# Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection

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## INTRODUCTION

We are at a major inflection point in our long-term effort to control the silent epidemic of chronic hepatitis C virus infection (HCV). With the advent of new medicines, the vast majority of patients with HCV infection who have access to them can be cured with treatment. Newer treatments are of shorter duration, have fewer side effects, and have higher cure rates. The goal of treatment of chronic HCV infection is a sustained virologic response (SVR), defined as absence of virus in the blood 12 weeks after the cessation of treatment. Patients achieving an SVR are considered cured, as studies show that 99 percent of patients who achieve an SVR remain free of detectable virus during long term follow up [1].

This topic will review patient selection for antiviral therapy in the context of the availability of all oral HCV regimens, as well as peginterferon and ribavirin-based regimens. The treatment of acute HCV and detailed information on the use of specific treatment regimens for chronic HCV infection are discussed separately:

- (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults".)
- (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults".)
- (See "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

## GUIDELINES

Guidelines for the diagnosis and management of HCV infection were released jointly by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in 2014, are continuously updated, and can be accessed at www.hcvguidelines.org [2]. The discussion in this topic is largely consistent with these guidelines.

Other guidelines include treatment recommendations from the European Association for the Study of the Liver (EASL) [3]. World Health Organization (WHO) also released guidelines in 2014 on screening and treatment of HCV, intended primarily for clinicians and policy-makers in low- and middle-income countries [4].

Links to these and other guidelines can be found below. (See 'Society guideline links' below.)

## BENEFITS OF TREATMENT

HCV is a serious systemic infection which causes substantial morbidity and mortality worldwide. Treatment is safe and effective, and can mitigate the serious consequences of this disease, and thus all patients, with the exception of those with life expectancy limited to <12 months due to non-related conditions, should be considered for treatment [2].

**Safety and virologic efficacy of treatment** — In locations where combination direct-acting antiviral regimens are available, these highly effective, well-tolerated, interferon-free regimens can result in sustained virologic response (SVR) in over 90 percent of HCV-infected patients [5]. Thus, achieving a cure of HCV, which results in improved survival, reduced morbidity, and higher quality of life in the vast majority of patients, has become more likely and much easier with the availability of newer agents. For this reason, all patients should be considered for treatment. (See 'Deciding when to treat' below.)

The selection of specific treatment regimens is discussed in detail elsewhere. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

**Reduction in mortality and liver-related morbidity** — The main risk of HCV infection is progression to cirrhosis and its attendant complications. Curing HCV prior to the development of decompensated cirrhosis results in decreased all-cause mortality, liver-related death, need

for liver transplantation, hepatocellular carcinoma rates, and liver-related complications [6-11]. As an example, in a systematic review that included over 30,000 patients with HCV infection, achievement of SVR was independently associated with a decreased mortality after a median follow-up of 5.4 years (adjusted hazard ratio [HR] 0.50, 95% CI 0.37-0.67) [7].

Achieving SVR through successful antiviral treatment can dramatically reduce HCV-related morbidity and mortality, even when advanced fibrosis (bridging fibrosis or cirrhosis) has already developed [7,12-15]. In a meta-analysis of 26 observational studies that assessed long-term outcomes of HCV-infected patients with advanced fibrosis after treatment, those who did not attain an SVR had a liver-related mortality rate of 2.7 percent per year. In contrast, those who did achieve an SVR had a much lower risk of liver-related mortality (relative risk [RR] 0.19; 95% CI 0.10-0.37) and were significantly less likely to develop HCC (RR 0.32) or hepatic decompensation (RR 0.13) [14]. Similarly, in a large observational study that included over 15,000 patients with HCV infection and advanced fibrosis, SVR was independently associated with reduced mortality (HR 0.26, 95% CI 0.22-0.31) [15].

**Improvement or prevention of extrahepatic complications** — Even patients with chronic HCV who have no evidence for advanced fibrosis (bridging fibrosis or cirrhosis) are still at significant risk for developing extrahepatic manifestations of HCV, some of which can be life threatening. A cure of HCV prevents the development of extrahepatic manifestations.

In a prospective, multicenter study of 321 patients with chronic HCV, 122 of them (38 percent) had at least one extrahepatic manifestation [16]. Extrahepatic manifestations that are associated with, and in most cases caused by, HCV include essential mixed cryoglobulinemia, B cell lymphoma, renal disease, membranoproliferative glomerulonephritis, neuropathy, leukocytoclastic vasculitis, and porphyria cutanea tarda. (See "Extrahepatic manifestations of hepatitis C virus infection".)

HCV is also associated with cardiovascular disease, diabetes mellitus, and insulin resistance, and successful treatment of HCV is associated with a reduced risk of these conditions [17,18]. As an example, in a retrospective study of United States veterans with HCV infections, the incidence of cardiovascular events was lower among patients who had received direct-acting antiviral (DAA) treatment compared with no treatment (16.3 versus 30.4 events per 1000 patient-years) [18]. (See "Extrahepatic manifestations of hepatitis C virus infection", section on 'Diabetes mellitus'.)

**Symptom alleviation** — Although chronic HCV infection is typically minimally symptomatic, some patients do complain of generalized symptoms, most commonly fatigue. Fatigue and overall quality of life improve in some patients who have an SVR following antiviral therapy [19-28].

As an example, a multicenter observational cohort study of 1601 patients treated with DAAs reported small but clinically meaningful improvements in fatigue, sleep, abdominal pain, and functional well-being, which were sustained at 12 months after therapy [28]. Patients with cirrhosis and Model for End-Stage Liver Disease (MELD) score ≥12 achieved the greatest benefit in functional well-being.

## EVALUATION

All patients should be considered for treatment. The urgency with which to treat chronic HCV infection and which regimen to use is based upon several factors, including the infecting genotype (in some cases), the natural history and stage of the disease, the expected efficacy of therapy, prior treatment history, potential side effects of and ability to tolerate the appropriate treatment regimen. Evaluation prior to management decisions should focus on these factors.

**HCV genotype** — Some commonly used regimens are pangenotypic (eg, they are effective and used for the same duration regardless of HCV genotype), and so knowledge of the HCV genotype has become less crucial in making treatment decisions. We do not routinely check genotype in patients who are treatment naïve and have no evidence of cirrhosis, although some insurers may require it before covering the medications. We continue to check genotype in other patient populations (eg, those with cirrhosis or prior treatment failure) among whom genotype is still relevant for treatment decisions with certain regimens. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

The HCV family of viruses is extremely heterogeneous, and at least six genotypes and numerous subtypes have been identified [29]. A variety of methods are available to identify genotypes. The commonly used method of genotyping is the line probe assay (INNO-LiPA HCV II, Siemens Healthcare Diagnostics), which provides genotype and subtype. Currently, only genotype (not subtype) is used in making clinical decisions regarding treatment. (See "Characteristics of the hepatitis C virus", section on 'Genotypes'.)

**Viral resistance testing** — In certain populations, testing for pre-existing resistance-associated substitutions (RASs) is warranted prior to the use of certain regimens. As an example, patients with genotype 3 infection who have cirrhosis or prior treatment failure should be tested for NS5A RASs if sofosbuvir-velpatasvir is being considered. The presence of RASs impacts the regimen duration and/or whether ribavirin should be added. This is discussed in detail elsewhere. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in

adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

**History of prior treatment** — Patients should be asked about any prior exposure to HCV antiviral treatment and their response, as future management decisions depend on specific aspects of the treatment history.

Patients who have never received any treatment for HCV infection are considered treatment naïve.

For patients who had failed prior treatment (ie, treatment-experienced patients), it is important to clarify what the failing regimen was, as the approach to regimen selection is different for those who failed peginterferon and ribavirin alone compared with those who failed a direct-acting antiviral regimen.

**Assessment of fibrosis stage** — The presence of advanced fibrosis (bridging fibrosis or cirrhosis) guides certain decisions regarding treatment, including optimal regimen and duration, and is a key factor that determines urgency of treatment. Fibrosis stage can be assessed indirectly through history, physical examination, laboratory tests, and other noninvasive studies (such as the FibroSure and ultrasound-based transient elastography). Although some practitioners still utilize liver biopsy for assessment of fibrosis stage, we do not routinely biopsy patients with HCV. (See 'Role of liver biopsy' below.)

**History, physical, and basic laboratory tests** — The history should include questions regarding nonspecific symptoms (eg, anorexia, weight loss, weakness) or specific complications (eg, a history of jaundice, ascites, hematemesis, and mental status changes) that could suggest underlying cirrhosis. History should also evaluate factors associated with accelerated disease progression, including alcohol use, metabolic complications associated with fatty liver, and menopausal status (in females). (See "Clinical manifestations and natural history of chronic hepatitis C virus infection", section on 'Factors associated with disease progression'.)

A directed physical examination should assess for signs consistent with cirrhosis (eg, spider angiomata, palmar erythema, gynecomastia, firm liver on palpation, and splenomegaly). However, clinicians should be aware that absence of any of these findings does not rule out the possibility of underlying cirrhosis. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Important laboratory testing includes a complete blood count, serum aminotransferase activity and measures of synthetic function (bilirubin, prothrombin time, and albumin). Common laboratory abnormalities in cirrhosis include elevated serum bilirubin, abnormal

aminotransferases, elevated alkaline phosphatase, a prolonged prothrombin time/elevated international normalized ratio (INR), low albumin, and thrombocytopenia. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Laboratory findings'.)

**Noninvasive tests for fibrosis** — Various noninvasive markers of liver fibrosis can be very helpful to assess to the degree of liver fibrosis present. Some of these, such as the AST/ALT ratio, the AST to platelet ratio index (APRI) (calculator 1), and the FIB-4 (calculator 2), can be calculated from results of routine laboratory tests. Other specialized noninvasive diagnostic tests include the FibroSure and ultrasound-based transient elastography. Potential benefits of these noninvasive markers are ease of administration and lower cost compared with liver biopsy. Also, they can be repeated over time to monitor progress of liver disease and may predict clinical outcomes better than liver biopsy [30]. A detailed discussion on noninvasive tests to assess hepatic fibrosis is found elsewhere. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations".)

Of note, knowledge of the presence of bridging fibrosis and cirrhosis is also important for assessing prognosis and indications for additional surveillance. As an example, patients with advanced fibrosis should undergo routine screening for hepatocellular carcinoma, and patients with established cirrhosis should be monitored for the development of complications. This includes evaluating for clinical signs of liver failure (including ascites, hepatic encephalopathy, or bleeding from gastroesophageal varices) as well as laboratory testing to identify hepatic dysfunction (hypoalbuminemia, hyperbilirubinemia, or hypoprothrombinemia). (See "Surveillance for hepatocellular carcinoma in adults" and "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

**Role of liver biopsy** — We do not routinely perform liver biopsy in patients with chronic HCV infection. Liver fibrosis has historically been the gold standard for assessing the liver stage and thus predicting the prognosis of the disease. However, it is not a reliable gold standard, noninvasive markers of fibrosis (such as the FibroSure test and ultrasound-based transient elastography) are becoming more widely available, and as treatment for HCV continues to become less toxic and more effective, there is less need to precisely stage the patient's liver disease through biopsy.

Limitations of liver biopsy include [31,32]:

- Sampling error, which leads to misinterpretation in 10 to 15 percent of patients. Thus, the diagnosis of cirrhosis can be missed, leading to false assurance for the clinician and the patient.

- Significant interobserver variability in the interpretation of liver biopsies.

- Expense and risk of complications, given its invasive nature.

However, unlike noninvasive markers of fibrosis, a liver biopsy can establish the presence of concomitant diseases (such as hemochromatosis, alcoholic hepatitis, nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, and hepatic sarcoidosis) and the degree to which these conditions contribute to the patient's liver disease.

We base our decision to treat HCV on history, physical exam, laboratory tests, and noninvasive assessment of liver fibrosis (such as FibroSure or ultrasound-based transient elastography). We perform liver biopsy only in select patients with HCV infection, including those with a liver transplant, suspected autoimmune liver disease, drug induced liver disease, and in those for whom the diagnosis is in doubt.

Another proposed strategy, if resources are available, is to use two types of noninvasive tests for fibrosis (ie, biomarker test and transient liver elastography) and reserve biopsy for those patients who have discordant results on these two tests [2,33].

**Evaluation for conditions that might affect therapy** — Prior to initiating antiviral therapy, a thorough evaluation for other types of liver disease should be obtained, and other medical conditions should be investigated as they may have a bearing on the treatment plan, depending on the planned regimen. The specific workup depends on the planned regimen.

In all patients, the following should be assessed:

- Renal function, with blood urea nitrogen (BUN), creatinine, and urinalysis (see 'Kidney disease' below)
- Complete blood count and differential (see 'Contraindications/precautions with anti-HCV agents' below)
- Concurrent alcohol or drug use (see 'Active drug use' below and 'Ongoing alcohol use' below)
- Extrahepatic manifestations of HCV infection (see 'Extrahepatic manifestations of HCV infection' below and "Extrahepatic manifestations of hepatitis C virus infection")
- HIV coinfection (see 'HIV coinfection' below)
- HBV coinfection (with HBV surface antigen [sAg], surface antibody [sAb], and core antibody [cAb] followed by HBV DNA testing for those who have a positive sAg or who have only cAb positive; HBV DNA testing is not necessary for those who have a positive sAb alone or positive sAb and cAb) (see 'HBV coinfection' below)

- Presence of severe co-morbidity (eg, cardiac disease) (see 'Contraindications/precautions with anti-HCV agents' below)
- Potential for drug interactions (see 'Contraindications/precautions with anti-HCV agents' below)
- Pregnancy test (for females of childbearing potential)

In patients whose regimen is to contain ribavirin, the following should be assessed:

- Contraceptive plan in patients of childbearing potential (see 'Ribavirin' below)

## DECIDING WHEN TO TREAT

As above, a cure of HCV results in improved survival, reduced morbidity, and higher quality of life in the vast majority of patients (see 'Benefits of treatment' above). Thus, all patients with virologic evidence of chronic HCV infection (ie, detectable HCV viral level over a six-month period), except for those with limited life expectancy (<12 months) due to non-related conditions, should be considered for treatment. Candidacy for treatment is limited mainly by the presence of contraindications to the available regimens. (See 'Contraindications/precautions with anti-HCV agents' below.)

Before the introduction of direct-acting antivirals (DAAs), antiviral treatment of HCV infection with peginterferon and ribavirin was variably effective for different patient populations, was associated with numerous contraindications and adverse effects, and in some cases required prolonged duration of therapy. In order to optimize administration of a difficult treatment regimen, management decisions focused on identifying patients who would be most likely to respond to therapy or who were most likely to suffer liver-related morbidity and mortality without successful treatment. With the availability of DAAs, treatment regimens that achieve very high SVR rates, have more favorable adverse effect profiles and greater ease of administration than earlier regimens, and have relatively short treatment durations are possible for many patients. Thus, curative, all-oral regimens are possible for the vast majority of patients who have access to these agents. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection".)

Nevertheless, if financial resources preclude more widespread delivery of antiviral therapy, it can be prioritized for those who would be most likely to benefit in the near-term, as recommended by the joint guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) [2]. The highest priority

patients include those who are at highest risk of substantial morbidity and mortality from untreated HCV infection, namely those with advanced fibrosis or compensated fibrosis, transplant recipients, and those with severe extrahepatic manifestations of HCV infection. High priority patients include those at high risk of fibrosis progression, such as patients with substantial fibrosis (eg, Metavir stage F2), HIV coinfection, coexisting liver disease, and diabetes mellitus. Symptomatic HCV infection (eg, with debilitating fatigue or other less severe extrahepatic manifestations) and the potential for transmission of HCV are additional considerations that might prioritize treatment in a given patient.

For patients who do defer antiviral treatment, liver wellness (eg, alcohol abstinence, maintaining a healthy weight, control of diabetes mellitus) and close monitoring of clinical status are warranted.

## CONTRAINDICATIONS/PRECAUTIONS WITH ANTI-HCV AGENTS

Direct-acting antivirals are well tolerated by the vast majority of patients, although some comorbidities preclude certain regimens. Additional precautions should be taken into account if the addition of ribavirin to the regimen is warranted.

For those who do not have access to interferon-free regimens, the adverse effects associated with interferon should be accounted for when determining candidacy for and timing of antiviral treatment. In some patients, interferon treatment is contraindicated due to the risk of side effects, whereas in others, treatment should be undertaken with extreme caution.

**Direct-acting antivirals** — There are generally few contraindications or precautions with the use of direct-acting antiviral agents.

The main precaution with direct-acting antivirals are drug interactions; these are more significant for regimens that contain HCV protease inhibitors (eg, simeprevir, paritaprevir, grazoprevir) but affect use of all direct-acting antiviral agents. Potential drug interactions with specific regimens are discussed in detail elsewhere and can be evaluated through the Lexicomp drug interactions program included with UpToDate. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection".)

Additionally, for patients with decompensated cirrhosis (Child-Pugh classes B and C), pibrentasvir-glecaprevir, sofosbuvir-velpatasvir-voxilaprevir, elbasvir-grazoprevir, simeprevir, and ombitasvir-paritaprevir-ritonavir-based regimens should be avoided. The US Food and Drug Administration has reiterated this caution and highlighted cases of worsening liver function or

liver failure in patients with advanced liver disease who were treated with one of these agents; in some cases, the severity of the underlying liver disease was not initially recognized [34].

Some of these patients were not initially known to have decompensated cirrhosis. Thus, some experts, including some UpToDate contributors, perform endoscopy in patients with cirrhosis if they have platelet count <150,000/microL or a transient elastography score >20 kPa prior to antiviral treatment and avoid protease inhibitor-containing regimens in those with evidence of any esophageal varices. (See "Direct-acting antivirals for the treatment of hepatitis C virus infection", section on 'Protease inhibitors and hepatic decompensation'.)

**Ribavirin** — The main adverse effect of ribavirin is hemolysis. This effect is generally only clinically relevant among patients with pre-existing anemia (eg, hemoglobin <12 g/dL for males and <11 g/dL for females), renal insufficiency (estimated glomerular filtration rate <60 mL/min per 1.73 $m^2$), and coronary artery disease, and so ribavirin should be used with caution in such patients [35]. In addition, ribavirin is excreted renally and may accumulate to toxic levels in patients with impaired renal function or on hemodialysis, which thus warrants significant dose reductions and careful monitoring when used in such patients. (See 'Kidney disease' below.)

Because of the risk of hemolysis, ribavirin should also be only used with caution, dose reduction, and frequent monitoring in patients with hemoglobinopathies.

Additionally, ribavirin is contraindicated in pregnant females because of significant **teratogenic and embryocidal effects**. It also should not be used in individuals of childbearing potential (males and females) who cannot or will not use contraception during treatment and for six (for males) or nine (for females) months afterwards.

Ribavirin generally does not have many interactions with other agents. Its use is contraindicated with didanosine; however, this HIV antiretroviral is rarely used anymore.

## SPECIAL SITUATIONS

Certain clinical characteristics should be taken into account when making decisions about antiviral treatment for HCV infection.

**Acute HCV** — For patients who are diagnosed with acute HCV, there is still the possibility that they might clear the virus spontaneously, which would obviate the need for treatment. This is discussed in greater detail elsewhere. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults".)

**Mild liver disease** — Even among patients with mild liver disease, successful therapy of chronic HCV is associated with improved mortality [36]. Thus, antiviral therapy should be offered to such patients. (See 'Benefits of treatment' above.)

If DAAs are available and the patient is willing and able to proceed with treatment, there is no reason to delay therapy unless the patient has contraindications to the regimen (see 'Contraindications/precautions with anti-HCV agents' above). If financial resources are constrained, it is reasonable to prioritize treatment for those who have a higher risk of fibrosis progression (eg, those with Metavir stage F2 fibrosis, HIV coinfection, coexisting liver disease, diabetes mellitus, and debilitating fatigue), significant symptoms associated with HCV infection, and high potential for transmission of HCV infection [2].

However, if interferon-free regimens are not yet available for the patient, but are expected to be in the near future, we favor deferring therapy until that time, as these newer treatments have higher SVR rates and fewer adverse effects. Patients who do not have clinical or laboratory evidence of advanced fibrosis, with noninvasive tests and/or liver biopsy suggesting mild fibrosis and minimal necroinflammatory changes are likely to have slow progression of liver disease [14,37] while awaiting new therapies. Patient preference should be an important factor in the decision to treat such patients now or wait.

**Bridging fibrosis and compensated cirrhosis** — As above, patients with advanced fibrosis (bridging fibrosis and compensated cirrhosis) have a substantial reduction in morbidity and mortality following cure of HCV with successful therapy, and thus they stand to benefit the most from the newer antiviral agents for HCV (see 'Reduction in mortality and liver-related morbidity' above). However, certain patients with cirrhosis (particularly those who have failed previous treatment with interferon and ribavirin) appear to have lower SVR rates with certain regimens compared with those without cirrhosis [38-40]. Thus, the presence of underlying cirrhosis affects the selection of the specific treatment regimen. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

If DAAs are available and the patient is willing and able to proceed with treatment, there is no reason to delay therapy unless the patient has contraindications to the regimen. (See 'Contraindications/precautions with anti-HCV agents' above.)

**Decompensated cirrhosis** — Decompensated cirrhosis refers to a history of or the presence of, ascites, hepatic encephalopathy or jaundice ( table 1). In addition, marked abnormalities in serum albumin, bilirubin, and prothrombin times are features of decompensation.

Hepatologists can consider antiviral therapy with direct-acting antiviral (DAA) combinations in patients with decompensated liver disease. Successful HCV treatment in such patients has been associated with improved survival, but interferon-based regimens were also associated with substantial side effects and drop-outs [41,42]. Subsequent studies have demonstrated promising results with the use of all-oral DAA regimens in this population [43-46]. Treatment has also been shown to be effective in patients with liver cancer awaiting liver transplantation [45].

Of note, certain direct-acting antiviral regimens should **not** be used in patients with evidence of liver decompensation. (See 'Contraindications/precautions with anti-HCV agents' above and "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'Decompensated cirrhosis (Child-Pugh class B or C)' and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults", section on 'Patients with decompensated cirrhosis'.)

**Recurrence after liver transplantation** — Recurrence of HCV occurs in more than 95 percent of patients after liver transplantation. Disease progression in this setting is more rapid, and complications are more frequent than in immunocompetent patients with HCV infection [14]. Disease progression correlates with HCV RNA levels at the time of transplantation, the age of the organ donor, and the degree of immunosuppression in the post-transplant period. Studies are demonstrating high SVR rates with DAA regimens in transplant populations [43,44]. All patients with post-liver transplant recurrence of HCV should be considered for treatment with new DAA regimens. (See "Hepatitis C virus infection in liver transplant candidates and recipients", section on 'Post-transplant antiviral therapy'.)

**Hepatocellular carcinoma** — For patients with chronic HCV and hepatocellular carcinoma (HCC), whether the patient is being considered for liver transplantation is a major factor that informs HCV treatment decisions. The approach to antiviral therapy in patients who are candidates for liver transplantation is discussed elsewhere (see "Hepatitis C virus infection in liver transplant candidates and recipients", section on 'Deciding to treat before or after transplant'). For patients with HCC who are not candidates for liver transplantation, we suggest antiviral therapy with standard DAA combination regimens. Generally, we administer antiviral therapy after completion of treatment of the HCC with modalities such as radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE). Many oncologists prefer to complete antiviral therapy prior to administering systemic chemotherapy, such as sorafenib or other chemotherapeutic agents. In patients with far-advanced HCC or advanced decompensated cirrhosis, palliative care is often the only option. In these circumstances, when

no HCC treatment is planned, antiviral therapy is unlikely to benefit the patient and should not be administered.

As in other populations, successful treatment of HCV can result in reduced morbidity and mortality in patients with HCC [47,48]. In a meta-analysis of observational studies of patients who underwent resection or loco-regional therapy for HCV-associated HCC, SVR following interferon-based therapy was associated with improved overall survival and progression-free survival [47]. Successful DAA-based therapy was similarly associated with survival in a retrospective study of 800 patients (hazard ratio 0.54, 95% CI 0.33-0.90) [49]. Since clinical trials of HCV therapy have largely excluded patients with HCC, most data on efficacy of DAA-based therapy in this population are from retrospective studies, which generally suggest a lower SVR rate than in the general population [50-53], although the mechanism for this is not well understood. In a systematic review of 49 studies, the pooled SVR rate was 89.6 percent among 3300 patients with HCC compared with 93.3 percent among 35,700 patients without HCC [53]. SVR rates were especially low among patients who had active or residual HCC (73 percent compared with 93 percent among those with inactive or ablated HCC).

Although some observational studies have suggested an unexpectedly high risk of HCC recurrence following DAA therapy [54-57], other large studies have not [58-61]. In a meta-analysis of 17 studies evaluating HCC recurrence following HCV treatment, the rate of recurrence was not different with DAA-based regimens compared with interferon-based regimens [62]. Given that there is no clear, consistent evidence supporting an increased rate of HCC recurrence following DAA therapy, this should not be a reason to withhold antiviral therapy in patients with HCC.

**Extrahepatic manifestations of HCV infection** — Successful eradication of the virus results in improvement in extrahepatic manifestations in most patients, thus those who have serious complications of HCV infection, such as essential mixed cryoglobulinemia and glomerulonephritis should be prioritized for treatment. However, among patients with severe vasculitic manifestations (eg, glomerulonephritis, cutaneous ulcers, and progressive neuropathy), immunosuppressive therapy may also be warranted, and potential drug interactions should be evaluated. (See "Treatment of chronic hepatitis C infection in adults with kidney function impairment", section on 'Timing of treatment' and "Mixed cryoglobulinemia syndrome: Treatment and prognosis", section on 'Hepatitis C infection'.)

In addition, some extrahepatic manifestations warrant additional management beyond antiviral therapy, such as management of iron overload in porphyria cutanea tarda. (See "Extrahepatic manifestations of hepatitis C virus infection" and "Mixed cryoglobulinemia syndrome: Treatment

and prognosis" and "Extrahepatic manifestations of hepatitis C virus infection", section on 'Porphyria cutanea tarda'.)

**Kidney disease** — Renal diseases commonly associated with HCV are mixed cryoglobulinemia, membranoproliferative glomerulonephritis (MPGN), membranous nephropathy, nephrotic syndrome, and polyarteritis nodosa. Achieving SVR has a beneficial effect on the kidney disease in most, but not all, patients. Patient and regimen selection for antiviral therapy in the setting of renal impairment is discussed in detail elsewhere. (See "Treatment of chronic hepatitis C infection in adults with kidney function impairment".)

**HIV coinfection** — Patients with HIV co-infection have an accelerated rate of progression of HCV and thus should be prioritized for treatment. Although studies with peginterferon and ribavirin therapy suggested that HIV/HCV co-infected patients had lower response rates compared with HCV monoinfected patients, SVR rates with regimens that contain a direct-acting antiviral appear to be comparable and result in high rates of cure in co-infected patients. The potential for drug interactions with antiretrovirals is a major consideration when selecting HCV antiviral regimens for co-infected patients. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults", section on 'HIV-HCV coinfection' and "Treatment of chronic hepatitis C virus infection in the patient with HIV", section on 'Potential drug interactions with ART'.)

**HBV coinfection** — Because reactivation of HBV infection, in some cases with fulminant hepatitis, has been reported in patients receiving DAA therapy [63-65], all patients should undergo testing for HBV coinfection prior to initiation of therapy. (See 'Evaluation for conditions that might affect therapy' above.)

In a systematic review of observational studies that evaluated patients with HBV infection undergoing HCV antiviral therapy, HBV reactivation (HBV DNA increase of ≥2 log or to >100 international units/mL if initially undetectable) was reported in 24 percent of 242 patients with chronic HBV infection (positive HBV surface antigen [HBsAg]), and 9 percent experienced HBV-related hepatitis. Among 1379 patients with resolved HBV infection (positive HBV core antibody [HBcAb] but negative HBsAg), reactivation occurred in 1.4 percent, and none had reactivation-associated hepatitis. In another study of 29 cases of HBV reactivation, two were fatal and one patient required liver transplant, reactivation occurred at an average of 53 days into DAA treatment, and it was not associated with a particular HCV genotype or DAA regimen [63,66].

Prior to initiating DAA therapy, antiviral therapy for HBV should be initiated for coinfected patients who meet criteria for HBV treatment. Otherwise, those who have evidence of HBV infection (ie, with positive HBcAb and negative HBV surface antibody [HBsAb]) should be

monitored for HBV reactivation during HCV treatment. (See "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy' and "Overview of the management of chronic hepatitis C virus infection", section on 'Monitoring for toxicity'.)

The mechanism behind HBV reactivation with HCV treatment is unknown. One theory is that HCV infection results in a host innate immune response that impacts control of HBV replication and is interrupted with DAA therapy [67].

**Active drug use** — We recommend antiviral therapy for chronic HCV infection regardless of active drug use, as long as patients are amenable to treatment [2]. Barriers to HCV treatment among individuals who are actively using drugs have included concerns about adherence, comorbid psychiatric conditions or unstable social situations, and the risk of reinfection [68,69].

Nevertheless, successful treatment of patients with injection drug use (IDU) has been reported in multiple studies, even in the setting of recent or active drug use and opioid substitution therapy (eg, methadone or buprenorphine) [70-77]. As an example, in a systematic review, the pooled SVR rates were 90 percent among 1700 patients on opioid substitution therapy and 88 percent among 540 patients who were actively using injection drugs [75].

Studies that have evaluated for reinfection following successful treatment in patients with IDU are limited in size and duration of follow-up, but do not suggest a high rate of reinfection [71,78].

Furthermore, an additional benefit of achieving SVR in an individual with active IDU is a decreased risk HCV transmission, which has the potential for positive public health consequences.

Antiviral treatment for chronic HCV infection among patients with active drug use is the same as in the general population. Additionally, an important adjunct to antiviral treatment is continued support from substance use disorder and psychiatric counseling services. (See "Opioid use disorder: Pharmacologic management" and "Substance use disorders: Clinical assessment".)

**Ongoing alcohol use** — Alcohol is an important cofactor in HCV disease progression, and the amount of alcohol that is safe during treatment is unknown. While a history of alcohol abuse is not an absolute contraindication to treatment, continued alcohol use accelerates disease progression and increases the risk of HCC [79,80]. Patients with chronic HCV infection should be encouraged to abstain from alcohol. There are limited data on the effectiveness of direct-acting antiviral-based regimens in patients who drink alcohol.

In patients who continue to drink alcohol, efforts to treat alcohol use disorder should accompany antiviral treatment. (See "Hepatitis C and alcohol" and "Alcohol use disorder: Psychosocial management".)

**Older adults** — We follow the same general principles in deciding which older patients with HCV to treat and when as we do for the general population. (See 'Deciding when to treat' above.)

Several retrospective studies have suggested that combination DAA regimens are highly effective in older adults, as in the general population [81-85]. However, older adults (eg, those >65 years old) were more likely to have significant drug interactions with DAA regimens and, in some studies, had a higher likelihood of adverse effects.

This is in contrast to prior studies of peginterferon and ribavirin for HCV infection, which had revealed lower SVR rates in older patients [86].

**Children** — The management of children with HCV infection is discussed elsewhere. (See "Hepatitis C virus infection in children", section on 'Management of chronic hepatitis C virus'.)

## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis C virus infection" and "Society guideline links: Hepatitis C infection in solid organ transplant candidates and recipients".)

## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5$^{th}$ to 6$^{th}$ grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10$^{th}$ to 12$^{th}$ grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Hepatitis C (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis C (Beyond the Basics)")

## SUMMARY AND RECOMMENDATIONS

- **Benefits of therapy** – Patients who achieve a sustained virologic response (SVR) following antiviral therapy (negative hepatitis C virus [HCV] RNA 12 weeks later) are considered cured, as studies show that 99 percent of such patients remain free of detectable virus during long term follow up. Curing HCV prior to the development of decompensated cirrhosis results in decreased all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications. A cure of HCV also prevents the development of extrahepatic manifestations, which can be life threatening. (See 'Benefits of treatment' above.)
- **Considerations prior to treatment** – We recommend direct-acting antiviral therapy for all patients with chronic HCV infection (**Grade 1A**). The urgency with which to treat chronic HCV infection and which regimen to use is based upon several factors, including the infecting genotype (in some cases), natural history and stage of the disease, availability of all oral antiviral therapies, expected efficacy of therapy, prior treatment history, and potential side effects of the appropriate treatment regimen. Evaluation prior to management decisions should focus on these factors. (See 'Evaluation' above.)
- **Assessment of liver disease** – A focused clinical exam, routine laboratory tests, and noninvasive markers of fibrosis (such as the FibroSure test or ultrasound-based transient elastography) can be used to assess the severity of liver disease. We generally limit liver biopsy to select HCV-infected patients, including those with a liver transplant or other causes of liver disease (such as autoimmune or drug induced liver disease). (See 'Assessment of fibrosis stage' above and "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations".)
- **Limited genotype testing** – With pangenotypic regimens, HCV genotype determination is less crucial to treatment decisions. We check genotype in patients with cirrhosis and prior treatment failure but do not routinely check it in other treatment-naïve patients unless required by payers. (See 'HCV genotype' above.)

- **Other evaluation** – Assessing for renal function, substance use, extrahepatic manifestations, HIV or HBV coinfection, pregnancy, and potential for drug interactions can help identify other patient factors that may impact treatment decisions. (See 'Evaluation for conditions that might affect therapy' above and 'Special situations' above.)

- **Priority populations for treatment** – In resource-constrained settings, it may be reasonable to prioritize treatment for patients who are expected to benefit the most in the short term. These include those with advanced fibrosis or cirrhosis, transplant consideration, severe extrahepatic manifestations, high risk for fibrosis progression, symptomatic disease, and high potential for transmission. (See 'Deciding when to treat' above and 'Bridging fibrosis and compensated cirrhosis' above and 'Extrahepatic manifestations of HCV infection' above and 'HIV coinfection' above.)

- **Treating patients with active substance use** – Active substance use is not a contraindication to antiviral treatment for patients who are willing to undergo treatment and monitoring. Ongoing support from drug/alcohol abuse and psychiatric counseling services is an important adjunct to antiviral therapy. (See 'Active drug use' above and 'Ongoing alcohol use' above.)



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Topic 15832 Version 71.0

## GRAPHICS

### Child-Pugh classification of severity of cirrhosis

| Parameter | Points assigned | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | Absent | Slight | Moderate |
| Bilirubin | <2 mg/dL (<34.2 micromol/L) | 2 to 3 mg/dL (34.2 to 51.3 micromol/L) | >3 mg/dL (>51.3 micromol/L) |
| Albumin | >3.5 g/dL (35 g/L) | 2.8 to 3.5 g/dL (28 to 35 g/L) | <2.8 g/dL (<28 g/L) |
| Prothrombin time (seconds over control) or | <4 | 4 to 6 | >6 |
| INR | <1.7 | 1.7 to 2.3 | >2.3 |
| Encephalopathy | None | Grade 1 to 2 | Grade 3 to 4 |

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

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Conflict of interest policy

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