

## Testing, Evaluation, and Monitoring of Hepatitis C


The following pages address testing, evaluation, and monitoring of patients with HCV before, during and after antiviral therapy.

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# HCV Testing and Linkage to Care

## One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING 
One-time hepatitis C testing is recommended for persons born <sup>a</sup> from 1945 through 1965 without prior ascertainment of risk.	I, B
<p>Other persons should be screened for HCV infection risk factors. One-time testing should be performed for all persons with behaviors, exposures, and conditions or circumstances associated with an increased risk of HCV infection.</p> <p><b>Risk Behaviors</b></p> <ul style="list-style-type: none"> <li>• Injection-drug use (current or ever, including those who injected only once)</li> <li>• Intranasal illicit drug use</li> </ul> <p><b>Risk Exposures</b></p> <ul style="list-style-type: none"> <li>• Persons on long-term hemodialysis (ever)</li> <li>• Persons with percutaneous/parenteral exposures in an unregulated setting</li> <li>• Healthcare, emergency medical, and public safety workers after needle-stick, sharps, or mucosal exposures to HCV-infected blood</li> <li>• Children born to HCV-infected women</li> <li>• Prior recipients of transfusions or organ transplants, including persons who:                         <ul style="list-style-type: none"> <li>◦ Were notified that they received blood from a donor who later tested positive for HCV</li> <li>◦ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992</li> <li>◦ Received clotting factor concentrates produced before 1987</li> </ul> </li> <li>• Persons who were ever incarcerated</li> </ul> <p><b>Other Conditions and Circumstances</b></p> <ul style="list-style-type: none"> <li>• HIV infection</li> <li>• Sexually-active persons about to start pre-exposure prophylaxis (PreP) for HIV</li> <li>• Unexplained chronic liver disease and/or chronic hepatitis, including elevated alanine aminotransferase (ALT) levels</li> <li>• Solid organ donors (deceased and living)</li> </ul>	I, B
<sup>a</sup> Regardless of country of birth	

There are an estimated 3.5 million HCV-infected persons in the United States, including 2.7 million in the general noninstitutionalized population ([Denniston, 2014](#)) and 800,000 incarcerated, institutionalized, or homeless persons ([Edlin,](#)

2015). Approximately 50% of all infected people are unaware that they have HCV ([Denniston, 2012](#)); ([Holmberg, 2013](#)).

HCV testing is recommended in select populations based on demographics, possible exposures, high-risk behaviors, and medical conditions. Testing recommendations are based on HCV prevalence in these populations; proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality; and the potential public health benefit of reducing transmission through early treatment, viral clearance, and reduced risk behaviors ([Smith, 2012](#)); ([USPSTF, 2013](#)); ([CDC, 1998](#)).

HCV is primarily transmitted through percutaneous exposure to infected blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection drug use. Sexual transmission also occurs but generally seems inefficient except among HIV-infected men who have unprotected sex with men ([Schmidt, 2014](#)).

Injection drug use poses the most significant risk for HCV infection, accounting for at least 60% of acute HCV infections in the United States. Healthcare exposures are important sources of transmission, including the receipt of blood products prior to 1992 (after which routine screening of the blood supply was implemented); receipt of clotting factor concentrates before 1987; long-term hemodialysis; needle-stick injuries among healthcare workers; and patient-to-patient transmission resulting from poor infection control practices.

Other risk factors include having been born to an HCV-infected mother, having been incarcerated, and percutaneous or parenteral exposures in an unregulated setting. Examples of these settings include tattoos received outside of licensed parlors and medical procedures done internationally or domestically where strict infection control procedures may not have been followed (eg, surgery before implementation of universal precautions) ([Hellard, 2004](#)).

The importance of these risk factors might differ based on geographic location and population ([USPSTF, 2013](#)); ([CDC, 1998](#)). An estimated 29% of incarcerated persons in North America are HCV-antibody-positive, supporting the recommendation to screen this population for HCV ([Larney, 2013](#)).


Because of shared transmission modes, persons with HIV infection are at risk for HCV. Sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men ([Hosein, 2013](#)); ([van de Laar, 2010](#)). Screening sexually active, non-HIV-infected persons before they start pre-exposure prophylaxis (PrEP) for HIV infection prevention should also be considered ([Volk, 2015](#)).

Recent data support testing in all deceased and living solid organ donors because of the risk of HCV infection posed to the recipient ([Seem, 2013](#)); ([Lai, 2013](#)). Although hepatitis C testing guidelines from the US Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) do not specifically recommend testing immigrants from countries with a high prevalence of HCV infection (eg, Egypt and Pakistan), such persons should be tested if they were born from 1945 through 1965, or if they have risk factors for infection (see [One-Time Testing Recommendations](#)).

CDC established risk-based HCV testing guidelines in 1998 ([CDC, 1998](#)). These guidelines were expanded in 2012 with a recommendation to offer a one-time HCV testing to all persons born from 1945 through 1965 without prior ascertainment of HCV risk factors (see [One-Time Testing Recommendations](#)). This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections, due in part to patient underreporting of their risk and provider limitations in ascertaining risk factor information. Furthermore, persons in the 1945 through 1965 birth cohort account for nearly 75% of all HCV infections, with a 5-fold higher prevalence (3.25%) than other adults. This reflects a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000 annually in the US, compared to an estimated 30,500 in 2014) ([CDC, 2016](#)). A retrospective analysis published in 2013 showed that 68% of persons with HCV infection would have been identified with a birth cohort testing strategy, whereas only 27% would have been screened with the risk-based approach ([Mahajan, 2013](#)). The cost-effectiveness of one-time birth cohort testing is comparable to that of current risk-based screening strategies ([Smith, 2012](#)).

Both CDC and the USPSTF recommend a one-time HCV test in asymptomatic persons belonging to the 1945 through 1965 birth cohort, as well as other individuals based on exposures, behaviors, and conditions or circumstances that increase HCV infection risk.


## HCV Testing for Persons With Ongoing Risk Factors

Recommendation for HCV Testing for Persons With Ongoing Risk Factors	
RECOMMENDED	RATING 
Annual HCV testing is recommended for <a href="#">persons who inject drugs</a> and for HIV-infected <a href="#">men who have unprotected sex with men</a> . Periodic testing should be offered to other persons with ongoing risk factors for HCV exposure.	Ila, C

Evidence regarding the frequency of testing in persons at risk for ongoing exposures to HCV is lacking. Therefore, clinicians should determine the periodicity of testing based on the risk of infection or reinfection. Because of the high incidence of HCV infection among persons who inject drugs and HIV-infected men who have unprotected sex with men, HCV testing at least annually is recommended for these populations ([Aberg, 2014](#)); ([Linás, 2012](#)); ([Wandeler, 2012](#)); ([Witt, 2013](#)); ([Bravo, 2012](#)); ([Williams, 2011](#)).

Implementation of clinical decision support tools or prompts for HCV testing in electronic health records could facilitate reminding clinicians of HCV testing when indicated ([Hsu, 2013](#)); ([Litwin, 2012](#)); (<http://nvhr.org/EMR>).

## Initial HCV Testing and Follow-Up

Recommendations for Initial HCV Testing and Follow-Up	
RECOMMENDED	RATING 
An HCV-antibody test is recommended for initial HCV testing. If the result is positive, current infection should be confirmed by a sensitive HCV-RNA test.	I, A
Among persons with a negative HCV-antibody test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered for persons who are immunocompromised.	I, C
Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an HCV-antibody test is expected to be positive.	I, C
Quantitative HCV-RNA testing is recommended prior to initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).	I, A
HCV genotype testing is recommended to guide selection of the most appropriate antiviral regimen.	I, A
Persons found to have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have evidence of current (active) HCV infection.	I, A

All persons recommended for HCV screening should initially be tested for HCV antibody ([CDC, 2013](#)); ([Alter, 2003](#)) using

an assay approved by the US Food and Drug Administration (FDA). FDA-approved tests include laboratory-based assays and a point-of-care assay (ie, OraQuick HCV Rapid Antibody Test [OraSure Technologies]) ([Lee, 2011](#)). The latter is an indirect immunoassay with a sensitivity and specificity similar to those of laboratory-based HCV-antibody assays.

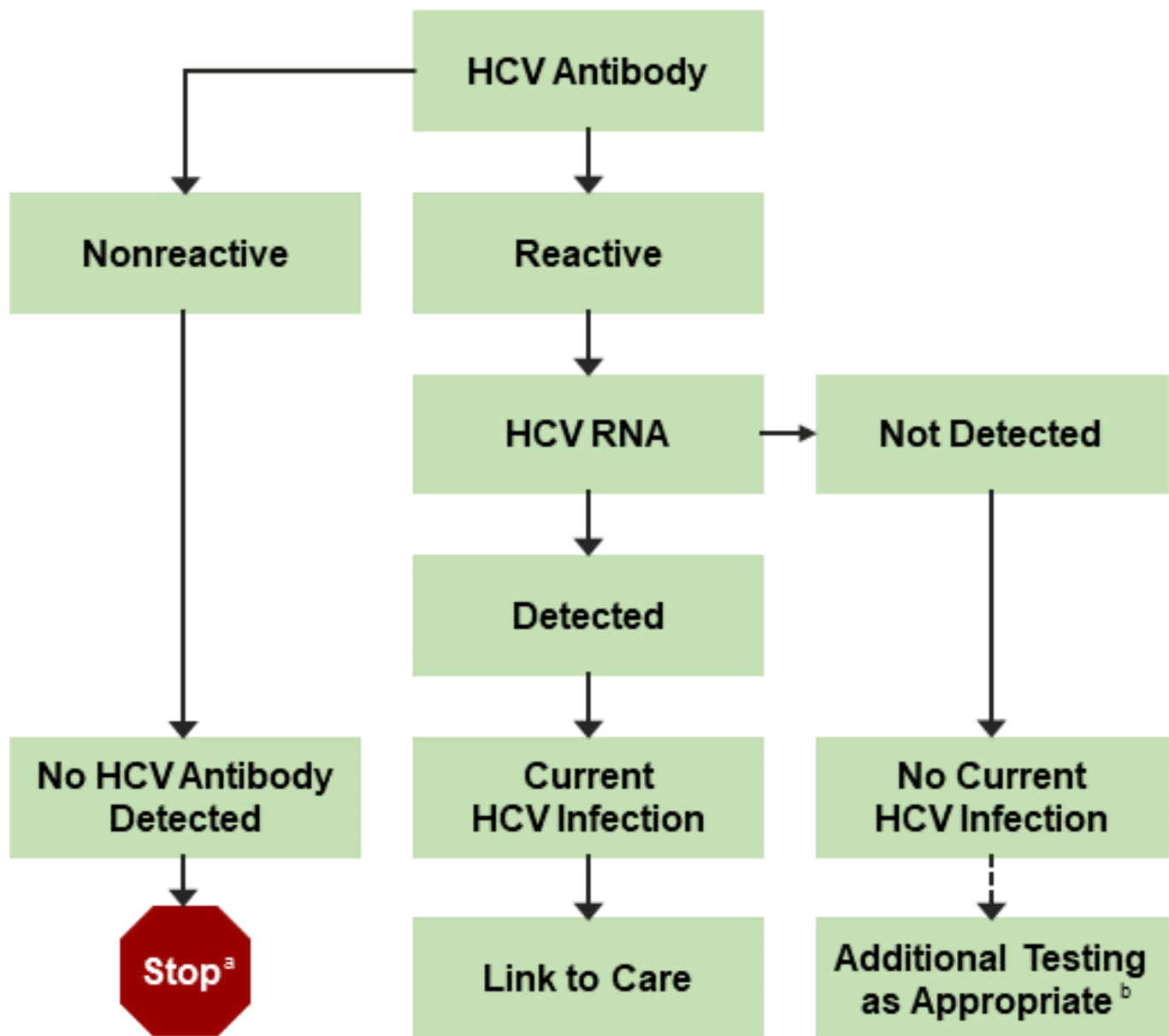
A positive test result for HCV antibody indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive result ([Pawlotsky, 2002](#)). Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm active HCV infection and guide clinical management, including initiation of HCV treatment. HCV-RNA testing should also be performed in persons with a negative HCV-antibody test who are either immunocompromised (eg, persons receiving chronic hemodialysis) ([KDIGO, 2008](#)) or who might have been exposed to HCV within the last 6 months because these persons may be HCV-antibody-negative. An HCV-RNA test is also needed to detect reinfection in HCV-antibody-positive persons after previous spontaneous or treatment-related viral clearance.

An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. Table 1 lists FDA-approved, commercially available HCV-antibody screening assays. Figure 1 shows the CDC-recommended testing algorithm.

**Table 1. FDA-Approved HCV-Antibody Screening Assays**

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott Laboratories Abbott Park, IL, USA	EIA <sup>a</sup> (manual)
Advia Centaur HCV	Siemens Healthcare Malvern, PA, USA	CIA <sup>b</sup> (automated)
Architect Anti-HCV	Abbott Laboratories Abbott Park, IL, USA	CMIA <sup>c</sup> (automated)
AxSYM Anti-HCV	Abbott Laboratories Abbott Park, IL, USA	MEIA <sup>d</sup> (automated)
OraQuick HCV Rapid Antibody Test	OraSure Technologies, Inc. Bethlehem, PA, USA	Immunochromatographic (manual)
Ortho HCV Version 3.0 ELISA Test System	Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA	EIA <sup>a</sup> (manual)
VITROS Anti-HCV	Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA	CIA <sup>b</sup> (automated)
<sup>a</sup> EIA: enzyme immunoassay <sup>b</sup> CIA: chemiluminescent immunoassay <sup>c</sup> CMIA: chemiluminescent microparticle immunoassay <sup>d</sup> MEIA: microparticle enzyme immunoassay Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.		

Figure 1. CDC-Recommended Testing Sequence for Identifying Current HCV Infection



<sup>a</sup> For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.

<sup>b</sup> To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV-antibody assay can be considered. Repeat HCV-RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.


Adapted from Centers for Disease Control and Prevention (CDC), 2013 ([CDC, 2013](https://www.cdc.gov/hepatitis/c/hcv/testing/))

Persons who have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current HCV infection. Additional HCV testing is typically unnecessary. The HCV-RNA test can be repeated when there is a high index of suspicion for recent infection or in patients with ongoing HCV infection risk.

Clinicians (or patients) may seek additional testing to determine whether a positive HCV-antibody test represents a remote HCV infection that has resolved or a false positive. For patients with no apparent risk for HCV infection, the likelihood of a false-positive HCV-antibody test is directly related to the HCV prevalence in the tested population. False-positive HCV-antibody tests most commonly occur in populations with a low prevalence of HCV infection ([Alter, 2003](#)). If further testing is desired to distinguish between a true positive vs biologic false positivity for HCV antibody, repeat testing may be done with a different FDA-approved, HCV-antibody assay. A biologic false result should not occur with two different assays ([Vermeersch, 2008](#)); ([CDC, 2013](#)).

Prior to initiation of antiviral therapy, quantitative HCV-RNA testing may be used to determine the baseline level of viremia (ie, viral load), which may affect treatment duration with certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response (SVR) in the era of direct-acting antiviral (DAA) therapy compared to previous interferon-based treatment (see [Pretreatment and On-Treatment Monitoring](#)). Testing for HCV genotype helps guide selection of the most appropriate antiviral regimen.

## Counseling Persons With Active HCV Infection

Recommendations for Counseling Persons With Active HCV Infection	
RECOMMENDED	RATING 
Persons with current HCV infection should receive education and interventions aimed at reducing liver disease progression and preventing HCV transmission.	IIa, B
Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.	IIa, B
Evaluation for other conditions that may accelerate liver fibrosis, including hepatitis B and HIV infections, is recommended for all persons with active HCV infection.	IIb, B
Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy, and to determine the need for initiating additional measures for cirrhosis management (eg, hepatocellular carcinoma screening) (see <a href="#">Monitoring</a> section).	I, A
Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.	IIa, C
Vaccination against pneumococcal infection is recommended for all patients with cirrhosis.	IIa, C
All persons with HCV infection should be provided education about how to avoid HCV transmission to others.	I, C



In addition to receiving antiviral therapy, HCV-infected persons should be educated about how to prevent further liver damage. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between excess alcohol use and the development or progression of liver fibrosis, and the development of hepatocellular carcinoma ([Poynard, 1997](#)); ([Harris, 2001](#)); ([Wiley, 1998](#)); ([Corrao, 1998](#)); ([Bellentani, 1999](#)); ([Noda, 1996](#)); ([Safdar, 2004](#)).

Daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also has a deleterious effect on the liver; however, these data are controversial ([Westin, 2002](#)); ([Younossi, 2013b](#)); ([Hagström, 2017](#)). Excess alcohol intake may also cause steatohepatitis. Alcohol screening and brief interventions, such as those outlined by the [National Institute on Alcohol Abuse and Alcoholism](#), have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily ([Whitlock, 2004](#)); ([Dieperink, 2010](#)); ([Proeschold-Bell, 2012](#)). Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

Hepatitis B virus (HBV) and HIV coinfection have been associated with a poorer HCV prognosis in cohort studies ([Zarski, 1998](#)); ([Thein, 2008a](#)); ([Kruse, 2014](#)); ([Puoti, 2017b](#)). Because of overlapping risk factors for these infections and benefits associated with their identification and treatment, HCV-infected persons should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard screening assays ([Moyer, 2013](#)); ([CDC, 2008](#)); (see [USPSTF HIV screening recommendations](#) and [CDC hepatitis B screening recommendations](#)). Patients should also be counseled about how to reduce their risk of acquiring these infections, including through HBV vaccination.

Patients with obesity and metabolic syndrome having underlying insulin resistance are at increased risk for nonalcoholic fatty liver disease, which is a risk factor for accelerated fibrosis progression in HCV-infected persons ([Hourigan, 1999](#)); ([Ortiz, 2002](#)). Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index of 25 to 29.9 kg/m<sup>2</sup>, and ≥30 kg/m<sup>2</sup>, respectively) should be counseled regarding strategies to reduce body weight and improve insulin resistance via diet, exercise, and medical therapies ([Musso, 2010](#)); ([Shaw, 2006](#)). HCV-infected patients with hyperlipidemia or cardiovascular comorbidities may also benefit from lipid-lowering drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease ([Kamal, 2017](#)); ([Lewis, 2007](#)). Therefore, these agents should not be withheld from HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease may have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit ([Ghany, 2011](#)). A liver biopsy can provide objective, semiquantitative information regarding the amount and pattern of collagen or scar tissue in the liver, which can help inform the development of treatment and monitoring plans. The Metavir fibrosis score (F0 to F4) and Ishak fibrosis score (0 to 6) are commonly used to quantify the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation and hepatic steatosis, and aid in excluding competing causes of liver injury ([Kleiner, 2005](#)). However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable ([Regev, 2002](#)).

Noninvasive methods frequently used to estimate liver disease severity include:

- Liver-directed physical exam (normal in most patients)
- Routine blood tests (eg, ALT, AST, albumin, bilirubin, international normalized ratio [INR], and CBC with platelet count)
- Serum fibrosis marker panels
- Liver imaging (eg, ultrasound, or CT scan)
- Transient elastography



Simple calculations derived from routine blood tests—such as the serum AST-to-platelet ratio index ([APRI](#)) ([Wai, 2003](#)) and fibrosis-4 ([FIB-4](#)) ([Sterling, 2006](#))—as well as assessment of liver surface nodularity and spleen size by liver ultrasound or other cross-sectional imaging modalities can help determine if patients with HCV have occult portal hypertension. The presence of portal hypertension is associated with a greater likelihood of developing future hepatic complications in untreated patients ([Chou, 2013](#)); ([Rockey, 2006](#)).

Liver elastography provides instant information regarding liver stiffness at the point of care and can reliably distinguish patients with a high versus low likelihood of cirrhosis ([Castera, 2012](#)); ([Bonder, 2014](#)). A more detailed discussion regarding fibrosis assessment is found in the [When and In Whom to Initiate Therapy](#) section.


Because persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require frequent follow-up. They should also avoid hepatotoxic drugs, such as excessive acetaminophen (>2 g/d) and certain herbal supplements. Nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, should also be avoided. Ongoing imaging surveillance for liver cancer and gastroesophageal varices is also recommended for these patients ([Sangiovanni, 2006](#)); ([Fontana, 2010](#)). Persons with cirrhosis are more susceptible to invasive pneumococcal infection ([Marrie, 2011](#)) and should receive pneumococcal vaccination ([CDC, 2012](#)).

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs given that HCV transmission in this population primarily results from sharing needles and other contaminated drug injection equipment. Epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described recently ([van de Laar, 2009](#)); ([Urbanus, 2009](#)); ([Fierer, 2008](#)). Table 2 outlines measures to avoid HCV transmission. HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water.

**Table 2. Measures to Prevent HCV Transmission**

HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
Persons should be counseled to stop using illicit drugs and enter substance abuse treatment. Those who continue to inject drugs should be counseled to: <ul style="list-style-type: none"> <li>• Avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment.</li> <li>• Use new sterile syringes and filters, and disinfected cookers.</li> <li>• Clean the injection site with a new alcohol swab.</li> <li>• Dispose of syringes and needles after 1 use in a safe, puncture-proof container.</li> </ul>
Persons with HCV infection should be advised not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
Persons with HIV infection and those with multiple sexual partners or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

## Linkage to Care

Recommendation for Linkage to Care	
RECOMMENDED	RATING 
All persons with active HCV infection should be linked to a clinician who is prepared to provide comprehensive management.	Ila, C

Improvement in identification of active HCV infection and advances in treatment regimens will have limited impact on HCV-related morbidity and mortality without concomitant improvement in linkage to care. All patients with current HCV infection and a positive HCV-RNA test result should be evaluated by a clinician with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (Metavir stage  $\geq$ F3), including possible referral for consideration of liver transplantation.

In the United States, only an estimated 13% to 18% of HCV-infected persons had received treatment by 2013 ([Holmberg, 2013](#)). Lack of appropriate clinician assessment and delays in linkage to care can result in negative health outcomes. Furthermore, patients who are lost to follow-up fail to benefit from evolving evaluation and treatment options.

Commonly cited patient-related barriers to treatment initiation include contraindications to treatment (eg, medical or psychiatric comorbidities); lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, low treatment efficacy, long treatment duration, and adverse effects); and lack of access to treatment (eg, cost and distance to specialist) ([Khokhar, 2007](#)); ([Arora, 2011](#)); ([Clark, 2012](#)).

Common clinician-related barriers include perceived patient-related barriers (eg, fear of adverse effects, treatment duration, cost, and effectiveness); lack of expertise in HCV treatment; lack of specialty referral resources; resistance to treating persons currently using illicit drugs or alcohol; and concern about the cost of HCV treatment ([Morrill, 2005](#)); ([Reilley, 2013](#)); ([McGowan, 2013](#)).

Data are lacking to support exclusion of HCV-infected persons from considerations for hepatitis C therapy based on the amount of alcohol intake or use of illicit drugs. Based on data from interferon-based treatment, SVR rates among people who inject drugs are comparable to those among people who do not inject drugs ([Aspinall, 2013](#)). Some possible strategies to address barriers to HCV treatment are listed in Table 3.

**Table 3. Common Barriers to HCV Treatment and Potential Strategies**

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	<ul style="list-style-type: none"> <li>• Conduct counseling and education</li> <li>• Refer for services (eg, psychiatry and opioid substitution therapy)</li> <li>• Optimize treatment with simpler, less toxic regimens</li> </ul>
Competing priorities and loss to follow-up	<ul style="list-style-type: none"> <li>• Conduct counseling and education</li> <li>• Engage case managers and patient navigators (HIV model)</li> <li>• Co-localize services (eg, primary care, medical homes, and drug treatment)</li> </ul>
Long treatment duration and adverse effects	<ul style="list-style-type: none"> <li>• Optimize treatment with simpler, better tolerated regimens</li> <li>• Conduct appropriate education and monitoring</li> <li>• Utilize directly observed therapy (tuberculosis model)</li> </ul>
Lack of access to treatment (eg, high cost, lack of insurance, geographic distance, and/or lack of availability of specialists)	<ul style="list-style-type: none"> <li>• Leverage expansion of coverage through the Patient Protection and Affordable Care Act</li> <li>• Participate in models of care involving close collaboration between primary care clinicians and specialists</li> <li>• Liaise with pharmaceutical patient assistance programs</li> <li>• Co-localize services (primary care, medical homes, drug treatment)</li> </ul>
Lack of practitioner expertise	<ul style="list-style-type: none"> <li>• Collaborate with specialists (eg, Project ECHO-like models and telemedicine)</li> <li>• Develop accessible, clear HCV treatment guidelines</li> <li>• Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)</li> </ul>

One strategy that addresses several barriers is co-localization (integrated care) of HCV screening, evaluation, and treatment with other medical or social services. Co-localization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities, needle exchange programs, substance abuse treatment centers, and methadone maintenance facilities) but this type of care is not uniformly available ([Islam, 2012](#)); ([Stein, 2012](#)); ([Bruggmann, 2013](#)). A study conducted by Ho and colleagues demonstrated that integrated care—consisting of multidisciplinary care coordination and patient case management—increased the proportion of patients with HCV infection and psychiatric illness or substance use who begin antiviral therapy and achieve a sustained virologic response, without serious adverse events ([Ho, 2015](#)).

A strategy that addresses lack of access to specialists—a primary barrier to hepatitis C care—is participation in models involving close collaboration between primary care practitioners and subspecialists ([Arora, 2011](#)); ([Rossaro, 2013](#));

([Miller, 2012](#)). Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists ([Arora, 2011](#)); ([Rossaro, 2013](#)). For example, Project ECHO ([Extension for Community Healthcare Outcomes](#)) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population ([Arora, 2011](#)). Through case-based learning and real-time feedback from a multidisciplinary team of specialists (gastroenterology, infectious disease, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV treatment in populations that might have otherwise remained untreated. The short duration of treatment and few serious adverse events associated with DAA therapy present an opportunity to expand the number of midlevel practitioners and primary care physicians engaged in the management and treatment of HCV infection.

Additional strategies for enhancing linkage to and retention in care could be adapted from other fields, such as tuberculosis and HIV. For example, use of directly observed therapy has enhanced adherence to tuberculosis treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care ([Govindasamy, 2012](#)). Recent hepatitis C testing and care programs have identified the use of patient navigators or care coordinators as important interventions in overcoming challenges associated with linkage to and retention in care ([Trooskin, 2015](#)); ([Coyle, 2015](#)). Ongoing assessment of efficacy and comparative effectiveness of this and additional strategies is a crucial area of future research for patients with HCV infection. Replication and expansion of best practices and new models for linkage to HCV care will also be crucial to maximize the public health impact of newer treatment paradigms.

**Last update:** May 24, 2018


## When and in Whom to Initiate HCV Therapy

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


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

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

### Goal of Treatment

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

### Recommendation for When and in Whom to Initiate Treatment

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

## Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of patients followed-up for  $\geq 5$  years ([Swain, 2010](#)); ([Manns, 2013](#)). Patients in whom SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology ([Marcellin, 1997](#)); ([Coppola, 2013](#)); ([Garcia-Bengochea, 1999](#)). 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  $\leq 25$  IU/mL.

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

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients ([Fabrizi, 2013](#)); ([Landau, 2010](#)); ([Sise, 2016](#)). HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection ([Gisbert, 2005](#)); ([Takahashi, 2012](#)); ([Svoboda, 2005](#)); ([Mazzaro, 2002](#)); ([Hermine, 2002](#)). These reductions in disease severity contribute to dramatic reductions in all-cause mortality ([van der Meer, 2012](#)); ([Backus, 2011](#)). Furthermore, patients who achieve SVR have a substantially improved quality of life, which spans their physical, emotional, and social health ([Boscarino, 2015](#)); ([Neary, 1999](#)); ([Younossi, 2013](#)); ([Gerber, 2016](#)). Because of the many benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving SVR, preferably early in the course of chronic HCV infection before the development of severe liver disease and other complications.

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

Initiating therapy in patients with lower-stage fibrosis augments the benefits of SVR. In a long-term follow-up study, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed for up to 20 years ([Jezequel, 2015](#)). The 15-year survival rate was significantly better for those who experienced SVR than for those whose treatment failed or for those who remained untreated (93%, 82%, and 88%, respectively;  $P = .003$ ). The study results argue for consideration of earlier initiation of treatment. Several modeling studies also suggest a greater mortality benefit if treatment is initiated at fibrosis stages prior to F3 ([Øvrehus, 2015](#)); ([Zahnd, 2015](#)); ([McCombs, 2015](#)).

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



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

## Considerations in Specific Populations

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

### ***Persons With Advanced Liver Disease***

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

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

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

### ***Persons Who Have Undergone Liver Transplantation***

In HCV-infected individuals, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients within the first 6 months following liver transplantation ([Neumann, 2004](#)). By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis ([Neumann, 2004](#)); ([Charlton, 1998](#)). A small proportion of patients (4% to 7%) develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection post transplantation is associated with decreased graft survival for recipients with HCV



infection compared to recipients who undergo liver transplantation for other indications ([Forman, 2002](#)).

Effective HCV therapy prior to transplantation resulting in SVR (virologic cure) prevents HCV recurrence post transplantation ([Everson, 2003](#)). In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases ([Forns, 2004](#)); ([Everson, 2005](#)). Preliminary data from a study of patients with complications of cirrhosis secondary to HCV infection who were wait-listed for liver transplantation (included patients with MELD scores up to 14 and CTP scores up to 8) found that treatment with sofosbuvir and weight-based ribavirin for up to 48 weeks was well tolerated and associated with an overall posttransplant SVR rate of 70% ([Curry, 2015](#)). Posttransplant SVR was nearly universal 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](#)); ([Picciotto, 2007](#)). The availability of effective, interferon-free antiviral therapy has addressed the major hurdles to treating HCV recurrence post transplantation—poor tolerability and efficacy. A multicenter, open-label study evaluated the efficacy of sofosbuvir plus ribavirin to induce virologic suppression in 40 patients after liver transplantation with compensated recurrence of HCV infection. Daily sofosbuvir plus ribavirin for 24 weeks achieved SVR12 in 70% of these patients ([Charlton, 2015](#)). No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to the study treatment. There were no drug interactions reported between sofosbuvir and any of the concomitant immunosuppressive agents. In contrast, treatment with sofosbuvir plus ribavirin, with or without peginterferon, in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 rate of 59% and a mortality rate of 13% ([Forns, 2015](#)). On an intent-to-treat basis, treatment was associated with clinical improvement in 57% and stable disease in 22% of patients. Given the clinical complexity (including drug interactions and the need for close monitoring), patients with liver transplant should be treated by physicians with experience in treating this population (see [Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation](#)).

### ***Persons at Increased Risk for Rapidly Progressive Fibrosis and Cirrhosis***

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

#### HIV/HCV Coinfection

HIV coinfection accelerates fibrosis progression among HCV-infected persons ([Benhamou, 1999](#)); ([Macias, 2009](#)); ([Konerman, 2014](#)), although control of HIV replication and restoration of CD4 cell count may mitigate this to some extent ([Benhamou, 2001](#)); ([Bräu, 2006](#)). However, antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfecting patients with 435 paired biopsies were prospectively evaluated ([Konerman, 2014](#)). Thirty-four percent 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 lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for HCV treatment in this population regardless of current fibrosis stage (see [Patients with HIV/HCV Coinfection](#)) ([Pineda, 2005](#)); ([Merchante, 2006](#)); ([Terrault, 2012](#)).

#### HBV/HCV Coinfection

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

such cases utilizes the same genotype-specific regimens as are recommended for HCV mono-infection (see [Initial Treatment of HCV Infection](#)). HBV infections in such cases should be treated as recommended for HBV mono-infection ([Lok, 2009](#)).

### Other Coexistent Liver Diseases

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

## ***Persons With Extrahepatic Manifestations of Chronic HCV Infection***

### Cryoglobulinemia

Chronic hepatitis C is associated with a syndrome of cryoglobulinemia, an immune complex and lymphoproliferative disorder that leads to arthralgias, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels ([Agnello, 1992](#)). Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (>50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. Interferon-based regimens can produce clinical remission; however, the adverse effects of interferon may mimic manifestations of cryoglobulinemia ([Saadoun, 2014](#)).

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli ([Johnson, 1993](#)). Successful treatment of HCV using interferon-based regimens can reverse proteinuria and nephrotic syndrome but usually does not fully ameliorate azotemia ([Johnson, 1994](#)). There is building new evidence of effective resolution of cryoglobulinemia upon clearance of HCV in most patients, making a strong case for HCV treatment in this clinical setting.

### Diabetes

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

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

### Fatigue

Fatigue is the most frequently reported symptom in patients with chronic hepatitis C, and has a major effect on quality of life and activity level as evidenced by numerous measures of impaired quality of life ([Foster, 1998](#)). The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis ([Poynard, 2002a](#)). Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection ([Bonkovsky, 2007](#)). In the Virahep-C study, 401 patients with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and

severity of fatigue ([Sarkar, 2012](#)). At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving SVR was associated with a substantial decrease in the frequency and severity of fatigue.

A recent analysis of 413 patients from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and achieved SVR12 demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level ([Younossi, 2014](#)). After achieving SVR12, participants had marked improvements in fatigue over their pretreatment scores, measured by 3 separate validated questionnaires. Additional studies support and extend these findings beyond fatigue, with improvements in overall health-related quality of life and work productivity observed following successful HCV therapy ([Gerber, 2016](#)); ([Younossi, 2015b](#)); ([Younossi, 2015c](#)); ([Younossi, 2015d](#)); ([Younossi, 2015e](#)); ([Younossi, 2016a](#)).

### Dermatologic Manifestations

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

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

## **Benefit of Treatment to Reduce Transmission**

Persons who have successfully achieved SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment of HCV infection 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](#)); ([Durier, 2012](#)); ([Martin, 2013b](#)); ([Hellard, 2012](#)); ([Harris, 2016](#)). 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](#)).

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

The Society for Healthcare Epidemiology of America (SHEA) advises that healthcare workers who have substantial HCV viral replication ( $\geq 10^4$  genome equivalents/mL) be restricted from performing procedures that are prone to exposure ([Henderson, 2010](#)) and that all healthcare workers with confirmed chronic HCV infection should be treated. For reasons already stated, the achievement of SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission ([Henderson, 2010](#)), the availability of effective, all-oral regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

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 target populations.

### ***Persons Who Inject Drugs***

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

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

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

### ***HIV-Infected Men Who Have Sex With Men***

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

### ***Incarcerated Persons***

Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% ([Post, 2013](#)) and the rate of acute infection is approximately 1% ([Larney, 2013](#)). Screening for HCV infection is relatively uncommon in state prison

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

### Persons on Hemodialysis


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

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

### Patients Unlikely to Benefit From HCV Treatment

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

### Pretreatment Assessment

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

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




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

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

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

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

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

Recommendation for Repeat Liver Disease Assessment	
RECOMMENDED	RATING 
Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.	I, C

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

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors ([Table 1](#)); ([Feld, 2006](#)). Fibrosis may not progress linearly. Some individuals (often those aged >50 years) may progress slowly for many years followed by 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; thus, a higher activity grade on liver biopsy and higher serum transaminase values are associated with more rapid fibrosis progression ([Ghany, 2003](#)). However, even patients with normal ALT levels may develop substantial liver fibrosis over time ([Pradat, 2002](#)); ([Nutt, 2000](#)). The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

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

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

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

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

**Table. Factors Associated With Accelerated Fibrosis Progression**

Host	Viral
<p><b>Nonmodifiable</b></p> <ul style="list-style-type: none"> <li>• Fibrosis stage</li> <li>• Inflammation grade</li> <li>• Older age at time of infection</li> <li>• Male sex</li> <li>• Organ transplant</li> </ul> <p><b>Modifiable</b></p> <ul style="list-style-type: none"> <li>• Alcohol consumption</li> <li>• Nonalcoholic fatty liver disease</li> <li>• Obesity</li> <li>• Insulin resistance</li> </ul>	<ul style="list-style-type: none"> <li>• Genotype 3 infection</li> <li>• Coinfection with hepatitis B virus or HIV</li> </ul>

**Last update:** September 21, 2017



## Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens

The hepatitis C guidance describes diagnosis, linkage to care, and treatment for people with HCV infection ([AASLD/IDSA, 2017](#)). However, reduced access to treatment is a common challenge due to restrictions on drug reimbursement. This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and addresses the cost-effectiveness of HCV treatment access. Although these terms may sound similar, the following discussion seeks to clarify them with regard to HCV therapy. This section aims to be informational. As explained, actual costs are rarely known. Accordingly, the HCV guidance does not utilize cost-effectiveness analysis to guide recommendations at this time.

### Drug Cost and Reimbursement

Many organizations are involved with hepatitis C drug distribution and each can impact costs as well as decisions about which regimens are reimbursed ([US GAO, 2015](#)); ([US CBO, 2015](#)). The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (analogous to a sticker price). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts to decrease the actual price paid.
- Pharmacy benefit managers (PBMs) act as intermediaries between pharmaceutical companies and health insurance companies. They negotiate contracts that may include restrictions on the types of providers or patients who can be reimbursed for treatment. They might also offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower negotiated prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets and use PBMs or directly negotiate drug pricing with pharmaceutical companies. Insurance companies determine formulary placement, which impacts the choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and have different formularies for each line of business.
- Medicaid is a heterogeneous consortium of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). For single-source drugs such as all-oral HCV treatments, Medicaid plans receive the lowest price offered to any other payer (outside of certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy ([Barua, 2015](#)); ([Canary, 2015](#)); ([Lo Re, 2016](#)). State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. As the price of HCV therapies has decreased, some states have loosened their Medicaid treatment restrictions with a growing number providing treatment to all infected persons. Most states, however, continue to restrict access to HCV treatment based on stage of liver fibrosis or history of recent drug use. Proposed rollbacks of Medicaid expansion implemented under the ACA threaten to reduce insurance coverage among HCV-infected people and could lead to new treatment restrictions.
- Medicare covers HCV drugs through part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may negotiate discounts or rebates with pharmaceutical companies.
- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule program, which sets drug prices for several government agencies (including the Department of Veterans Affairs, federal prisons, and the Department of Defense) and typically receives substantial discounts over average wholesale price (AWP).
- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating leverage of larger organizations and, therefore, may pay higher prices than most other organizations.

- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support and/or management of adverse effects, and outcome measurements, such as early discontinuation rates and sustained virologic response rates.
- Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs offered by pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

Except for mandated rebates, negotiated drug prices are considered confidential business contracts. Therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs ([Saag, 2015](#)). However, the average negotiated discount of 22% in 2014 increased to 46% less than the WAC in 2015, implying that many payers are paying well below the WAC for HCV medications ([Committee on Finance US Senate, 2016](#)).

## Cost-Effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of 2 or more interventions. CEA explicitly recognizes budget limitations for healthcare spending and seeks to maximize public health benefits within those budgetary constraints. The core question that CEA addresses is whether to invest limited healthcare dollars in a new treatment/therapy, or use that money to invest in another healthcare intervention that would provide better outcomes for the same monetary investment. The focus of CEA is, therefore, not simply cost or saving money but health benefits. It assumes that all available resources will be spent and provides a framework for prioritizing among available treatment options by formally assessing the comparative costs and health benefits accrued from a new treatment relative to current treatment.

The cost-effectiveness of a treatment is typically expressed as an incremental cost-effectiveness ratio (ICER).

$$\frac{\text{cost new treatment} - \text{cost current treatment}}{\text{benefit new treatment} - \text{benefit current treatment}}$$

### Estimating and interpreting the ICER requires that we answer three questions:

1. *How much more money will be spent with the new treatment versus the old treatment?*

The additional cost of new treatment includes that of new medications as well as the costs that will be avoided by preventing disease complications. Prevention of long-term complications is especially important when considering the cost-effectiveness of HCV treatments because the costs of the therapy are immediate, while those avoided by preventing advanced liver disease and other complications of chronic infection often accrue years in the future.

2. *How much more benefit will occur with the new versus the old treatment?*

Life expectancy is a valuable measure of benefit, but considering only mortality benefits fails to recognize the value of treatments that improve quality of life. The quality-adjusted life-year (QALY) provides a measure that integrates both longevity and quality of life and is the preferred outcomes for CEA.

3. *How is the ICER to be interpreted?*

The ideal CEA would list every possible healthcare intervention, its lifetime medical cost, and QALYs lived. Such a list would allow for perfect theoretical prioritization of spending to maximize QALY across the population. In reality, CEA compares the ICER for a specific treatment to a threshold value and rejects treatments with an ICER exceeding a particular threshold as not being cost-effective. The threshold value is referred to as the societal willingness-to-pay threshold. It is not meant to be a valuation of how much society is willing to pay to save a life. Rather, it is meant to reflect the average return in QALY expected if the available budget was not used to provide a new treatment but instead invested into the current healthcare system. In the United States, the willingness-to-pay threshold is typically considered to be \$50,000 or \$100,000/QALY gained.

## Affordability

An intervention that is cost-effective is not necessarily affordable. Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a new therapy for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budgetary impact of interventions being implemented in the real world.

### 1. *Perspective on cost*

CEA seeks to inform decisions about how society should prioritize healthcare spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.

### 2. *Time horizon*

CEA uses a lifetime time horizon, meaning it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have no impact on spending decisions today because they have little bearing on the solvency of the current budget.

### 3. *Weak association between willingness to pay and the real-world bottom line*

Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little relationship to a payer's bottom line. Willingness to pay is meant to be an estimate of the opportunity cost of investing in a new therapy. In economics, opportunity cost refers to how else that money could have been spent and the benefits lost from not investing in that alternative. When payers make a decision about coverage, the calculation is more straightforward and relates to the short-term cost of medications and the budgetary impact. Given the rapid development of new technologies and therapies, funding all of them (even if they all fell below the societal willingness-to-pay threshold) would likely lead to uncontrolled growth in demand and exceed the limited healthcare budget.

There is no formula that provides a good means of integrating the concerns of value and affordability. When new therapies for HCV are deemed cost-effective, it indicates that these therapies provide good benefit for the resources invested, and providing such therapy to more people would be a good long-term investment. Determining the total resources that can be spent on HCV treatment, however, depends on political and economic factors that are not captured by cost-effectiveness determinations.

## Cost-Effectiveness of Current Direct-Acting Antiviral Regimens for Hepatitis C Treatment

Since the first direct-acting antivirals (DAAs) received US Food and Drug Administration approval in 2011, several cost-effectiveness investigations have compared DAA-based regimens to previous standard-of-care regimens to calculate ICERs. They have also investigated the cost-effectiveness of eliminating HCV treatment restrictions. Compared to interferon-based regimens, the ICER for DAAs has consistently been estimated at <\$100,000/QALY for all genotypes and fibrosis stages.

Several studies have compared DAA regimens against one another. In general, when given a choice between recommended HCV DAA regimens, the less costly regimen is preferred as a more efficient use of resources (even if it requires multiple tablet dosing). Because of the similar efficacy of most DAA regimens, cost becomes the critical factor driving cost-effectiveness. Recent studies have also estimated the cost-effectiveness of HCV treatment in special populations, including patients awaiting liver transplantation, HIV/HCV coinfecting patients, those with chronic kidney disease, and persons who inject drugs—all with favorable ICERs. At this time, it is reasonable to conclude that DAA regimens provide good value for the resources invested.

## Cost vs Affordability for HCV Treatment

Despite a growing body of evidence that HCV treatment is cost-effective and may even be cost saving over the long term in some cases, many US payers—especially those offering Medicaid insurance products—continue to limit access to HCV treatment. Access has improved as cost has decreased but limitations remain. Proposed reductions in healthcare spending for Medicaid would likely exacerbate the problem as the value of the HCV medications would remain unchanged but the resources available to provide them would shrink.

## Conclusions


Several recent studies have demonstrated the economic value of HCV treatment and made it clear that HCV therapy is cost-effective ([Chahal, 2016](#)); ([Chatwal, 2015](#)); ([Chidi, 2016](#)); ([Linias, 2015](#)); ([Martin, 2016a](#)); ([Najafzadeh, 2015](#)); ([Rein, 2015](#)); ([Tice, 2015](#)); ([Younossi, 2015a](#)). The high cost of these medications combined with the high prevalence of disease has led to limiting access for some patients. The issue is complex. Although the wholesale acquisition costs of HCV drugs often make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing and few actually pay this much-publicized price. Negotiated pricing and cost structure for pharmaceutical products in the US are not transparent, however. Thus, it is therefore difficult to estimate the true budgetary impact of providing HCV drugs. Competition and negotiated pricing have reduced prices but cost continues to limit the public health impact of new DAA therapies. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all persons in need of treatment are able to afford and readily access it.

**Last update:** September 21, 2017

# Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy

This section provides guidance on monitoring patients with chronic hepatitis C who are starting treatment, are on treatment, or have completed treatment. The section is divided into 3 parts: pretreatment and on-treatment monitoring; post-treatment follow-up for persons in whom treatment has failed to clear the virus; and post-treatment follow-up for those who achieved a sustained virologic response (SVR; virologic cure).


## Pretreatment and On-Treatment Monitoring

Recommended Assessments Prior to Starting Antiviral Therapy	
RECOMMENDED	RATING 
<p>Staging of hepatic fibrosis is essential prior to HCV treatment (see <a href="#">Testing and Linkage to Care</a> and see <a href="#">When and in Whom to Treat</a>).</p> <p>Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy.</p> <ul style="list-style-type: none"> <li>Patients should also be educated about the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment.</li> </ul> <p><b>The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:</b></p> <ul style="list-style-type: none"> <li>Complete blood count (CBC)</li> <li>International normalized ratio (INR)</li> <li>Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels)</li> <li>Calculated glomerular filtration rate (eGFR)</li> </ul> <p><b>The following laboratory tests are recommended at any time prior to starting antiviral therapy:</b></p> <ul style="list-style-type: none"> <li>HCV genotype and subtype</li> <li>Quantitative HCV RNA (HCV viral load)</li> </ul>	I, C
<p>Patients scheduled to receive an HCV NS3 protease inhibitor (ie, paritaprevir, simeprevir, grazoprevir, voxilaprevir, glecaprevir) should be assessed for a history of decompensated liver disease and for liver disease severity using the Child-Turcotte-Pugh (CTP) score (see third-party <a href="#">calculator</a>).</p> <ul style="list-style-type: none"> <li>Patients with current or prior history of decompensated liver disease or with a current CTP score <math>\geq 7</math> should <b>not</b> receive treatment with regimens that contain NS3 protease inhibitors due to increased blood levels and/or lack of safety data.</li> </ul>	I, A

## Recommended Assessments Prior to Starting Antiviral Therapy

<ul style="list-style-type: none"> <li>Similarly, patients with a CTP score of 5 or 6 who cannot be closely monitored for laboratory or clinical symptoms during treatment should <b>not</b> receive treatment with a regimen that contains paritaprevir/ritonavir.</li> </ul>	
All patients initiating HCV direct-acting antiviral (DAA) therapy should be assessed for HBV coinfection with HBsAg testing, and for evidence of prior infection with anti-HBs and anti-HBc testing.	Ila, B
Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the <a href="#">Initial Treatment</a> and the <a href="#">Retreatment</a> sections.	IIb, B


## Recommended Monitoring During Antiviral Therapy

RECOMMENDED	RATING 
Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence, and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications.	I, B
<p>Creatinine level, calculated glomerular filtration rate (eGFR), and a hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated.</p> <p>More frequent assessment for drug-related adverse effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated.</p> <p>Patients receiving elbasvir/grazoprevir should be monitored with a hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).</p>	I, B
<p>A 10-fold increase in alanine aminotransferase (ALT) activity at any time during treatment should prompt discontinuation of therapy.</p> <p>An increase in ALT &lt;10-fold that is accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio (INR) should also prompt discontinuation of therapy.</p> <p>Asymptomatic increases in ALT &lt;10-fold should be closely monitored with repeat testing at 2-week intervals. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.</p>	I, B
<p>Quantitative HCV viral load testing is recommended after 4 weeks of therapy and 12 weeks after completion of therapy.</p> <p>Antiviral drug therapy should <b>not</b> be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.</p>	I, B

## Recommended Monitoring During Antiviral Therapy


<p>Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.</p>	<p>I, B</p>
<p>For HBsAg-positive patients who are not already on HBV suppressive therapy, the following are recommended:</p> <ul style="list-style-type: none"> <li>• For patients whose HBV DNA level meets <a href="#">AASLD criteria for treatment</a>, antiviral therapy for HBV should be initiated.</li> <li>• For patients whose baseline HBV DNA level does not meet criteria for treatment, one of two approaches may be taken:             <ul style="list-style-type: none"> <li>◦ Initiate prophylactic antiviral therapy for those with low or undetectable HBV DNA levels. If this course is elected, pending further data, prophylaxis should be continued until 12 weeks after completion of DAA therapy.</li> <li>◦ Monitor HBV DNA levels during and immediately after DAA therapy for HCV. Antiviral treatment for HBV should be given in the event of a rise in HBV DNA &gt;10-fold above baseline or to &gt;1000 IU/mL in those with a previously undetectable or unquantifiable HBV DNA level.</li> </ul> </li> </ul>	<p>IIa, B</p>

## Recommendations for Discontinuation of Treatment Because of Lack of Efficacy

RECOMMENDED	RATING 
<p>If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by &gt;10-fold (&gt;1 log<sub>10</sub> IU/mL) on repeat testing at week 6 (or thereafter), discontinuation of HCV treatment is recommended.</p>	<p>III, C</p>
<p>The significance of a positive HCV-RNA test result at week 4 that remains positive but lower at week 6 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.</p>	<p>III, C</p>



## Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin

RECOMMENDED	RATING 
Women of childbearing age should be counseled not to become pregnant while receiving a ribavirin-containing antiviral regimen, and for at least 6 months after stopping the regimen.	I, C
Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving a ribavirin-containing antiviral regimen, and for up to 6 months after stopping the regimen.	I, C
Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin.	I, C
Since the safety of DAA regimens that do not include ribavirin has not been established during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment.	I, C
Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment.	I, C

The pretreatment testing described assumes that a decision to treat with antiviral medications has already been made and that the testing involved in deciding to treat—including testing for HCV genotype and assessment of hepatic fibrosis—has already been completed (see [When and in Whom to Initiate HCV Therapy](#)).

Prior to starting treatment, patients should be evaluated for potential drug-drug interactions with selected antiviral medications by consulting the prescribing information and using other resources (eg, <http://www.hep-druginteractions.org>). The table below lists known drug-drug interactions between HCV DAAs and selected medications.

**Table. Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications**

X = Assess potential drug interaction. Hover over column labels for complete treatment name.

Concomitant Medications	DCV	LDV	PrOD	SMV	SOF	EBV/GRZ	VEL
Acid-reducing agents <sup>a</sup>		X	X				X
Alfuzosin/tamsulosin			X				
Amiodarone	X	X	X	X	X		X
Anticonvulsants <sup>a</sup>	X	X	X	X	X	X	X
Antiretrovirals <sup>a</sup>	See <a href="#">HIV section</a>						
Azole antifungals <sup>a</sup>	X <sup>b</sup>		X	X		X	
Buprenorphine/naloxone			X				
Calcineurin inhibitors <sup>a</sup>			X	X		X	
Calcium channel blockers <sup>a</sup>	X		X	X		X	
Cisapride			X	X		X	
Digoxin	X	X		X		X	
Ergot derivatives			X				
Ethinyl estradiol-containing products			X				
Furosemide			X				
Gemfibrozil			X				
Glucocorticoids <sup>a</sup>	X		X (inhaled, intranasal)	X		X	
Herbals St. John's wort Milk thistle	X	X	X	X X	X	X X	X
HMG-CoA reductase inhibitors (statins) <sup>a</sup>	X	X	X	X		X	
Macrolide antimicrobials <sup>a</sup>	X <sup>b</sup>			X		X	
Other antiarrhythmics <sup>a</sup>			X	X		X	
Phosphodiesterase inhibitors <sup>a</sup>			X	X		X	
Pimozide			X				
Rifamycin antimicrobials <sup>a</sup>	X	X	X	X	X	X	X
Salmeterol			X				
Sedatives <sup>a</sup>			X	X		X	

<sup>a</sup> Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.

<sup>b</sup> Requires a daclatasvir dose modification

The education of patients and caregivers about potential adverse effects of therapy and their management is an integral component of treatment and is important for a successful outcome in all patient populations. During treatment, individuals should be followed at clinically appropriate intervals to ensure medication adherence, assess adverse events and potential

drug-drug interactions, and monitor blood test results necessary for patient safety. The frequency and type of contact (eg, clinic visit, phone call, etc) are variable but need to be sufficient to assess patient safety and response to treatment, as outlined above.

The assessment of HCV viral load at week 4 of therapy is useful to determine initial response to therapy and adherence. In phase 3 clinical trials, almost all patients who did not have cirrhosis had an undetectable HCV RNA level at week 4. Those with cirrhosis may require more than 4 weeks of treatment before the HCV RNA level is undetectable. There are minimal data on how to use the HCV RNA level during treatment to determine when to stop treatment for futility. The current recommendation to repeat quantitative HCV RNA testing at week 6 of treatment and to discontinue treatment if the quantitative HCV RNA level increases by >10-fold (>1 log<sub>10</sub> IU/mL) is based on expert opinion. There are no data to support stopping treatment based on detectable HCV RNA at weeks 2, 3, or 4 of treatment, or that detectable HCV RNA at these time points signifies medication nonadherence.

Although HCV RNA testing is recommended at week 4 of treatment, failure to test for HCV RNA at week 4 is not a reason to discontinue therapy. HCV RNA assessment at the end of treatment allows for the differentiation of relapse from nonresponse/breakthrough for patients who fail to achieve SVR. Nevertheless, testing for HCV RNA at the end of treatment is optional. On the other hand, it is essential to test for HCV RNA 12 weeks (or longer) after treatment completion. Undetectable or unquantifiable HCV RNA 12 weeks or longer after treatment completion is defined as a sustained virologic response (SVR), which is consistent with cure of hepatitis C infection. Virologic relapse is rare 12 weeks or longer after treatment completion. Nevertheless, repeat quantitative HCV-RNA testing can be considered at 24 or more weeks after completing treatment for patients in whom ALT increases to above the upper limit of normal.

During clinical trials with elbasvir/grazoprevir, with or without ribavirin, 1% of subjects experienced ALT elevations from normal levels to >5 times the upper limit of normal, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing therapy or completion of therapy. Higher rates of late ALT elevations occurred in females, those of Asian descent, and patients aged ≥65 years. Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12 ([Zepatier Package Insert, 2017](#)).

Patients with compensated cirrhosis (Child's A) who are receiving a paritaprevir/ritonavir-based regimen should be followed closely. Patients with compensated cirrhosis who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy, or serum bilirubin >3 mg/dL) and for biochemical evidence of liver injury with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment. Paritaprevir/ritonavir-based regimens should be discontinued if a patient develops ascites, encephalopathy, or a significant increase in direct bilirubin, ALT, or AST. Please see the statement on the FDA [warning](#) regarding use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Patients being treated with amiodarone should not receive sofosbuvir-based regimens due to risk of life-threatening arrhythmias. Because of its long half-life, it is advised that persons should be off amiodarone for at least 6 months before initiating sofosbuvir. If the decision is made to start sofosbuvir in this setting, continued vigilance for bradycardia should be exercised.

### Pregnancy

Ribavirin causes fetal death and fetal abnormalities in animals. Thus, it is imperative for persons of childbearing potential who receive ribavirin to use at least 2 reliable forms of effective contraception during treatment and for a period of 6 months thereafter. It is recommended that the healthcare practitioner document the discussion of the potential teratogenic effects of ribavirin in the patient's medical record. Ethinyl estradiol-containing contraceptives should be avoided in those receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir due to the risk of developing elevated transaminase levels.


No adequate human data are available to establish whether DAAs pose a risk to pregnancy outcomes. It is recommended that female patients have a thorough discussion of potential pregnancy-related drug effects prior to starting antiviral treatment. Given the relatively short duration of treatment and the potential to use ribavirin-free regimens in most patients, the potential risks and benefits of delaying pregnancy until HCV antiviral treatment is completed should be considered. For additional information on HCV and pregnancy, [click here](#).


Reactivation of HBV

Cases of HBV reactivation, occasionally fulminant, during or after DAA therapy have been reported in HBV/HCV coinfecting patients who were not receiving HBV suppressive therapy ([Hayashi, 2016](#)); ([Takayama, 2016](#)); ([Ende, 2015](#)); ([Collins, 2015](#)); ([De Monte, 2016](#)); ([Sulkowski, 2016](#)); ([Wang, 2016](#)); ([Bersoff-Matcha, 2017](#)). In light of these observations and consistent with general recommendations for the assessment of the HCV-infected patient, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg testing, and for prior infection with anti-HBs and anti-HBc testing. HBV vaccination is recommended for all susceptible individuals. A test for HBV DNA should be obtained prior to DAA therapy in patients who are HBsAg positive. HBsAg positivity does not represent a contraindication to HCV DAA therapy. Patients meeting criteria for treatment of active HBV infection should be started on therapy at the same time (or before) HCV DAA therapy is initiated ([Terrault, 2015](#)).

Patients with low or undetectable HBV DNA levels can either receive prophylactic treatment for HBV for the duration of the DAA treatment to SVR12 or be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV-DNA testing. If monitoring is elected, HBV treatment should be started if the HBV DNA level increases >10-fold or is >1000 IU/mL in a patient with undetectable or unquantifiable HBV DNA prior to DAA treatment. There are insufficient data to provide clear recommendations for the monitoring of HBV DNA among patients testing positive either for anti-HBc alone (isolated anti-HBc) or for anti-HBs and anti-HBc (immune recovery). However, the possibility of HBV reactivation should be considered in these patients in the event of an unexplained increase in liver enzymes during and/or after completion of DAA therapy.

**Post-Treatment Follow-Up for Patients in Whom Treatment Failed**

<b>Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response</b>	
RECOMMENDED	RATING 
Disease progression assessment every 6 to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended.	I, C
Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).	I, C
Endoscopic screening for esophageal varices is recommended if cirrhosis <sup>a</sup> is present.	I, A
Evaluation for retreatment is recommended as effective alternative treatments become available.	I, C
<sup>a</sup> For <a href="#">decompensated cirrhosis</a> , please refer to the appropriate section.	


<b>The Following Monitoring Is Not Recommended During or After Therapy</b>	
NOT RECOMMENDED	RATING 
Monitoring for HCV drug resistance-associated substitutions during or after therapy is not recommended.	IIb, C

Patients who do not achieve SVR retain the possibility of continued liver injury and the potential to transmit HCV to others. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available (see [Retreatment of Persons in Whom Prior Therapy Has Failed](#)).

Given that persons in whom treatment failed remain at risk for ongoing liver injury and liver fibrosis progression ([Dienstag, 2011](#)), these patients should be monitored for signs and symptoms of cirrhosis. Patients in whom antiviral therapy failed may harbor viruses that are resistant to 1 or more of the antivirals at the time of virologic breakthrough ([Lawitz, 2014a](#)); ([Schneider, 2014](#)). However, there is no evidence to date that the presence of resistance-associated substitutions (RASs) results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. Additional information about RASs is available in the [HCV Resistance Primer](#) section. If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert in the treatment of HCV infection may be useful.

Information regarding retreatment of patients whose initial treatment regimen failed is available in the [Retreatment](#) section.

## Post-Treatment Follow-Up for Patients Who Achieved a Sustained Virologic Response

Recommended Follow-Up for Patients Who Achieved a Sustained Virologic Response (SVR)	
RECOMMENDED	RATING 
For patients who do not have advanced fibrosis (ie, those with Metavir stage F0, F1, or F2), recommended follow-up is the same as if they were never infected with HCV.	I, B
Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV-RNA test rather than an HCV-antibody test is recommended to assess for HCV recurrence or reinfection.	I, A
Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve SVR.	I, C
A baseline endoscopy is recommended to screen for varices if cirrhosis <sup>a</sup> is present. Patients in whom varices are found should be treated and followed as indicated.	I, C
Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving SVR.	I, C
<sup>a</sup> For <a href="#">decompensated cirrhosis</a> , please refer to the appropriate section.	

Patients who have undetectable HCV RNA in the serum, as assessed by a sensitive polymerase chain reaction (PCR) assay,  $\geq 12$  weeks after treatment completion are deemed to have achieved SVR. In these patients, HCV-related liver injury stops, although they remain at risk for non-HCV-related liver disease, such as fatty liver disease or alcoholic liver disease. Patients with cirrhosis or advanced fibrosis remain at risk for developing hepatocellular carcinoma (HCC).

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving SVR among adherent, immunologically competent, treatment-naive patients with compensated liver disease generally exceeds 95%. Among patients who achieved SVR with peginterferon/ribavirin treatment, more than 99% have remained free of HCV infection when followed for 5 years after treatment completion ([Manns, 2013](#)). Thus, achieving SVR is considered a virologic cure of HCV infection.

SVR typically aborts progression of liver injury with regression of liver fibrosis in most, but not all, treated patients ([Morisco, 2013](#)); ([Morgan, 2010](#)); ([George, 2009](#)); ([Morgan, 2013](#)); ([Singal, 2010](#)). Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0, F1, or F2) who achieve SVR should receive standard medical care that is recommended for patients who were never infected with HCV.

Among patients with advanced liver fibrosis (ie, Metavir stage F3 or F4) who achieve SVR, decompensated liver disease (with the exception of HCC) rarely develops during follow-up, and overall survival is prolonged ([Morisco, 2013](#)); ([Morgan, 2010](#)); ([George, 2009](#)); ([Morgan, 2013](#)); ([Singal, 2010](#)). Liver fibrosis and liver function test results improve in most patients who achieve SVR ([Morisco, 2013](#)); ([Morgan, 2010](#)); ([George, 2009](#)); ([Morgan, 2013](#)); ([Singal, 2010](#)). Bleeding from esophageal varices is rare after SVR ([Morisco, 2013](#)); ([Morgan, 2010](#)); ([George, 2009](#)); ([Morgan, 2013](#)); ([Singal, 2010](#)). Patients with cirrhosis should receive routine surveillance endoscopy for detection of esophageal varices if not previously done; if varices are found, they should be treated or followed as indicated ([Garcia-Tsao, 2007](#)).


The risk of developing HCC among cirrhotic patients who receive DAA treatment is debated. Multiple studies of cirrhotic patients who achieved SVR with peginterferon/ribavirin reported a significant reduction in the risk of developing HCC ([Morisco, 2013](#)); ([Morgan, 2010](#)); ([George, 2009](#)); ([Morgan, 2013](#)); ([Singal, 2010](#)). A recent report suggested a higher than expected frequency of HCC in patients with HCV-related cirrhosis treated successfully with DAAs ([Reig, 2016](#)). However, a meta-analysis evaluating the incidence of HCC among persons achieving SVR with DAAs found that the risk of HCC did not exceed that seen in patients who experienced SVR with interferon-based treatment after adjustment for baseline risk factors for HCC ([Waziry, 2017](#)).

Patients with cirrhosis who achieve SVR remain at risk for HCC. Thus, they should continue to undergo regular surveillance for HCC despite the lowered risk that results after viral eradication ([Bruix, 2011](#)). The risk of HCC among patients with advanced fibrosis prior to treatment but who have regression to minimal fibrosis after treatment is not known. In the absence of data to the contrary, such patients remain at some risk for HCC and should be monitored at regular intervals for HCC. Alpha-fetoprotein (AFP) alone is considered an inadequate screening test for HCC ([Bruix, 2011](#)).

Patients in whom SVR is achieved but who have another potential cause of liver disease (eg, excessive alcohol use, metabolic syndrome with or without proven fatty liver disease, or iron overload) remain at risk for fibrosis progression. It is recommended that such patients be educated about the risk of liver disease and monitored for liver disease progression with periodic physical examination, blood tests, and potentially, tests for liver fibrosis by a liver disease specialist.

Patients who achieve SVR can be reinfected with HCV if they are re-exposed to the virus. Annual testing for HCV reinfection among patients with ongoing risk for HCV infection (eg, [injection drug use](#) or [high-risk sexual exposure](#)) is recommended. A flare in liver enzyme levels should prompt immediate evaluation for HCV reinfection (see [Management of Acute HCV Infection](#)). HCV antibody (anti-HCV) remains positive in most patients following SVR. Thus, testing for HCV reinfection using an assay that detects HCV RNA (ie, a quantitative HCV-RNA test) is recommended.

## Monitoring for HCV During Chemotherapy and Immunosuppression

NOT RECOMMENDED	RATING 
Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc) is <b>not</b> routinely recommended.	III, C

Acute liver injury is common among patients receiving chemotherapy or immunosuppressive agents. Testing for hepatitis viruses should be included in the laboratory assessment of the cause of liver injury in these patients. Approximately 23% of patients with active HCV infection—especially those with a hematologic malignancy—have a flare in their HCV RNA level (>10-fold) during chemotherapy. An ALT level increase is less common and clinical symptoms of hepatitis are

uncommon ([Torres, 2017](#)). Among patients who have recovered from hepatitis C, either spontaneously or with DAA treatment, reactivation of HCV (ie, detectable HCV RNA) during chemotherapy is distinctly uncommon and is not anticipated to occur since there is no residual reservoir for the virus. Thus, in this latter group, routine testing for HCV RNA during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

**Last update:** May 24, 2018



# HCV Resistance Primer

## Introduction

Understanding principles of the emergence of drug-resistant viruses is critical when using targeted antiviral therapies. The best example of these principles can be gleaned from the study of HIV. Like HIV, HCV is an approximately 9.5 kilobase RNA virus that replicates very rapidly (billions of viruses daily). The production of each new virus is performed by an enzyme that results in 1 to 3 errors per replication cycle, on average. Many of these errors either have no effect on the progeny virus product or result in progeny viruses that are nonreplication competent (ie, dead viruses). For some newly produced viruses, however, the transcription errors result in changes in critical coding regions that may, by chance, change the susceptibility of the virus to 1 or more drugs used to treat the virus. The emergence of such drug-resistant viruses most often occurs when drug levels are subtherapeutic, thereby creating selective pressure for the resistant viruses to emerge as the dominant species. These newly formed resistant viruses have a selective growth advantage that allows them to replicate in the presence of antiviral drugs. In a subset of patients with chronic HCV infection, viral variants harboring substitutions associated with resistance to HCV directing-acting antivirals (DAAs) are detectable prior to antiviral therapy and, particularly in the case of NS5A inhibitor-containing regimens, may negatively impact treatment response. These substitutions often are referred to as baseline resistance-associated substitutions (RASs).

In the case of HCV DAAs, resistant viruses are also selected for and/or enriched in patients for whom a DAA regimen fails. These viruses contain substitutions that are designated as treatment-emergent (or treatment-selected) RASs. NS5A and NS3 RASs are frequently selected in patients with failure of NS5A or NS3 inhibitor-containing regimens, respectively. In contrast, NS5B nucleotide RASs are rarely detected (1% of failures) even after exposure to a failing DAA regimen containing a nucleotide inhibitor ([Svarovskaia, 2014](#)); ([Wyles, 2017](#)). This is likely due to the highly conserved catalytic site region that nucleotides bind, making substitutions in this region extremely rare—often referred to as a high barrier to resistance. Additionally, any such substitution would likely render the virus replication incompetent. Compounding the clinical impact of NS5A RASs is their ability to maintain high replication competence (aka, relative fitness) in the absence of continued drug pressure, allowing them to remain the dominant viral quasispecies for prolonged periods (years) relative to NS3 protease or NS5B nucleotide polymerase inhibitor RASs, which are typically less fit and tend to disappear over several months, being overcome by more fit wild-type virus species.

The magnitude of the negative impact of RASs, both baseline and selected, on treatment outcome varies according to regimen (coadministered drugs); patient factors that impact treatment response (cirrhosis); and the fold change decrease in potency conferred by the specific RAS(s). Given these considerations, RAS testing alone will not dictate optimal DAA regimen selection. In addition, a drug predicted to suffer a significant loss of potency in the presence of a RAS still may be used in specific clinical settings/regimens.

## Terminology, Thresholds of Clinical Relevance, and Assays

### Terminology

#### 1. Naming Convention for Hepatitis C Proteins

The hepatitis C genome codes for approximately 5 HCV-specific proteins, which are essential to: 1) form the viral structure (core and envelope proteins); 2) cut the HCV polyprotein; 3) provide enzymatic functions for replication and escape from the innate immune response (NS3/NS4A protease); 4) replicate the HCV RNA (NS5B RNA-dependent RNA polymerase); and 5) bind the HCV replication complex during replication and assembly (NS5A).

#### 2. Polymorphism (Substitution)

A reference (or consensus) nucleotide—and therefore amino acid sequence—has been defined for each HCV genotype. A polymorphism (or substitution) is a difference in an amino acid at a defined position of the HCV protein between a patient's HCV and the reference HCV protein. Substitution is the preferred terminology among most experts. However, the US Food and Drug Administration currently uses the term polymorphism.

To define a polymorphism, it is necessary to define: the HCV genotype (eg, genotype 1, 2, 3, etc) and subtype (eg,

1a vs 1b); the HCV protein (eg, NS5A); and the amino acid position (eg, 93). Polymorphisms are reported as letter-number-letter (eg, Y93H). The first letter refers to the amino acid typically expected for that position in the reference protein. The number refers to the amino acid position, and the final letter refers to the amino acid that is found in the patient's HCV isolate. Thus, NS5A Y93H refers to amino acid position 93 of the NS5A protein. The amino acid at this position in the reference strain is Y (ie, tyrosine) and the amino acid in the tested strain is H (ie, histidine). For some patients, multiple variants are present and several amino acids may be found at a given position. Thus, it is possible to have a virus with NS5A Y93H/M. Such a patient would have viruses with the amino acids histidine (H) or methionine (M) at position 93 of the NS5A protein.

### 3. Resistance-Associated Substitutions

A resistance-associated substitution describes any amino acid change from the consensus sequence at a position that has been associated with reduced susceptibility of a virus to 1 or more antiviral drugs. A specific RAS may or may not confer a phenotypic loss of susceptibility to other/multiple antiviral agents.

### 4. Drug-Class RASs

Drug-class RASs are amino acid substitutions that reduce the susceptibility of a virus to any (and at least 1) member of a drug class or, alternatively, the viral variants with reduced susceptibility that carry these substitutions. Class RASs may or may not confer resistance to a specific drug in that class.

### 5. Drug-Specific RASs

Drug-specific RASs are amino acid substitutions that reduce the susceptibility of a virus to a specific drug. When assessing the potential clinical impact of RASs on a given regimen, drug-specific RASs should be used. In an HCV-infected population not previously exposed to a DAA drug or class, drug-specific RASs will be found less frequently than class RASs.

## **Thresholds of Clinical Relevance**

HCV resistance to DAAs is a rapidly evolving field with demonstrated clinical impact in specific situations with currently available DAA regimens. Presently, the most clinically significant RASs are in the NS5A position for genotypes 1a and 3.

Data from clinical trials have demonstrated that RASs are commonly, but not always, found at the time of virologic failure. Viruses that are resistant to NS3/4A protease inhibitors seem to be less fit and may disappear from peripheral blood within a few weeks to months, whereas NS5A inhibitor-resistant viruses may persist for years, which could have implications for treatment and retreatment.

In general, drug-specific RASs need to be present in at least 15% of the viruses of a given patient to reduce the likelihood of achieving SVR ([Pawlotsky, 2016](#)). Drug-specific RASs that are found at a lower frequency may not convey sufficient resistance to reduce SVR with currently available DAA regimens.

## Assays

Methods to detect RASs include population sequencing (aka, Sanger sequencing) and deep sequencing (aka, next generation sequencing [NGS]). Both methods depend on sequencing the HCV RNA, calculating the amino acid sequence, and then inferring the presence of RASs. The methods differ in their sensitivity for detecting RASs. For the purposes of clinical care and decisions regarding which DAA regimen to use, both methods can be considered equivalent if a  $\geq 15\%$  cut point is used for determination of RASs by NGS. Recent studies have shown that NGS at a 1% level of sensitivity often result in the identification of additional RASs that are not associated with clinical failure ([Jacobson, 2015b](#)); ([Sarrazin, 2016](#)); ([Zeuzem, 2017](#)).

### 1. Genotypic Analysis

#### a. Population-Based Sequencing (Sanger)

Population sequencing of the HCV coding region of interest may be performed using reverse transcription polymerase chain reaction (PCR) and standard Sanger sequencing of the bulk PCR product. The sensitivity for detection of resistance substitutions varies but is generally 15% to 25%. As a standard, substitutions are reported as differences compared with a genotype-specific, wild-type strain.

#### b. Deep Sequencing Analysis

NGS (deep sequencing approaches) can increase the sensitivity of detection for minor variants. After sequencing HCV coding regions using PCR, a software algorithm is used to process and align sequencing data via a multistep method to identify the substitutions present at a predetermined level. This level, or threshold, can vary but is often set as low as  $>1\%$  for research purposes. To approximate results obtained by population sequencing, NGS thresholds are often set to  $\geq 10\%$ .

### 2. Phenotypic Analysis

Phenotypic analysis involves laboratory techniques whereby the degree of drug resistance conferred by an amino acid change as well as the replicative capacity (fitness) of a particular RAS can be estimated in the presence of a wild-type or consensus strain. These research techniques are not routinely used for clinical practice. To assess the level of resistance, RASs are typically introduced as point mutations into the backbone of an existing standard HCV genome within an existing cell culture/replicon or enzyme-based assay. Isolates harboring these RASs are then challenged by appropriate antiviral agents at increasing concentrations and fold changes—based on  $EC_{50}$  or  $IC_{50}$  and  $EC_{90}$  or  $IC_{90}$  values—are determined for inhibition of replication or enzyme activity, respectively, in comparison to wild-type virus. Comparison of replication levels for variants and wild-type constructs in the absence of drug allows for estimation of fitness.


### 3. Assay Summary Points

- Either population sequencing or deep sequencing can be used to detect the presence of RASs in NS3, NS5A, and NS5B.
- For clinical decisions, population sequencing or deep sequencing with at least 15% prevalence of RASs as the cutoff is recommended. The presence of RASs with  $<15\%$  prevalence should not be considered clinically significant.
- When assessing the potential clinical effect of RASs, it is important to determine the drug-specific RASs.

Resistance Testing in Clinical Practice

<b>Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice</b>	
RECOMMENDED	RATING
<p><b>Elbasvir/grazoprevir</b></p> <p>NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered.</p>	I, A
<p><b>Ledipasvir/sofosbuvir</b></p> <p>NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important<sup>a</sup> resistance is present, a different recommended therapy should be used.</p> <p>NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important<sup>a</sup> resistance is present, a different recommended therapy should be used.</p>	I, A
<p><b>Sofosbuvir/velpatasvir</b></p> <p>NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used.</p>	I, A
<p><b>Daclatasvir plus sofosbuvir</b></p> <p>NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added.</p> <p>NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used.</p>	I, B
<p><sup>a</sup> Clinically important = greater than 100-fold resistance</p>	

## Regimen-Specific Clinical Practice Situations in Which RAS Testing Is Not Recommended

NOT RECOMMENDED	RATING 
<p><b>Elbasvir/grazoprevir</b> RAS testing is not recommended for any genotype 1b-infected patients being considered for elbasvir/grazoprevir therapy.</p>	I, A
<p><b>Glecaprevir/pibrentasvir</b> RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for glecaprevir/pibrentasvir for 8, 12, or 16 weeks.</p>	I, A
<p><b>Ledipasvir/sofosbuvir</b> NS5A RAS testing is not recommended for any genotype 1b-infected patients being considered for ledipasvir/sofosbuvir therapy.</p>	I, A
<p>NS5A RAS testing is not recommended for genotype 1a-infected, treatment-naive patients being considered for ledipasvir/sofosbuvir therapy.</p>	I, A
<p>NS5A RAS testing is not recommended for genotype 1a- or 1b-infected, treatment-naive patients without cirrhosis and with a viral load &lt;6 million IU/mL being considered for an 8-week course of ledipasvir/sofosbuvir therapy.</p>	I, A
<p><b>Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin</b> RAS testing is not recommended for genotype 1- or 4-infected, treatment-naive or -experienced patients being considered for therapy with paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin, respectively.</p>	I, A
<p><b>Sofosbuvir/velpatasvir</b> RAS testing is not recommended for patients with genotype 1, 2, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir therapy.</p>	I, A
<p><b>Sofosbuvir/velpatasvir/voxilaprevir</b> RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir/voxilaprevir therapy.</p>	I, A

Resistance testing is most important in clinical practice when the results would modify treatment management by impacting the duration of therapy and/or inclusion of ribavirin, or result in selection of alternative therapy. Unfortunately, at this time, the utility of RAS testing varies by both patient characteristics and DAA regimen.

### Approaches to Overcome Resistance

Data for currently approved DAAs provide limited insight on optimal retreatment approaches for patients with a previous DAA therapy failure and high fold change RASs, particularly those in NS5A. Until regimens combining multiple drugs predicted to be active (based on the available resistance profile) are available and adequate phase 2/3 studies in DAA

treatment failure populations are accomplished, other aspects of therapy must be optimized in treatment-experienced patients with RASs. In general, optimization involves appropriately characterizing the patient along with use of an extended duration of therapy and the addition of ribavirin (unless an absolute contraindication to ribavirin exists).

### Characterizing Patients at Risk

The characteristics that increase the risk of DAA treatment failure are different for each oral regimen. Thus, understanding the population at risk is imperative. Generally, this requires accurate assessment of liver fibrosis and clarification of prior therapy.

### Virus

Determination of HCV genotype, subtype, and baseline RASs may be necessary to fully characterize a patient's risk for therapeutic failure and optimize the treatment approach.

### Treatment Duration

The duration of therapy should always be optimized to attain a cure. Although short-duration therapy has been associated with a higher chance of relapse, careful selection of patients for shortened therapy may minimize relapse risk and lead to significant cost savings. In contrast, extension of therapy (often to 24 weeks) in conjunction with the addition of ribavirin has been associated with reasonable SVR rates during retreatment of patients with past DAA therapy failure, even in the presence of significant drug-specific RASs prior to retreatment ([Cooper, 2016](#)); ([Gane, 2016](#)).

### Ribavirin

The addition of ribavirin increases SVR in patient populations with an increased risk for treatment failure (eg, decompensated cirrhosis). It also improves SVR rates among patients with baseline NS5A RASs and prior DAA treatment failure.

### Complementary Therapy

Although data are limited, patients with multiclass RASs can achieve SVR by combining triple or quadruple drug class regimens (see section on [retreatment](#) in prior DAA failure). This approach may become less necessary with the approval of standalone dual- or triple-drug regimens composed of second-generation protease and NS5A inhibitors with improved activity against common RASs.

## Considerations With Current Antiviral Regimens

### Daclatasvir + Sofosbuvir

Daclatasvir plus sofosbuvir is most commonly used for genotype 3-infected individuals. The phase 3 ALLY-3 study had an overall SVR rate of 89% in treatment-naïve and -experienced, genotype 3-infected patients treated with 12 weeks of daclatasvir plus sofosbuvir without ribavirin. This study demonstrated that lower SVR rates were observed in patients with cirrhosis, irrespective of treatment experience (97% [73/75] SVR without cirrhosis vs 58% [11/19] SVR with cirrhosis). When RAS impact was assessed, the presence of baseline Y93H was associated with a lower SVR rate in those with cirrhosis. Thirteen patients had Y93H at baseline; 67% (6/9) without cirrhosis achieved SVR whereas only 25% (1/4) with cirrhosis achieved SVR ([Nelson, 2015](#)). The subsequent ALLY-3+ study evaluated 12 weeks or 16 weeks of daclatasvir plus sofosbuvir and ribavirin in treatment-naïve or -experienced patients with genotype 3 infection and advanced fibrosis or compensated cirrhosis. The overall SVR rate was 90%. Again, virologic failure was higher in individuals with cirrhosis (86% SVR) compared to those with stage 3 fibrosis (100% SVR). Increased treatment duration did not appear to improve efficacy. Eight patients had a baseline RAS, including 2 with Y93H, 5 with A30K, and 1 with A30A/K. The only relapse occurred in a patient with the Y93H RAS ([Leroy, 2016](#)).

### Elbasvir/Grazoprevir

Elbasvir/grazoprevir is indicated for treatment-naïve and -experienced patients with genotype 1 or 4 infection. The presence of NS3 RASs has no significant impact on SVR12 in patients treated with elbasvir/grazoprevir. The presence of NS5A RASs has no significant impact in genotype 1b infection.

In treatment-naïve, genotype 1a-infected patients (with or without cirrhosis) treated with 12 weeks of therapy, the



presence of NS3 RASs has no impact ([Zeuzem, 2015](#)). In treatment-naïve or prior relapse patients treated for 12 weeks with elbasvir/grazoprevir without ribavirin, the presence of high fold change NS5A RASs (at amino acid positions 28, 30, 31, and 93) decreased SVR to 58% (14/24) compared to 98% SVR in those without NS5A RASs. The presence of NS5A RASs had a similar impact on treatment-experienced patients (with or without cirrhosis) who received 12 weeks of elbasvir/grazoprevir without ribavirin (SVR12 29% vs 97%, respectively) ([Jacobson, 2015b](#)).

### **Glecaprevir/Pibrentasvir**

In a study of the resistance profiles of glecaprevir and pibrentasvir using cell cultures ([Ng, 2017](#)), selection of genotypes 1a, 1b, 2a, 3a, 4a, and 6a replicons for reduced susceptibility to glecaprevir resulted in the emergence of RASs at A156 or D/Q168. The A156 RAS resulted in the greatest reductions (>100-fold) in glecaprevir susceptibility. The D/Q168 RAS had varying effects on glecaprevir susceptibility depending on genotype/subtype and specific amino acid change; the greatest reductions (>30-fold) were observed in genotypes 1a (D168F/Y), 3a (Q168R), and 6a (D168A/G/H/V/Y). However, these RASs are rarely detected clinically. Pibrentasvir selected no viable colonies in genotype 1b, 2b, 4a, 5a, and 6a. Of the few RASs selected by pibrentasvir, Y93H/N conferred <7-fold resistance.

The presence of RAS at baseline had minimal impact on SVR rates with glecaprevir/pibrentasvir in registration trials, that predominantly enrolled non-cirrhotic subjects. In a pooled analysis of NS3/4A protease inhibitor- and NS5A inhibitor-naïve patients who received glecaprevir/pibrentasvir in phase 2 and 3 studies ([Forns, 2017](#)); ([Foster, 2017](#)); ([Asselah, 2018b](#)); ([Zeuzem, 2016](#)); ([Kwo, 2017b](#)), baseline RASs in patients with genotype 1, 2, 4, 5, or 6 infection had no impact on SVR12 ([Krishnan, 2018](#)). Among treatment-naïve genotype 3-infected patients without cirrhosis who received glecaprevir/pibrentasvir for 8 weeks, the A30K polymorphism was detected in 10%, of whom 78% achieved SVR12. There are insufficient data to characterize the impact of A30K in genotype 3-infected patients with cirrhosis or prior treatment experience. All genotype 3-infected patients with Y93H prior to treatment achieved SVR12.

### **Ledipasvir/Sofosbuvir**

Several comprehensive analyses of genotype 1-infected patients treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies have helped clarify the impact of baseline RASs on SVR rates with this regimen ([Sarrazin, 2016](#)); ([Zeuzem, 2017](#)). In a pooled analysis of patients with genotype 1a or 1b infection who received ledipasvir/sofosbuvir, 93.5% (316/338) of those with baseline NS5A RASs achieved SVR12 compared to an SVR12 rate of 98.4% (1,741/1,770) in patients without baseline NS5A RASs ([Sarrazin, 2016](#)). In this analysis, the reduction in SVR rate was driven predominantly by patients with genotype 1a NS5A RASs. The SVR12 rates for genotype 1a-infected patients with and without NS5A RASs were 92.3% and 98.3%, respectively. A slightly lower SVR12 rate of 90% was observed for genotype 1a-infected patients with NS5A RASs using a 15% deep sequencing cutoff value.

Notably, other factors further delineated populations at risk for relapse in this analysis, including high-level baseline NS5A RASs (>100-fold resistance with Q30H/R, L31M/V, and Y93C/H/N in genotype 1a) and a shorter duration therapy (8 weeks or 12 weeks vs 24 weeks). SVR12 rates were 97.4% to 100% in treatment-experienced patients without NS5A RASs or with RASs with <100-fold resistance treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks. However, when RASs with >100-fold resistance were present, SVR12 rates dropped to 64.7% (11/17) with 12 weeks of therapy compared to 100% (6/6) with 24 weeks of therapy. In this small subset of patients, the addition of ribavirin did not appear to offer the same benefit as extension of therapy to 24 weeks in this pooled analysis. SVR12 rate was 81.8% in those with >100-fold NS5A resistance who received 12 weeks of ledipasvir/sofosbuvir with ribavirin. In contrast, in the SIRIUS trial, all 8 treatment-experienced cirrhotic patients with >100-fold resistance treated for 12 weeks with ledipasvir/sofosbuvir plus ribavirin achieved SVR12.

### **Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir ± Ribavirin**

Paritaprevir/ritonavir/ombitasvir plus dasabuvir is currently indicated for genotype 1-infected patients. Paritaprevir/ritonavir/ombitasvir is indicated for genotype 4-infected patients, including those with prior peginterferon/ribavirin therapy failure. Patients with genotype 1a or 4 infection receive the addition of ribavirin whereas genotype 1b-infected patients do not. RAS testing has not been demonstrated to impact SVR rates, partially due to the addition of ribavirin in those patients at higher risk for treatment failure in the setting of RASs. Use of paritaprevir/ritonavir/ombitasvir plus dasabuvir alone in patients with a history of prior DAA treatment failure is not recommended.



**Sofosbuvir/Velpatasvir**

Sofosbuvir/velpatasvir is a pangenotypic therapy indicated for treatment-naïve and -experienced patients with or without cirrhosis. The presence of NS5A RASs had no impact on SVR12 for patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir/velpatasvir for 12 weeks in the ASTRAL studies ([Hézode, 2018](#)). The presence of Y93H in genotype 3-infected patients decreased the SVR12 rate to 84% (21/25 patients) compared to 97% (242/249) in those without this RAS ([Foster, 2015a](#)). This appeared to be more impactful in patients with cirrhosis and/or prior treatment experience with an interferon-based regimen. Ribavirin was not used in these trials and thus, an evidence-based strategy to improve efficacy in those with genotype 3 infection and the NS5A Y93H RAS is not known.

**Sofosbuvir/Velpatasvir/Voxilaprevir**

Sofosbuvir/velpatasvir/voxilaprevir fills an important role as a pangenotypic regimen for patients who have experienced treatment failure with DAA therapy. The presence of NS3, NS5A, or NS5B RASs prior to treatment did not influence the likelihood of SVR12, and 12 weeks of treatment produced high SVR12 rates (96%) in DAA-experienced patients. RAS testing has not been demonstrated to impact SVR rates with sofosbuvir/velpatasvir/voxilaprevir therapy ([Bourlière, 2017](#)).

**Table 1. Most Common, Clinically Important RASs by DAA, Genotype, and Fold Change**

DAA	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N
Ledipasvir	20x	>100x	>100x / >100x	>1000x / >10,000	>100x / >50x	>100x / --
Ombitasvir	>1000x	>100x	<3x >100x	>10,000x / >10,000x	<10x	20x / 50x
Daclatasvir	>100x	>1000x	>100x / >1000x	>1000x / >10,000x	<10x	20x / 50x
Elbasvir	20x	>100x	>10x >100x	>1000x / >1000x	<10x	>100x / --
Velpatasvir	<10x	<3x	20x / 50x	>100x / >1000x	<3x	<3x / --

Color Key: light green = <3-fold change; dark green = <10-fold change; orange = >10- to 100-fold change; pink = >100-fold change

**Table 2. Clinically Important RASs by DAA Regimen and Genotype**

DAA Regimen	Genotype		
	1a	1b	3
Ledipasvir/sofosbuvir	Q30H/R L31M/V Y93C/H/N	L31V ?Y93H	n/a
Elbasvir/grazoprevir	M28A/T Q30H/R L31M/V Y93C/H/N	Y93H	n/a
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin	n/a	n/a	n/a
Sofosbuvir/velpatasvir	n/a	n/a	Y93H

**Table 3. NS5A RAS Testing Recommendations Prior to Initiation of DAA Treatment Among Genotype 1 Patients by DAA Regimen, Virus Subtype, Prior Treatment Experience, and Cirrhosis Status**

DAA Regimen	1b TN <sup>a</sup> or TE <sup>b</sup>	1a TN	1a TE No Cirrhosis	1a TE Cirrhosis
Ledipasvir/sofosbuvir	No	No	Yes	Yes
Elbasvir/grazoprevir	No	Yes	Yes	Yes
Sofosbuvir/velpatasvir	No	No	No	No
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin	No	No	No	No

<sup>a</sup> TN = treatment naive  
<sup>b</sup> TE = treatment experienced

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## Related References

- AASLD-IDSA . [Recommendations for testing, managing, and treating hepatitis C](http://hcvguidelines.org/) [Internet]. 2017. <http://hcvguidelines.org/>
- Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. [Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America](#). Clin Infect Dis. 2014;58(1):1-10.
- Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR, et al. [Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study](#). Clin. Gastroenterol. Hepatol. 2015;13(4):772-779.
- Agnello V, Chung RT, Kaplan LM. [A role for hepatitis C virus infection in type II cryoglobulinemia](#). N Engl J Med. 1992;327(21):1490-1495.
- Allison RD, Tong X, Moorman AC, Ly KN, Rupp L, Xu F, et al. [Increased incidence of cancer and cancer-related mortality among persons with chronic hepatitis C infection, 2006-2010](#). J Hepatol. 2015;63(4):822-828.
- Alter MJ, Kuhnert WL, Finelli L. [Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus](#). Centers for Disease Control and Prevention. MMWR Recomm Rep. 2003;52(RR-3):1-13, 15.
- Amon JJ, Garfein RS, Ahdieh-Grant L, Armstrong GL, Ouellet LJ, Latka MH, et al. [Prevalence of hepatitis C virus infection among injection drug users in the United States, 1994-2004](#). Clin Infect Dis. 2008;46(12):1852-1858.
- Arase Y, Suzuki F, Suzuki Y, Akuta N, Kobayashi M, Kawamura Y, et al. [Sustained virological response reduces incidence of onset of type 2 diabetes in chronic hepatitis C](#). Hepatology. 2009;49(3):739-744.
- Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, et al. [Outcomes of treatment for hepatitis C virus infection by primary care providers](#). N Engl J Med. 2011;364(23):2199-2207.
- Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. [Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis](#). Clin Infect Dis. 2013;57(Suppl 2):S80-S89.
- Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, et al. [Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Patients With Hepatitis C Virus Genotype 2, 4, 5, or 6 Infection Without Cirrhosis](#). Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association. 2018;16(3):417 - 426.
- Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. [A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C](#). Clin Gastroenterol Hepatol. 2011;9(6):509-516.
- Barua S, Greenwald R, Grebely J, Dore GJ, Swan T, Taylor LE. [Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States](#). Ann Intern Med. 2015;163(3):215-223.
- Bedossa P, Dargère D, Paradis V. [Sampling variability of liver fibrosis in chronic hepatitis C](#). Hepatology. 2003;38(6):1449-1457.
- Bellentani S, Pozzato G, Saccoccio G, Crovatto M, Croce LS, Mazzoran L, et al. [Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study](#). Gut. 1999;44(6):874-880.
- Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. [Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group](#). Hepatology. 1999;30(4):1054-1058.

- Benhamou Y, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, et al. [Factors affecting liver fibrosis in human immunodeficiency virus- and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy](#). Hepatology. 2001;34(2):283-287.
- Berenguer M, Palau A, Aguilera V, Rayon JM, Juan FS, Prieto M. [Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation](#). Am J Transplant. 2008;8(3):679-687.
- Berenguer J, Álvarez-Pellicer J, Martín PM, López-Aldeguer J, Von-Wichmann MA, Quereda C, et al.. [Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfecting with human immunodeficiency virus and hepatitis C virus](#). Hepatology. 2009;50(2):407-413.
- Berenguer M, Schuppan D. [Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment](#). J Hepatol. 2013;58(5):1028-1041.
- Bersoff-Matcha SJ, Cao K, Jason M, Ajao A, S. Jones C, Meyer T, et al. [Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System](#). Annals of Internal Medicine. 2017;166(11):792 - 798.
- Bochud PY, Cai T, Overbeck K, Bochud M, Dufour JF, Mullhaupt B, et al. [Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C](#). J Hepatol. 2009;51(4):655-666.
- Bonder A, Afdhal NH. [Utilization of FibroScan in clinical practice](#). Curr Gastroenterol Rep. 2014;16(2):372.
- Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, et al. [Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis](#). J Hepatol. 2007;46(3):420-431.
- Boscarino JA, Lu M, Moorman AC, Gordon SC, Rupp LB, Spradling PR, et al. [Predictors of poor mental and physical health status among patients with chronic hepatitis C infection: the Chronic Hepatitis Cohort Study \(CHeCS\)](#). Hepatology (Baltimore, Md.). 2015;61(3):802 - 811.
- Bourliere M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. [Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection](#). The New England Journal of Medicine. 2017;376(22):2134 - 2146.
- Boursier J, de Ledinghen V, Zarski JP, Fouchard-Hubert I, Gallois Y, Oberti F, et al. [Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive](#). Hepatology. 2012;55(1):58-67.
- Brau N, Salvatore M, Ríos-Bedoya CF, Fernández-Carbia A, Paronetto F, Rodríguez-Orengo JF, et al.. [Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy](#). J Hepatol. 2006;44:47-55.
- Bravo MJ, Vallejo F, Barrio G, Brugal MT, Molist G, Pulido J, et al. [HCV seroconversion among never-injecting heroin users at baseline: no predictors identified other than starting injection](#). Int J Drug Policy. 2012;23(5):415-419.
- Bruggmann P, Litwin AH. [Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all](#). Clin Infect Dis. 2013;57(2):S56-S61.
- Bruix J, Sherman M. [Management of hepatocellular carcinoma: an update](#). Hepatology. 2011;53(3):1020-1022.
- Butt AA, McGinnis K, Skanderson M, Justice AC. [A comparison of treatment eligibility for hepatitis C virus in HCV-monoinfected versus HCV/HIV-coinfected persons in electronically retrieved cohort of HCV-infected veterans](#). AIDS Res Hum Retroviruses. 2011;27(9):973-979.
- Canary LA, Klevens RM, Holmberg SD. [Limited Access to New Hepatitis C Virus Treatment Under State Medicaid](#)

[Programs](#). Ann Intern Med. 2015;163:226-228.

Castera L, Vergniol J, Foucher J, Le BB, Chanteloup E, Haaser M, et al. [Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C](#). Gastroenterology. 2005;128(2):343-350.

Castera L, Sebastiani G, Le BB, de Ledinghen V, Couzigou P, Alberti A. [Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C](#). J Hepatol. 2010;52(2):191-198.

Castera L. [Noninvasive methods to assess liver disease in patients with hepatitis B or C](#). Gastroenterology. 2012;142(6):1293-1302.

[CDC. Recommendations for prevention and control of hepatitis C virus \(HCV\) infection and HCV-related chronic disease](#). MMWR Morb Mortal Wkly Rep. 1998;47(RR-19):1-39.

[CDC: Recommendations for preventing transmission of infections among chronic hemodialysis patients](#). MMWR Recomm Rep. 2001;50(RR-5):1-43.

[CDC: Recommendations for identification and public health management of persons with chronic hepatitis B virus infection](#). MMWR. 2008;57(RR-8).

[CDC: Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices \(ACIP\)](#). MMWR. 2012;61(40):816-819.

[Centers for Disease Control and Prevention \(CDC\). Testing for HCV infection: an update of guidance for clinicians and laboratorians](#). MMWR Morb Mortal Wkly Rep. 2013;62(18):362-365.

[CDC Statistics and Surveillance. HCV](#). 2016.

Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK, et al. [Cost-effectiveness of Early Treatment of Hepatitis C Virus Genotype 1 by Stage of Liver Fibrosis in a US Treatment-Naive Population](#). JAMA Intern Med. 2016;176:65-73.

Charlton MR, Seaberg E, Wiesner R, Everhart J, Zetterman R, Lake J, et al. [Predictors of patient and graft survival following liver transplantation for hepatitis C](#). Hepatology. 1998;28(3):823-830.

Charlton MR, Gane EJ, Manns MP, Brown, Jr. RS, Curry MP, Kwo PY, et al. [Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation](#). Gastroenterology. 2015;148(1):108-117.

Chatwal J, Kanwal F, Roberts MS, Dunn MA. [Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States](#). Ann Intern Med. 2015;162(6):397-406.

Chew KW, Allen SA, Taylor LE, Rich JD, Feller E. [Treatment outcomes with pegylated interferon and ribavirin for male prisoners with chronic hepatitis C](#). J Clin Gastroenterol. 2009;43(7):686-691.

Chidi AP, Rogal S, Bryce CL, Bryce CL. [Cost-Effectiveness of New Antiviral Regimens for Treatment-Naive US Veterans with Hepatitis C](#). Hepatology. 2016;63(2):428-36.

Chou R, Wasson N. [Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review](#). Ann Intern Med. 2013;158(11):807-820.

Chu CJ, Lee SD. [Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment](#). J Gastroenterol Hepatol. 2008;23(4):512-520.

- Clark BT, Garcia-Tsao G, Fraenkel L. [Patterns and predictors of treatment initiation and completion in patients with chronic hepatitis C virus infection](#). Patient Prefer Adherence. 2012;6:285-295.
- Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA, et al. [Hepatitis B Virus Reactivation During Successful Treatment of Hepatitis C Virus With Sofosbuvir and Simeprevir](#). Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2015;61(8):1304 - 1306.
- Conjeevaram HS, Wahed AS, Afdhal NH, Howell CD, Everhart JE, Hoofnagle JH. [Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C](#). Gastroenterology. 2011;140(2):469-477.
- Cooper CL, Naggie S, Saag M, Yang JC, Stamm LM, Dvory-Sobol H, et al. [Retreatment of HCV/HIV-Coinfected Patients Who Failed 12 Weeks of LDV/SOF \[Abstract 573\]](#). In 23rd Conference on Retroviruses and Opportunistic Infections, February 22-25. 2016.
- Coppola N, De PS, Pisaturo M, Paradiso L, Macera M, Capoluongo N, et al. [Sustained virological response to antiviral treatment in chronic hepatitis C patients may be predictable by HCV-RNA clearance in peripheral blood mononuclear cells](#). J Clin Virol. 2013;58(4):748-750.
- Corrao G, Arico S. [Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis](#). Hepatology. 1998;27(4):914-919.
- Coyle C, Viner K, Hughes E, Kwakwa H, Zibbell JE, Vellozzi C, et al. [Identification and Linkage to Care of HCV-Infected Persons in Five Health Centers - Philadelphia, Pennsylvania, 2012-2014](#). MMWR Morb Mortal Wkly Rep. 2015;64(17):459-463.
- Curry MP, Forns X, Chung RT, Terrault NA, Brown, Jr. RS, Fenkel JM, et al. [Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study](#). Gastroenterology. 2015;148(1):100-107.
- De Monte A, Courjon J, Anty R, Cua E, Naqvi A, Mondain V, et al. [Direct-acting antiviral treatment in adults infected with hepatitis C virus: Reactivation of hepatitis B virus coinfection as a further challenge](#). Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology. 2016;78:27 - 30.
- Denniston MM, Klevens RM, McQuillan GM, Jiles RB. [Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008](#). Hepatology. 2012;55(6):1652-1661.
- Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. [Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010](#). Ann Intern Med. 2014;160(5):293-300.
- Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, et al. [Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon](#). N Engl J Med. 2008;359(23):2429-2441.
- Dienstag JL, Ghany MG, Morgan TR, Di Bisceglie AM, Bonkovsky HL, Kim HY, et al. [A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C](#). Hepatology. 2011;54(2):396-405.
- Dieperink E, Ho SB, Heit S, Durfee JM, Thuras P, Willenbring ML. [Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic](#). Psychosomatics. 2010;51(2):149-156.
- Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. [Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial](#). Annals of Internal Medicine. 2016;165(9):625 - 634.
- Durier N, Nguyen C, White LJ. [Treatment of hepatitis C as prevention: a modeling case study in Vietnam](#). PLoS One. 2012;7(4):e34548.



- [EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis.](#) J Hepatol. 2015;63(1):237-264.
- Edlin BR, Eckhardt BJ, Shu MA, Shu MA. [Toward a more accurate estimate of the prevalence of hepatitis C in the United States.](#) Hepatology. 2015;62(5):1353-63.
- Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. [Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report.](#) Journal of Medical Case Reports. 2015;9:164.
- Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, et al. [Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial.](#) Gastroenterology. 2009;137(2):549-557.
- Everhart JE, Wright EC, Goodman ZD, Dienstag JL, Hoefs JC, Kleiner DE, et al. [Prognostic value of Ishak fibrosis stage: findings from the hepatitis C antiviral long-term treatment against cirrhosis trial.](#) Hepatology. 2010;51(2):585-594.
- Everson GT. [Treatment of patients with hepatitis C virus on the waiting list.](#) Liver Transpl. 2003;9(11):S90-S94.
- Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, et al. [Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy.](#) Hepatology. 2005;42(2):255-262.
- Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, et al. [Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial.](#) Hepatology. 2006;44(6):1675-1684.
- Fabrizi F, Poordad F, Martin P. [Hepatitis C infection and the patient with end-stage renal disease.](#) Hepatology. 2002;36(1):3-10.
- Fabrizi F, Takkouche B, Lunghi G, Dixit V, Messa P, Martin P. [The impact of hepatitis C virus infection on survival in dialysis patients: meta-analysis of observational studies.](#) J Viral Hepat. 2007;14(10):697-703.
- Fabrizi F, Messa P, Martin P. [Health-related quality of life in dialysis patients with HCV infection.](#) Int J Artif Organs. 2009;32(8):473-481.
- Fabrizi F, Dixit V, Messa P. [Antiviral therapy of symptomatic HCV-associated mixed cryoglobulinemia: meta-analysis of clinical studies.](#) J Med Virol. 2013;85(6):1019-1027.
- Fabrizi F, Martin P, Dixit V, Messa P. [Meta-analysis of observational studies: hepatitis C and survival after renal transplant.](#) J Viral Hepat. 2014;21(5):314-324.
- Feld JJ, Liang TJ. [Hepatitis C -- identifying patients with progressive liver injury.](#) Hepatology. 2006;43(2 Suppl 1):S194-S206.
- Fierer DS, Uriel AJ, Carriero DC, Klepper A, Dieterich D, Mullen MP, et al. [Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study.](#) J Infect Dis. 2008;198(5):683-686.
- Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. [National surveillance of dialysis-associated diseases in the United States, 2002.](#) Semin Dial. 2005;18(1):52-61.
- Fissell RB, Bragg-Gresham JL, Woods JD, Jadoul M, Gillespie B, Hedderwick SA, et al. [Patterns of hepatitis C prevalence and seroconversion in hemodialysis units from three continents: the DOPPS.](#) Kidney Int. 2004;65(6):2335-2342.
- Fontana RJ, Sanyal AJ, Ghany MG, Lee WM, Reid AE, Naishadham D, et al. [Factors that determine the development and progression of gastroesophageal varices in patients with chronic hepatitis C.](#) Gastroenterology. 2010;138(7):2321-31,

2331.

Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. [The association between hepatitis C infection and survival after orthotopic liver transplantation](#). *Gastroenterology*. 2002;122:889-896.

Forns X, Navasa M, Rodes J. [Treatment of HCV infection in patients with advanced cirrhosis](#). *Hepatology*. 2004;40(2):498.

Forns X, Charlton MR, Denning J, McHutchison JG, Symonds WT, Brainard D, et al. [Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation](#). *Hepatology*. 2015;61(5):1485-1494.

Forns X, Lee SS, Valdes J, Lens S, Ghalib R, Aguilar H, et al. [Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis \(EXPEDITION-1\): a single-arm, open-label, multicentre phase 3 trial](#). *The Lancet. Infectious Diseases*. 2017;17(10):1062-8.

Foster GR, Goldin RD, Thomas HC. [Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis](#). *Hepatology*. 1998;27(1):209-212.

Foster GR, Afdhal NH, Roberts SK. [Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection](#). *N Engl J Med*. 2015;373(27):2608-17.

Foster GR, Gane E, Asatryan A, Asselah T, Ruane PJ, Pol S, et al. [ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis](#). *Journal of Hepatology [Internet]*. 2017;66(1):S33. [http://dx.doi.org/10.1016/S0168-8278\(17\)30326-4](http://dx.doi.org/10.1016/S0168-8278(17)30326-4)

Gane EJ, Shiffman ML, Etzkorn K, Morelli G, Stedman C, Davis MN, et al. [Sofosbuvir/Velpatasvir in Combination With Ribavirin for 24 Weeks Is Effective Retreatment for Patients Who Failed Prior NS5A-Containing DAA Regimens: Results of the Retreatment Study](#). In 51st Annual Meeting of the European Association for the Study of the Liver (EASL). April 13-17. Barcelona, Spain; 2016.

Garcia-Bengoechea M, Basaras M, Barrio J, Arrese E, Montalvo II, Arenas JI, et al. [Late disappearance of hepatitis C virus RNA from peripheral blood mononuclear cells in patients with chronic hepatitis C in sustained response after alpha-interferon therapy](#). *Am J Gastroenterol*. 1999;94(7):1902-1905.

Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. [Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis](#). *Hepatology*. 2007;46(3):922-938.

George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. [Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients](#). *Hepatology*. 2009;49(3):729-738.

Gerber L, Estep M, Stepanova M, Escheik C, Weinstein A, Younossi ZM. [Effects of Viral Eradication With Ledipasvir and Sofosbuvir, With or Without Ribavirin, on Measures of Fatigue in Patients With Chronic Hepatitis C Virus Infection](#). *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association*. 2016;14(1):156 - 164.e3.

Ghany MG, Kleiner DE, Alter H, Doo E, Khokar F, Promrat K, et al. [Progression of fibrosis in chronic hepatitis C](#). *Gastroenterology*. 2003;124(1):97-104.

Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. [An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases](#). *Hepatology*. 2011;54(4):1433-1444.

Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. [Prevalence of hepatitis C virus infection in porphyria cutanea tarda: systematic review and meta-analysis](#). *J Hepatol*. 2003;39(4):620-627.

- Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. [Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection](#). *Aliment Pharmacol Ther*. 2005;21(6):653-662.
- Govindasamy D, Ford N, Kranzer K. [Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review](#). *AIDS*. 2012;26(16):2059-2067.
- Grady BP, Schinkel J, Thomas XV, Dalgard O. [Hepatitis C virus reinfection following treatment among people who use drugs](#). *Clin Infect Dis*. 2013;57(Suppl 2):S105-S110.
- Grebely J, Matthews GV, Hellard M, Shaw D, Shaw D, Petoumenos K, Yeung B, et al. [Adherence to treatment for recently acquired hepatitis C virus \(HCV\) infection among injecting drug users](#). *J Hepatol*. 2011;55(1):76-85.
- Gumber SC, Chopra S. [Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations](#). *Ann Intern Med*. 1995;123(8):615-620.
- Hagström H. [Alcohol Consumption in Concomitant Liver Disease: How Much is Too Much?](#). *Current Hepatology Reports*. 2017;16(2):152 - 157.
- Harris DR, Gonin R, Alter HJ, Wright EC, Buskell ZJ, Hollinger FB, et al. [The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse](#). *Ann Intern Med*. 2001;134(2):120-124.
- Hayashi K, Ishigami M, Ishizu Y, Ishizu Y. [A case of acute hepatitis B in a chronic hepatitis C patient after daclatasvir and asunaprevir combination therapy: hepatitis B virus reactivation or acute self-limited hepatitis?](#). *Clin J Gastroenterol*. 2016;.
- He T, Li K, Roberts MS, Spaulding AC, Ayer T, Grefenstette JJ, et al. [Prevention of Hepatitis C by Screening and Treatment in U.S. Prisons](#). *Ann Intern Med*. 2016;164(2):84-92.
- Hellard ME, Hocking JS, Crofts N. [The prevalence and the risk behaviours associated with the transmission of hepatitis C virus in Australian correctional facilities](#). *Epidemiol Infect*. 2004;132(3):409-15.
- Hellard ME, Jenkinson R, Higgs P, Stoope MA, Sacks-Davis R, Gold J, et al. [Modelling antiviral treatment to prevent hepatitis C infection among people who inject drugs in Victoria, Australia](#). *Med J Aust*. 2012;196(10):638-641.
- Hellard M, Doyle JS, Sacks-Davis R, Thompson AJ, McBryde E. [Eradication of hepatitis C infection: the importance of targeting people who inject drugs](#). *Hepatology*. 2014;59(2):366-369.
- Henderson DK, Dembry L, Fishman NO, Grady C, Lundstrom T, Palmore TN, et al. [SHEA guideline for management of healthcare workers who are infected with hepatitis B virus, hepatitis C virus, and/or human immunodeficiency virus](#). *Infect Control Hosp Epidemiol*. 2010;31(3):203-232.
- Hermine O, Lefrere F, Bronowicki JP, Mariette X, Jondeau K, Eclache-Saudreau V, et al. [Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection](#). *N Engl J Med*. 2002;347(2):89-94.
- Hezode C, Reau N, Svarovskaia ES, Doehle BP, Shanmugam R, Dvory-Sobol H, et al. [Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies](#). *Journal of Hepatology*. 2018;68(5):895 - 903.
- Ho SB, Brau N, Cheung R, Liu L, Sanchez C, Sklar M, et al. [Integrated Care Increases Treatment and Improves Outcomes of Patients With Chronic Hepatitis C Virus Infection and Psychiatric Illness or Substance Abuse](#). *Clin Gastroenterol Hepatol*. 2015;.
- Holmberg SD, Spradling PR, Moorman AC, Denniston MM. [Hepatitis C in the United States](#). *N Engl J Med*. 2013;368(20):1859-1861.

- Holmes HM, Hayley DC, Alexander GC, Sachs GA. [Reconsidering medication appropriateness for patients late in life](#). Arch Intern Med. 2006;166(6):605-609.
- Hosein SR, Wilson DP. [HIV, HCV, and drug use in men who have sex with men](#). Lancet. 2013;382(9898):1095-1096.
- Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, et al. [Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis](#). Hepatology. 1999;29(4):1215-1219.
- Hsu L, Bowlus CL, Stewart SL, Nguyen TT, Dang J, Chan B, et al. [Electronic messages increase hepatitis B screening in at-risk Asian American patients: a randomized, controlled trial](#). Dig Dis Sci. 2013;58(3):807-814.
- Hsu YC, Lin JT, Ho HJ, Kao YH, Huang YT, Hsiao NW, et al. [Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients](#). Hepatology. 2014;59(4):1293-1302.
- Hsu YC, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, et al. [Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection](#). Gut. 2015;64(3):495-503.
- Hung CH, Wang JH, Hu TH, Chen CH, Chang KC, Yen YH, et al. [Insulin resistance is associated with hepatocellular carcinoma in chronic hepatitis C infection](#). World J Gastroenterol. 2010;16(18):2265-2271.
- Islam MM, Topp L, Conigrave KM, White A, Reid SE, Grummett S, et al. [Linkage into specialist hepatitis C treatment services of injecting drug users attending a needle syringe program-based primary healthcare centre](#). J Subst Abuse Treat. 2012;43(4):440-445.
- Jacobson IM, Asante-Appiah E, Wong P, Black T, Howe A, Wahl J, et al. [Prevalence and Impact of Baseline NSA Resistance Associated Variants \(RAVs\) on the Efficacy of Elbasvir/Grazoprevir \(EBR/GZR\) Against GT1a Infection \[Abstract LB-22\]](#). In 66th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 13-17, 2015. San Francisco, CA; 2015.
- Jadoul M, Cornu C, van Ypersele de Strihou C. [Universal precautions prevent hepatitis C virus transmission: a 54 month follow-up of the Belgian Multicenter Study. The Universitaires Cliniques St-Luc \(UCL\) Collaborative Group](#). Kidney Int. 1998;53(4):1022-1025.
- Jezequel C, Bardou-Jacquet E, Desille Y, Renard I, Laine F, Lelan C, et al. [Survival of patients infected by chronic hepatitis C and F0F1 fibrosis at baseline after a 15 year follow-up](#). 50th Annual Meeting of the European Association for the Study of the Liver (EASL). 2015;:S589.
- Johnson RJ, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, et al. [Membranoproliferative glomerulonephritis associated with hepatitis C virus infection](#). N Engl J Med. 1993;328(7):465-470.
- Johnson RJ, Gretch DR, Couser WG, Alpers CE, Wilson J, Chung M, et al. [Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy](#). Kidney Int. 1994;46(6):1700-1704.
- Kamal S, Khan MAli, Seth A, Cholankeril G, Gupta D, Singh U, et al. [Beneficial Effects of Statins on the Rates of Hepatic Fibrosis, Hepatic Decompensation, and Mortality in Chronic Liver Disease: A Systematic Review and Meta-Analysis](#). The American Journal of Gastroenterology. 2017;112(10):1495 - 1505.
- Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. [HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV](#). Hepatology. 2014;60(1):98-105.
- [KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease](#). Kidney Int Suppl. 2008;(109):S1-99.
- Khokhar OS, Lewis JH. [Reasons why patients infected with chronic hepatitis C virus choose to defer treatment: do they](#)

[alter their decision with time?](#). Dig Dis Sci. 2007;52(5):1168-1176.

Kleiner DE. [The liver biopsy in chronic hepatitis C: a view from the other side of the microscope](#). Semin Liver Dis. 2005;25(1):52-64.

Konerman MA, Mehta SH, Sutcliffe CG, Vu T, Higgins Y, Torbenson MS, et al. [Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfecting adults: prospective analysis of 435 liver biopsy pairs](#). Hepatology. 2014;59(3):767-775.

Krishnan P, Pilot-Matias T, Schnell G, Tripathi R, Ng TI, Reisch T, et al. [Pooled Resistance Analysis in HCV Genotype 1-6 Infected Patients Treated With Glecaprevir/Pibrentasvir in Phase 2 and 3 Clinical Trials \[Epub ahead of print\]](#). Antimicrobial Agents and Chemotherapy. 2018;.

Kruse RL, Kramer JR, Tyson GL, Duan Z, Chen L, El-Serag HB, et al. [Clinical outcomes of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients](#). Hepatology (Baltimore, Md.). 2014;60(6):1871 - 1878.

Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, et al. [Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis](#). Journal of Hepatology. 2017;67(2):263 - 271.

Lai JC, Kahn JG, Tavakol M, Peters MG, Roberts JP. [Reducing infection transmission in solid organ transplantation through donor nucleic Acid testing: a cost-effectiveness analysis](#). Am J Transplant. 2013;13(10):2611-2618.

Lambers FA, Prins M, Thomas X, Molenkamp R, Kwa D, Brinkman K, et al. [Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM](#). AIDS. 2011;25(17):F21-F27.

Landau DA, Scerra S, Sene D, Resche-Rigon M, Saadoun D, Cacoub P. [Causes and predictive factors of mortality in a cohort of patients with hepatitis C virus-related cryoglobulinemic vasculitis treated with antiviral therapy](#). J Rheumatol. 2010;37(3):615-621.

Larney S, Kopinski H, Beckwith CG, Zaller ND, Jarlais DD, Hagan H, et al. [Incidence and prevalence of hepatitis C in prisons and other closed settings: Results of a systematic review and meta-analysis](#). Hepatology. 2013;58(4):1215-1224.

Lawitz EJ, Poordad F, Pang PS, Hyland RH, Ding X, Mo H, et al. [Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection \(LONESTAR\): an open-label, randomised, phase 2 trial](#). Lancet. 2014;383(9916):515-523.

Lee SR, Kardos KW, Schiff ER, Berne CA, Mounzer K, Banks AT, et al. [Evaluation of a new, rapid test for detecting HCV infection, suitable for use with blood or oral fluid](#). J Virol Methods. 2011;172(1-2):27-31.

Leroy V, Angus P, Bronowicki JP, Dore GJ, Hézode C, Pianko S, et al. [Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study \(ALLY-3+\)](#). Hepatology. 2016 Mar 4.th ed. 2016;63(5):1430-41.

Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R. [Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial](#). Hepatology. 2007;46(5):1453-1463.

Linas BP, Wong AY, Schackman BR, Kim AY, Freedberg KA. [Cost-effective screening for acute hepatitis C virus infection in HIV-infected men who have sex with men](#). Clin Infect Dis. 2012;55(2):279-290.

Linas BP, Barter DM, Morgan JR, Pho MT, Leff JA, Schackman BR, et al. [The cost-effectiveness of sofosbuvir-based regimens for treatment of hepatitis C virus genotype 2 or 3 infection](#). Ann. Intern. Med. 2015;162(9):619-629.

Litwin AH, Smith BD, Drainoni ML, McKee D, Gifford AL, Koppelman E, et al. [Primary care-based interventions are](#)



[associated with increases in hepatitis C virus testing for patients at risk](#). Dig Liver Dis. 2012;44(6):497-503.

Lo Re V, Gowda C, Urick PN, Halladay JT, Binkley A, Carbonari DM, et al. [Disparities in Absolute Denial of Modern Hepatitis C Therapy by Type of Insurance](#). Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association. 2016;14(7):1035 - 1043.

Lok AS, McMahon BJ. [Chronic hepatitis B: update 2009. AASLD practice guideline update](#). Hepatology. 2009;50(3):661-662.

Louie KS, St Laurent S, Forssen UM, Mundy LM, Pimenta JM. [The high comorbidity burden of the hepatitis C virus infected population in the United States](#). BMC Infect Dis. 2012;12:86.

Macias J, Berenguer J, Japon MA, Giron JA, Rivero A, Lopez-Cortes LF, et al. [Fast fibrosis progression between repeated liver biopsies in patients coinfecting with human immunodeficiency virus/hepatitis C virus](#). Hepatology. 2009;50(4):1056-1063.

Maddison AR, Fisher J, Johnston G. [Preventive medication use among persons with limited life expectancy](#). Prog Palliat Care. 2011;19(1):15-21.

Mahajan R, Liu SJ, Klevens RM, Holmberg SD. [Indications for testing among reported cases of HCV infection from enhanced hepatitis surveillance sites in the United States, 2004-2010](#). Am J Public Health. 2013;103(8):1445-1449.

Manns MP, Pockros PJ, Norkrans G, Smith CI, Morgan TR, Haussinger D, et al. [Long-term clearance of hepatitis C virus following interferon alpha-2b or peginterferon alpha-2b, alone or in combination with ribavirin](#). J Viral Hepat. 2013;20(8):524-529.

Marcellin P, Boyer N, Gervais A, Martinot M, Pouteau M, Castelnau C, et al. [Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy](#). Ann Intern Med. 1997;127(10):875-881.

Marrie TJ, Tyrrell GJ, Garg S, et al. [Factors predicting mortality in invasive pneumococcal disease in adults in Alberta](#). Medicine (Baltimore). 2011;90(3):171-9.

Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. [Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy](#). Clin Infect Dis. 2013;57(Suppl 2):S39-S45.

Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. [Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals](#). Hepatology. 2013;58(5):1598-1609.

Martin NK, Thornton A, Hickman M, Sabin C, Nelson M, Cooke GS, et al. [Can Hepatitis C Virus \(HCV\) Direct-Acting Antiviral Treatment as Prevention Reverse the HCV Epidemic Among Men Who Have Sex With Men in the United Kingdom? Epidemiological and Modeling Insights](#). Clin Infect Dis. 2016 Feb 16.th ed. 2016;62(9):1072-80.

Martin NK, Vickerman P, Dore GJ, Grebely J, Miners A, Cairns J, et al. [Prioritization of HCV treatment in the directacting antiviral era: An economic evaluation](#). J Hepatol. 2016;65(1):17-25.

Matheï C, Bourgeois S, Blach S, Brixko C, Mulkay JP, Razavi H, et al.. [Mitigating the burden of hepatitis C virus among people who inject drugs in Belgium](#). Acta Gastro-Enterologica Belgica. 2016;79(2):227 - 232.

Mazzaro C, Little D, Pozzato G. [Regression of splenic lymphoma after treatment of hepatitis C virus infection](#). N Engl J Med. 2002;347(26):2168-2170.

McCombs JS, Tonnu-MiHara I, Matsuda T, McGinnis J, Fox S. [Can hepatitis C treatment be safely delayed? Evidence](#)



- [from the Veterans Administration Healthcare System](#). 50th Annual Meeting of the European Association for the Study of the Liver (EASL). 2015;:S191.
- McGowan CE, Monis A, Bacon BR, Mallolas J, Goncales, Jr. FL, Goulis I, et al. [A global view of hepatitis C: physician knowledge, opinions, and perceived barriers to care](#). Hepatology. 2013;57(4):1325-1332.
- Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL. [Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States](#). Ann Intern Med. 2000;133(8):592-599.
- Merchante N, Giron-Gonzalez JA, Gonzalez-Serrano M, Torre-Cisneros J, Garcia-Garcia JA, Arizcorreta A, et al. [Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease](#). AIDS. 2006;20(1):49-57.
- Midgard H, Bramness JG, Skurtveit S, Haukeland JW, Dalgard O. [Hepatitis C Treatment Uptake among Patients Who Have Received Opioid Substitution Treatment: A Population-Based Study](#). PLoS One. 2016;11(11):e0166451.
- Miller L, Fluker SA, Osborn M, Liu X, Strawder A. [Improving access to hepatitis C care for urban, underserved patients using a primary care-based hepatitis C clinic](#). J Natl Med Assoc. 2012;104(5-6):244-250.
- Mira JA, Rivero-Juárez A, Lopez-Cortes LF, Giron-Gonzalez JA, Tellez F, Santos-Gil ID, et al. [Benefits from sustained virologic response to pegylated interferon plus ribavirin in HIV/hepatitis C virus-coinfected patients with compensated cirrhosis](#). Clin Infect Dis. 2013;56(11):1646-1653.
- Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. [Outcome of sustained virological responders with histologically advanced chronic hepatitis C](#). Hepatology. 2010;52(3):833-844.
- Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. [Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies](#). Ann Intern Med. 2013;158(5 Pt 1):329-337.
- Morisco F, Granata R, Stroffolini T, Guarino M, Donnarumma L, Gaeta L, et al. [Sustained virological response: a milestone in the treatment of chronic hepatitis C](#). World J Gastroenterol. 2013;19(18):2793-2798.
- Morrill JA, Shrestha M, Grant RW. [Barriers to the treatment of hepatitis C. Patient, provider, and system factors](#). J Gen Intern Med. 2005;20(8):754-758.
- Moyer VA. [Screening for HIV: U.S. Preventive Services Task Force Recommendation Statement](#). Ann Intern Med. 2013;159(1):51-60.
- Murphy SM, Dweik D, McPherson S, Roll JM. [Association between hepatitis C virus and opioid use while in buprenorphine treatment: preliminary findings](#). The American Journal of Drug and Alcohol Abuse. 2015;41(1):88 - 92.
- Musso G, Gambino R, Cassader M, Pagano G. [A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease](#). Hepatology. 2010;52(1):79-104.
- Najafzadeh M, Andersson K, Shrank WH, et al. [Cost-effectiveness of novel regimens for the treatment of hepatitis C virus](#). Ann Intern Med. 2015;162(6):407-19.
- Neary MP, Cort S, Bayliss MS, Ware, Jr. JE. [Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients](#). Semin Liver Dis. 1999;19(Suppl 1):77-85.
- Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. [Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews](#). Lancet. 2011;378(9791):571-583.
- Nelson DR, Cooper JN, Lalezari JP, Lawitz EJ, Pockros PJ, Gitlin N, et al. [All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study](#). Hepatology.

2015;61(4):1127-1135.

Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, Neuhaus R, et al. [Fibrosis progression after liver transplantation in patients with recurrent hepatitis C](#). J Hepatol. 2004;41(5):830-836.

Ng T, Lu L, Reisch T, Krishnan P, Schnell G, Tripathi R, et al. [Resistance selection using glecaprevir and pibrentasvir in replicons of major hepatitis C virus genotypes](#). Journal of Hepatology [Internet]. 2017;66(1):S324. [http://dx.doi.org/10.1016/S0168-8278\(17\)30972-8](http://dx.doi.org/10.1016/S0168-8278(17)30972-8)

Noda K, Yoshihara H, Suzuki K, Yamada Y, Kasahara A, Hayashi N, et al. [Progression of type C chronic hepatitis to liver cirrhosis and hepatocellular carcinoma--its relationship to alcohol drinking and the age of transfusion](#). Alcohol Clin Exp Res. 1996;20(1 Suppl):95A-100A.

Nutt AK, Hassan HA, Lindsey J, Lamps LW, Raufman JP. [Liver biopsy in the evaluation of patients with chronic hepatitis C who have repeatedly normal or near-normal serum alanine aminotransferase levels](#). Am J Med. 2000;109(1):62-64.

Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. [Contribution of obesity to hepatitis C-related fibrosis progression](#). Am J Gastroenterol. 2002;97(9):2408-2414.

Pawlotsky JM. [Use and interpretation of virological tests for hepatitis C](#). Hepatology. 2002;36(5 Suppl 1):S65-S73.

Pawlotsky J-M. [Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens](#). Gastroenterology. 2016;151(1):70 - 86.

Petta S, Camma C, di Marco V, Alessi N, Cabibi D, Caldarella R, et al. [Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection](#). Am J Gastroenterol. 2008;103(5):1136-1144.

Petta S, Maida M, Macaluso FS, Barbara M, Licata A, Craxi A, et al. [Hepatitis C Virus Infection Is Associated With Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies](#). Gastroenterology. 2015 Sep 18th ed. 2016;150(1):145-155.e4.

Picciotto FP, Tritto G, Lanza AG, Addario L, De LM, Di Costanzo GG, et al. [Sustained virological response to antiviral therapy reduces mortality in HCV reinfection after liver transplantation](#). J Hepatol. 2007;46(3):459-465.

Pineda JA, Romero-Gomez M, Díaz-García F, Giron-Gonzalez JA, Montero JL, Torre-Cisneros J, et al.. [HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis](#). Hepatology. 2005;41:779-789.

Post JJ, Arain A, Lloyd AR. [Enhancing assessment and treatment of hepatitis C in the custodial setting](#). Clin Infect Dis. 2013;57(Suppl 2):S70-S74.

Poynard T, Bedossa P, Opolon P. [Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups](#). Lancet. 1997;349(9055):825-832.

Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison JG, Albrecht J. [Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c](#). J Hepatol. 2001;34(5):730-739.

Poynard T, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, et al. [Fatigue in patients with chronic hepatitis C](#). J Viral Hepat. 2002;9(4):295-303.

Poynard T, McHutchison JG, Manns M, Trepo C, Lindsay K, Goodman Z, et al. [Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C](#). Gastroenterology. 2002;122(5):1303-1313.

Pradat P, Alberti A, Poynard T, Esteban JI, Weiland O, Marcellin P, et al. [Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study](#). Hepatology. 2002;36(4 Pt 1):973-977.

- Proeschold-Bell RJ, Patkar AA, Naggie S, Coward L, Mannelli P, Yao J, et al. [An integrated alcohol abuse and medical treatment model for patients with hepatitis C](#). Dig Dis Sci. 2012;57(4):1083-1091.
- Puoti M, Lorenzini P, Cozzi-Lepri A, Gori A, Mastroianni C, Rizzardini G, et al. [Incidence and progression to cirrhosis of new hepatitis C virus infections in persons living with human immunodeficiency virus](#). Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases. 2017;23(4):267.e1 - 267.e4.
- Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. [Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection](#). Am J Gastroenterol. 2002;97(10):2614-2618.
- Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. [Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy](#). Journal of Hepatology. 2016;65(4):719 - 726.
- Reilly B, Leston J, Redd JT, Geiger R. [Lack of Access to Treatment as a Barrier to HCV Screening: A Facility-Based Assessment in the Indian Health Service](#). J Public Health Manag Pract. 2013;.
- Rein DB, Wittenborn JS, Smith BD, et al. [The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus](#). Clin Infect Dis. 2015;61(2):157-68.
- Rockey DC, Bissell DM. [Noninvasive measures of liver fibrosis](#). Hepatology. 2006;43(2 Suppl 1):S113-S120.
- Rossaro L, Torruellas C, Dhaliwal S, Botros J, Clark G, Li CS, et al. [Clinical Outcomes of Hepatitis C Treated with Pegylated Interferon and Ribavirin via Telemedicine Consultation in Northern California](#). Dig Dis Sci. 2013;58(12):3620-3625.
- Saadoun D, Resche RM, Thibault V, Longuet M, Pol S, Blanc F, et al. [Peg-IFN \$\alpha\$ /ribavirin/protease inhibitor combination in hepatitis C virus associated mixed cryoglobulinemia vasculitis: results at week 24](#). Ann Rheum Dis. 2014;73(5):831-837.
- Saag MS. [Editorial Commentary: Getting Smart in How We Pay for HCV Drugs: KAOS vs CONTROL](#). Clin. Infect. Dis. 2015;61(2):169-170.
- Safdar K, Schiff ER. [Alcohol and hepatitis C](#). Semin Liver Dis. 2004;24(3):305-315.
- Samandari T, Tedaldi E, Armon C, Hart R, Chmiel JS, Brooks JT, et al. [Incidence of Hepatitis C Virus Infection in the Human Immunodeficiency Virus Outpatient Study Cohort, 2000-2013](#). Open Forum Infectious Diseases. 2017;4(2):ofx076.
- Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, et al. [The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients](#). Hepatology. 2006;43(6):1303-1310.
- Sarkar S, Jiang Z, Evon DM, Wahed AS, Hoofnagle JH. [Fatigue before, during and after antiviral therapy of chronic hepatitis C: results from the Virahep-C study](#). J Hepatol. 2012;57(5):946-952.
- Sarrazin C, Dvory-Sobol H, Svarovskaia ES, Doehle BP, Pang PS, Chuang SM, et al. [Prevalence of Resistance-Associated Substitutions in HCV NS5A, NS5B, or NS3 and Outcomes of Treatment With Ledipasvir and Sofosbuvir](#). Gastroenterology. 2016 June 11th ed. 2016;151(3):501-512.E1.
- Sayiner M, Golabi P, Farhat F, Younossi ZM. [Dermatologic Manifestations of Chronic Hepatitis C Infection](#). Clinics in Liver Disease. 2017;21(3):555 - 564.
- Schmidt AJ, Falcato L, Zahno B, et al. [Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection?](#) BMC Public Health. 2014;14(1):3.
- Schneider MD, Sarrazin C. [Antiviral therapy of hepatitis C in 2014: do we need resistance testing?](#) Antiviral Res.

2014;105:64-71.

Sebastiani G, Halfon P, Castera L, Pol S, Thomas DL, Mangia A, et al. [SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C](#). *Hepatology*. 2009;49(6):1821-1827.

Seem DL, Lee I, Umscheid CA, Kuehnert MJ. [Excerpt from PHS guideline for reducing HIV, HBV and HCV transmission through organ transplantation](#). *Am J Transplant*. 2013;13(8):1953-1962.

Selph S, Chou R. [Impact of contacting study authors on systematic review conclusions: diagnostic tests for hepatic fibrosis](#). 2014.

Shaw K, Gennat H, O'Rourke P, Del MC. [Exercise for overweight or obesity](#). *Cochrane Database Syst Rev*. 2006;(4):CD003817.

Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. [A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus](#). *Clin Gastroenterol Hepatol*. 2010;8(3):280-8, 288.

Sise ME, Bloom AK, Wisocky J, Lin MV, Gustafson JL, Lundquist AL, et al. [Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents](#). *Hepatology (Baltimore, Md.)*. 2016;63(2):408 - 417.

Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, et al. [Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965](#). *MMWR Recomm Rep*. 2012;61(RR-4):1-32.

Spaulding AC, Weinbaum CM, Lau DT, Sterling RK, Seeff LB, Margolis HS, et al. [A framework for management of hepatitis C in prisons](#). *Ann Intern Med*. 2006;144(10):762-769.

Stein MR, Soloway IJ, Jefferson KS, Roose RJ, Arnsten JH, Litwin AH. [Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program](#). *J Subst Abuse Treat*. 2012;43(4):424-432.

Sterling RK, Lissen E, Clumeck N, et al. [Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection](#). *Hepatology*. 2006;43:1317-1325.

Sulkowski MS, Chuang WL, Kao JH, et al. [No Evidence of Reactivation of Hepatitis B Virus Among Patients Treated With Ledipasvir-Sofosbuvir for Hepatitis C Virus Infection](#). *Clin Infect Dis*. 2016;.

Svarovskaia ES, Dvory-Sobol H, Parkin N, Hebner C, Gontcharova V, Martin R, et al. [Infrequent development of resistance in genotype 1-6 hepatitis C virus-infected subjects treated with sofosbuvir in phase 2 and 3 clinical trials](#). *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*. 2014;59(12):1666 - 1674.

Svoboda J, Andreadis C, Downs LH, Miller WT, Tsai DE, Schuster SJ. [Regression of advanced non-splenic marginal zone lymphoma after treatment of hepatitis C virus infection](#). *Leuk Lymphoma*. 2005;46(9):1365-1368.

Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich D, et al. [A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin](#). *Gastroenterology*. 2010;139(5):1593-1601.

Takahashi K, Nishida N, Kawabata H, Haga H, Chiba T. [Regression of Hodgkin lymphoma in response to antiviral therapy for hepatitis C virus infection](#). *Intern Med*. 2012;51(19):2745-2747.

Takayama H, Sato T, Ikeda F, Ikeda F. [Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection](#). *Hepatology Res*. 2015 Sep 30th ed. 2016;46(5):489-91.

- Takikawa H, Yamazaki R, Shoji S, Miyake K, Yamanaka M. [Normalization of urinary porphyrin level and disappearance of skin lesions after successful interferon therapy in a case of chronic hepatitis C complicated with porphyria cutanea tarda](#). J Hepatol. 1995;22(2):249-250.
- Terrault NA, Roland ME, Schiano T, Dove L, Wong MT, Poordad F, et al. [Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection](#). Liver Transpl. 2012;18(6):716-726.
- Thein HH, Yi Q, Dore GJ, Krahn MD. [Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis](#). AIDS. 2008;22(15):1979-1991.
- Thomas DL, Villano SA, Riestler KA, Hershov R, Mofenson LM, Landesman SH, et al. [Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and Infants Transmission Study](#). J Infect Dis. 1998;177(6):1480-1488.
- Tice JA, Chahal HS, Ollendorf DA. [Comparative clinical effectiveness and value of novel interferon-free combination therapy for hepatitis C genotype 1 summary of California technology assessment forum report](#). JAMA Internal Medicine. 2015;175(9):1559-1560.
- Torres HA, Mahale P. [Most patients with HCV-associated lymphoma present with mild liver disease: a call to revise antiviral treatment prioritization](#). Liver Int. 2015;35(6):1661-1664.
- Torres HA, Hosry J, Mahale P, Economides MP, Jiang Y, Lok AS. [Hepatitis C virus reactivation in patients receiving cancer treatment: A prospective observational study \[Epub ahead of print\]](#). Hepatology (Baltimore, Md.). 2017;.
- Trooskin SB, Poceta J, Towey CM, Yolken A, Rose JS, Luqman NL, et al. [Results from a Geographically Focused, Community-Based HCV Screening, Linkage-to-Care and Patient Navigation Program](#). J Gen Intern Med. 2015;30(7):950-957.
- Tyson GL, Kramer JR, Duan Z, Davila JA, Richardson PA, El-Serag HB. [Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients](#). Hepatology. 2013;58(2):538-545.
- Urbanus AT, van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. [Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic](#). AIDS. 2009;23(12):F1-F7.
- [U.S. Congressional Budget Office. Prescription drug pricing in the private sector](#). 2015.
- [US GAO. An overview of approaches to negotiate drug prices used by other countries and US private payers and federal programs \[Internet\]](#). 2015. <http://www.gao.gov/products/GAO-07-358T>
- [US Senate Committee on Finance. The Price of Sovaldi and its impact on the U.S. Health Care System](#). 2016.
- [US Preventive Services Task Force. Screening for hepatitis C virus infection in adults: US Preventive Services Task Force recommendation statement](#). 2013.
- van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. [Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men](#). Gastroenterology. 2009;136(5):1609-1617.
- van de Laar TJ, Matthews GV, Prins M, Danta M. [Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection](#). AIDS. 2010;24(12):1799-1812.
- van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. [Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis](#). JAMA. 2012;308(24):2584-2593.
- Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. [Sustained virologic response and](#)



[clinical outcomes in patients with chronic hepatitis C and advanced fibrosis](#). Ann Intern Med. 2007;147(10):677-684.

Vermeersch P, Van RM, Lagrou K. [Validation of a strategy for HCV antibody testing with two enzyme immunoassays in a routine clinical laboratory](#). J Clin Virol. 2008;42(4):394-398.

Volk JE, Marcus JL, Phengrasamy T, et al. [No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting](#). Clin Infect Dis. 2015;61(10):1601-3.

Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. [A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C](#). Hepatology. 2003;38(2):518-526.

Wandeler G, Gsponer T, Bregenzer A, Gunthard HF, Clerc O, Calmy A, et al. [Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic](#). Clin Infect Dis. 2012;55(10):1408-1416.

Wang C, et al. [Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents](#). Clin Gastro Hep. 2016;.

Waziry R, Hajarizadeh B, Grebely J, Dore GJ. [No evidence for a higher risk of hepatocellular carcinoma occurrence or recurrence following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta- regression. \[Abstract PS-160.\]](#). In EASL International Liver Congress. Amsterdam, April 19-23EASL International Liver Congress. Amsterdam, April 19-23. 2017.

Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Frankova S, Esmat GE, et al. [Strategies to manage hepatitis C virus \(HCV\) disease burden](#). J Viral Hepat. 2014;21(Suppl 1):60-89.

Westin J, Lagging LM, Spak F, Aires N, Svensson E, Lindh M, et al. [Moderate alcohol intake increases fibrosis progression in untreated patients with hepatitis C virus infection](#). J Viral Hepat. 2002;9(3):235-241.

White DL, Ratziu V, El-Serag HB. [Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis](#). J Hepatol. 2008;49(5):831-844.

Whitlock EP, Polen MR, Green CA, Orleans T, Klein J. [Behavioral counseling interventions in primary care to reduce risky/harmful alcohol use by adults: a summary of the evidence for the U.S. Preventive Services Task Force](#). Ann Intern Med. 2004;140(7):557-568.

Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. [Impact of alcohol on the histological and clinical progression of hepatitis C infection](#). Hepatology. 1998;28(3):805-809.

Williams IT, Bell BP, Kuhnert W, Alter MJ. [Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006](#). Arch Intern Med. 2011;171(3):242-248.

Witt MD, Seaberg EC, Darilay A, Young S, Badri S, Rinaldo CR, et al. [Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984-2011](#). Clin Infect Dis. 2013;57(1):77-84.

Wyles D, Mangia A, Cheng W, Shafran S, Schwabe C, Ouyang W, et al. [Long-term persistence of HCV NS5A resistance associated substitutions after treatment with the HCV NS5A inhibitor, ledipasvir, without sofosbuvir \[Epub ahead of print\]](#). Antiviral Therapy. 2017;.

Yoneda M, Saito S, Ikeda T, Fujita K, Mawatari H, Kirikoshi H, et al. [Hepatitis C virus directly associates with insulin resistance independent of the visceral fat area in nonobese and nondiabetic patients](#). J Viral Hepat. 2007;14(9):600-607.

Younossi ZM, Stepanova M, Henry L, Gane EJ, Jacobson IM, Lawitz EJ, et al. [Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C](#). Clin Gastroenterol Hepatol. 2013;[Epub ahead of print].



- Younossi ZM, Zheng L, Stepanova M, Venkatesan C, Mir HM. [Moderate, excessive or heavy alcohol consumption: each is significantly associated with increased mortality in patients with chronic hepatitis C](#). *Alimentary Pharmacology & Therapeutics*. 2013;37(7):703 - 709.
- Younossi ZM, Stepanova M, Nader F, Jacobson IM, Gane EJ, Nelson DR, et al. [Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens](#). *Hepatology*. 2014;59(6):2161-2169.
- Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. [Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection](#). *Aliment. Pharmacol. Ther.* 2015;41(6):544-563.
- Younossi ZM, Jiang Y, Smith NJ, Stepanova M, Beckerman R. [Ledipasvir/sofosbuvir regimens for chronic hepatitis C infection: Insights from a work productivity economic model from the United States](#). *Hepatology*. 2015;61(5):1471-1478.
- Younossi ZM, Stepanova M, Afdhal NH, Kowdley KV, Zeuzem S, Henry L, et al. [Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir](#). *J Hepatol*. 2015;63(2):337-345.
- Younossi ZM, Stepanova M, Sulkowski MS, Naggie S, Puoti M, Orkin C, et al. [Sofosbuvir and ribavirin for treatment of chronic hepatitis C in patients coinfecting with hepatitis C virus and HIV: the impact on patient-reported outcomes](#). *J Infect Dis*. 2015;212(3):367-377.
- Younossi ZM, Stepanova M, Feld J, Zeuzem S, Jacobson I, Agarwal K, et al. [Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: Results from ASTRAL-1 placebo-controlled trial](#). *Journal of Hepatology*. 2016;65(1):33 - 39.
- Younossi ZM, Stepanova M, Henry L, Nader F, Hunt S. [An In-Depth Analysis of Patient-Reported Outcomes in Patients With Chronic Hepatitis C Treated With Different Anti-Viral Regimens](#). *The American Journal of Gastroenterology*. 2016;111(6):808 - 816.
- Zahnd C, Salazar-Vizcaya LP, Dufour JF, Mullhaupt B, Wandeler G, Kouyos R, et al. [Impact of deferring HCV treatment on liver-related events in HIV+ patients](#). In Conference on Retroviruses and Opportunistic Infections (CROI) February 23-26. Seattle, WA; 2015.
- Zarski JP, Bohn B, Bastie A, Pawlotsky JM, Baud M, Bost-Bezeaux F, et al. [Characteristics of patients with dual infection by hepatitis B and C viruses](#). *J Hepatol*. 1998;28(1):27-33.
- [Merck & Co. Inc. Zepatier prescribing information](#). 2017 Whitehouse Station, NJ,: Merck Sharp & Dohme Corp.; 2017.
- Zeuzem S, Ghalib R, K. Reddy R, Pockros PJ, Ben Ari, iv Z, Zhao Y, et al. [Grazoprevir-Elbasvir Combination Therapy for Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial](#). *Annals of Internal Medicine*. 2015;163(1):1 - 13.
- Zeuzem S, Feld J, Wang S. [ENDURANCE-1: Efficacy and Safety of 8- versus 12-week Treatment with ABT-493/ABT-530 in patients with Chronic HCV Genotype 1 Infection \[Abstract 253\]](#). In 67th Annual Meeting of the American Association for the Study of Liver diseases, November 11-15. 2016.
- Zeuzem S, Mizokami M, Pianko S, Mangia A, Han KH, Martin R, et al. [NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: Prevalence and effect on treatment outcome](#). *J Hepatol*. 2017;66(5):910-918.
- Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. [Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C](#). *Hepatology*. 2005;41(1):48-54.
- Øvrehus ALH, Blach S, Christensen PB, Gerstoft J, Weis N, Krarup H, et al.. [Impact of prioritizing treatment in a high resource setting - minimizing the burden of HCV related disease in 15 years](#). 50th Annual Meeting of the European Association for the Study of the Liver (EASL). 2015;:S591.

