references#sangiovanni2006
[26] http://hcvguidelines.org/full-report/references#everson2006
[27] http://hcvguidelines.org/full-report/references#dibisceglie2008
[28] http://hcvguidelines.org/full-report/references#dienstag2011
[29] http://hcvguidelines.org/full-report/references#berenguer2009
[30] http://hcvguidelines.org/full-report/references#mira2013
[31] http://www.hcvguidelines.org/node/92
[32] http://hcvguidelines.org/full-report/references#neumann2004
[33] http://hcvguidelines.org/full-report/references#charlton1998
[34] http://hcvguidelines.org/full-report/references#forman2002
[35] http://hcvguidelines.org/full-report/references#everson2003
[36] http://hcvguidelines.org/full-report/references#forns2004
[37] http://hcvguidelines.org/full-report/references#everson2005
[38] http://hcvguidelines.org/full-report/references#curry2013b
[39] http://hcvguidelines.org/full-report/references#berenguer2008
[40] http://hcvguidelines.org/full-report/references#picciotto2007
[41] http://hcvguidelines.org/full-report/references#charlton2013
[42] http://hcvguidelines.org/full-report/references#forns2013c
[43] http://hcvguidelines.org/full-report/references#benhamou1999
[44] http://hcvguidelines.org/full-report/references#macias2009
[45] http://hcvguidelines.org/full-report/references#konerman2014
[46] http://hcvguidelines.org/full-report/references#benhamou2001
[47] http://hcvguidelines.org/full-report/references#brau2006
[48] http://hcvguidelines.org/full-report/references#pineda2005
[49] http://hcvguidelines.org/full-report/references#merchante2006
[50] http://hcvguidelines.org/full-report/references#terrault2012
[51] http://hcvguidelines.org/full-report/references#tyson2013
[52] http://hcvguidelines.org/full-report/references#chu2008
[53] http://hcvguidelines.org/node/71
[54] http://hcvguidelines.org/full-report/references#lok2009
[55] http://hcvguidelines.org/full-report/references#agnello1992
[56] http://hcvguidelines.org/full-report/references#saadoun2014
[57] http://hcvguidelines.org/full-report/references#johnson1993
[58] http://hcvguidelines.org/full-report/references#johnson1994
[59] http://hcvguidelines.org/full-report/references#white2008
[60] http://hcvguidelines.org/full-report/references#mehta2000
[61] http://hcvguidelines.org/full-report/references#yoneda2007
[62] http://hcvguidelines.org/full-report/references#petta2008
[63] http://hcvguidelines.org/full-report/references#hung2010
[64] http://hcvguidelines.org/full-report/references#arase2009
[65] http://hcvguidelines.org/full-report/references#hsu2014
[66] http://hcvguidelines.org/full-report/references#foster1998
[67] http://hcvguidelines.org/full-report/references#poynard2002a
[68] http://hcvguidelines.org/full-report/references#bonkovsky2007

[69] http://hcvguidelines.org/full-report/references#sarkar2012
[70] http://hcvguidelines.org/full-report/references#younossi2014
[71] http://hcvguidelines.org/full-report/references#gisbert2003
[72] http://hcvguidelines.org/full-report/references#takikawa1995
[73] http://hcvguidelines.org/full-report/references#gumber1995
[74] http://hcvguidelines.org/full-report/references#martin2013a
[75] http://hcvguidelines.org/full-report/references#durier2012
[76] http://hcvguidelines.org/full-report/references#martin2013b
[77] http://hcvguidelines.org/full-report/references#hellard2012
[78] http://hcvguidelines.org/full-report/references#wedemeyer2014
[79] http://hcvguidelines.org/full-report/references#amon2008
[80] http://hcvguidelines.org/full-report/references#nelson2011
[81] http://hcvguidelines.org/full-report/references#aspinall2013
[82] http://hcvguidelines.org/full-report/references#grady2013
[83] http://hcvguidelines.org/full-report/references#vandelaar2010
[84] http://hcvguidelines.org/full-report/references#lambers2011
[85] http://hcvguidelines.org/full-report/references#post2013
[86] http://hcvguidelines.org/full-report/references#larney2013
[87] http://hcvguidelines.org/full-report/references#spaulding2006
[88] http://hcvguidelines.org/full-report/references#chew2009
[89] http://hcvguidelines.org/full-report/references#fissell2004
[90] http://hcvguidelines.org/full-report/references#cdc2001
[91] http://hcvguidelines.org/full-report/references#finelli2005
[92] http://hcvguidelines.org/full-report/references#jadoul1998
[93] http://hcvguidelines.org/full-report/references#fabrizi2002
[94] http://hcvguidelines.org/full-report/references#fabrizi2007
[95] http://hcvguidelines.org/full-report/references#fabrizi2009
[96] http://hcvguidelines.org/full-report/references#fabrizi2014
[97] http://hcvguidelines.org/full-report/references#butt2011
[98] http://hcvguidelines.org/full-report/references#louie2012
[99] http://hcvguidelines.org/full-report/references#holmes2006
[100] http://hcvguidelines.org/full-report/references#maddison2011
[101] http://hcvguidelines.org/full-report/references#everhart2010
[102] http://hcvguidelines.org/full-report/references#garcia-tsao2007
[103] http://hcvguidelines.org/full-report/references#bruix2011
[104] http://hcvguidelines.org/full-report/references#bedossa2003
[105] http://hcvguidelines.org/full-report/references#selph2014
[106] http://hcvguidelines.org/full-report/references#ziol2005
[107] http://hcvguidelines.org/full-report/references#boursier2012
[108] http://hcvguidelines.org/full-report/references#sebastiani2009
[109] http://hcvguidelines.org/full-report/references#castera2010
[110] http://hcvguidelines.org/full-report/references#chou2013b
[111] http://hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy#table3
[112] http://hcvguidelines.org/full-report/references#feld2006
[113] http://hcvguidelines.org/full-report/references#ghany2003
[114] http://hcvguidelines.org/full-report/references#pradat2002
[115] http://hcvguidelines.org/full-report/references#nutt2000
[116] http://hcvguidelines.org/full-report/references#poynard2001
[117] http://hcvguidelines.org/full-report/references#everhart2009
[118] http://hcvguidelines.org/full-report/references#berenguer2013
[119] http://hcvguidelines.org/full-report/references#kanwal2014

[120] http://hcvguidelines.org/full-report/references#bochud2009