Published on *Recommendations for Testing, Managing, and Treating Hepatitis C* (http://www.hcvguidelines.org)

HCV TESTING AND LINKAGE TO CARE

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

A summary of recommendations for Testing and Linkage to Care is found in the BOX.

Recommendations for One-time HCV Testing

- **One-time HCV testing is recommended for persons born between 1945 and 1965,* without prior ascertainment of risk.**
  Rating: Class I, Level B

- **Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.**

1. ***Risk behaviors***
   - Injection-drug use (current or ever, including those who injected once)
   - Intranasal illicit drug use
2. ***Risk exposures***
   - Persons on long-term hemodialysis (ever)
   - Persons with percutaneous/parenteral exposures in an unregulated setting
   - Healthcare, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
   - Children born to HCV-infected women
   - Prior recipients of transfusions or organ transplants, including persons who:
     - Were notified that they received blood from a donor who later tested positive for HCV infection
     - Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
     - Received clotting factor concentrates produced before 1987
   - Persons who were ever incarcerated
3. ***Other considerations***

- HIV infection
- Sexually active persons about to start pre-exposure prophylaxis (PreP) for HIV
- Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
- Solid organ donors (deceased and living)

Rating: Class I, Level B

*Regardless of country of birth

There are an estimated 3.5 million HCV-infected persons in the United States, 2.7 million in the general non-institutionalized population (Denniston, 2014), plus an additional 800,000 incarcerated, institutionalized, or homeless (Edlin, 2015); about half of all infected people are unaware they are infected (Denniston, 2012); (Holmberg, 2013).

HCV testing is recommended in select populations based on demography, prior exposures, high-risk behaviors, and medical conditions. Recommendations for testing 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); (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998).

HCV is primarily transmitted through percutaneous exposure to blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection drug use; sexual transmission also occurs but generally seems to be inefficient except among HIV-infected men who have unprotected sex with men (Schmidt, 2014). The most important risk for HCV infection is injection drug use, 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 before 1992 (after which routine screening of blood supply was implemented), receipt of clotting factor concentrates before 1987, long-term hemodialysis, needlestick 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 are tattoos received outside of licensed parlors and medical procedures done internationally or domestically where strict infection control procedure may not have been followed (eg surgery before the implementation of universal precautions) (Hellard, 2004).

The importance of these risk factors might differ based on geographic location and population (US Preventive Services Task Force, 2013); (Centers for Disease Control and Prevention, 1998). An estimated 29% of incarcerated persons in North America are anti-HCV positive, supporting the recommendation to test 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 prevention of HIV infection should also be considered (Volk, 2015). Recent data also 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 Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force hepatitis C testing guidelines do not specifically recommend testing immigrants from countries with a high

prevalence (eg, Egypt or Pakistan) of hepatitis C virus infection, such persons should be tested if they were born from 1945 through 1965 or if they have risk factors (listed in **Summary Box**) for infection.

In 2012, CDC expanded its guidelines originally issued in 1998 (Centers for Disease Control and Prevention, 1998) for risk-based HCV testing with a recommendation to offer a one-time (see **Summary Box**) HCV test to all persons born from 1945 through 1965, without prior ascertainment of HCV risk-factors. This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections in part due to patient underreporting of their risk and provider limitations in ascertaining risk-factor information. Furthermore, persons in the 1945 to 1965 birth cohort accounted for nearly three-fourths of all HCV infections, with a five-times higher prevalence (3.25%) than other persons, reflecting a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000, compared with 15,000 in 2009). A recent retrospective review showed that 68% of persons with HCV infection would have been identified through 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).

CDC and the US Preventive Services Task Force (USPSTF) both recommend a one-time HCV test in asymptomatic persons belonging to the 1945 to 1965 birth cohort and other persons based on exposures, behaviors, and conditions that increase risk for HCV infection.

Recommendation for HCV Testing Those with Ongoing Risk Factors

- **Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.**
  Rating: Class IIA, Level C

Evidence regarding the frequency of testing in persons at risk for ongoing exposure to HCV is lacking; therefore, clinicians should determine the periodicity of testing based on the risk of reinfection. Because of the high incidence of HCV infection among persons who inject drugs and among HIV-infected MSM who have unprotected sex (Aberg, 2013); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011), at least annual HCV testing is recommended in these subgroups.

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).

Recommendations for Follow-up of Initial Testing

- **An anti-HCV test is recommended for HCV testing, and if the result is positive, current infection should be confirmed by a sensitive HCV RNA test.**
  Rating: Class I, Level A

- **Among persons with a negative anti-HCV 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 six months; testing for HCV RNA can also be considered in persons who are immunocompromised.**
  Rating: Class I, Level C

- **Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an anti-HCV test is expected to be positive.**
  Rating: Class I, Level C

- **Quantitative HCV-RNA testing is recommended prior to the initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).**
  Rating: Class I, Level A

- **Testing for HCV genotype is recommended to guide selection of the most appropriate antiviral regimen.**
  Rating: Class I, Level A

- **If found to have positive results for anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR), persons should be informed that they do not have evidence of current (active) HCV infection.**
  Rating: Class I, Level A

All persons recommended for HCV testing should first be tested for HCV antibody (anti-HCV) (Centers for Disease Control and Prevention [CDC], 2013); (Alter, 2003) using an FDA-approved test. 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 FDA-approved laboratory-based HCV antibody assays.

A positive test result for anti-HCV indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive test result (Pawlotsky, 2002). Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm current (active) HCV infection and guide clinical management, including initiation of HCV treatment. HCV RNA testing should also be performed in persons with a negative anti-HCV test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or who might have been exposed to HCV within the last six months because these persons may be anti-HCV negative. An HCV RNA test is also needed to detect reinfection in anti-HCV–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. **Testing and Linkage to Care Table 1** lists FDA-approved, commercially available anti-HCV screening assays. **Testing and Linkage to Care Figure 1** shows the CDC-recommended testing algorithm.

Persons who have positive results for an anti-HCV test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current (active) 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 risk factors for HCV infection.

Practitioners or persons may seek additional testing to learn if the HCV antibody test represents a remote HCV infection that has resolved or a false-positive result. 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 test results for anti-HCV are most common for populations with a low prevalence of HCV infection (Alter, 2003). If further testing is desired to distinguish between true positivity and biologic false positivity for HCV antibody, testing may be done with a second FDA-approved HCV antibody assay that is different from the assay used for initial antibody testing. A biologic false result should not occur with two different tests (Vermeersch, 2008); (Centers for Disease Control and Prevention [CDC]), 2013). Prior to the initiation of HCV therapy, quantitative HCV RNA testing may be used to determine the baseline level of viremia (ie, viral load) in order to define the duration of treatment for certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response in the era of direct-acting antiviral therapy (see **Pretreatment and On-Treatment Monitoring**). Testing for HCV genotype helps to guide selection of the most appropriate treatment regimen.

Recommendations for Counseling Those with Current (Active) HCV Infection

- **Persons with current (active) HCV infection should receive education and interventions aimed at reducing progression of liver disease and preventing transmission of HCV.**
  Rating: Class IIa, Level B

1. *Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.*
   Rating: Class IIa, Level B
2. *Evaluation for other conditions that may accelerate liver fibrosis, including HBV and HIV infections, is recommended for all persons with HCV infection.*
   Rating: Class IIb, Level B
3. *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 the management of cirrhosis (eg, hepatocellular carcinoma screening) (see When and in Whom to Initiate HCV Therapy).*
   Rating: Class I, Level A
4. *Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.*
   Rating: Class IIa, Level C
5. *Vaccination against pneumococcal infection is recommended to all patients with cirrhosis* (Marrie, 2011).
   Rating: Class IIa, Level C
6. *All persons with HCV infection should be provided education on how to avoid HCV transmission to others.*
   Rating: Class I, Level C

In addition to receiving therapy, HCV-infected persons should be educated about how to prevent further

damage to their liver. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between the use of excess alcohol 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).

The 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). Excess alcohol intake may also cause steatohepatitis. Alcohol screening and brief interventions such as those outlined by the National Institute of Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm) 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 human immunodeficiency virus-1 (HIV) coinfection have been associated with poorer prognosis of HCV in cohort studies (Thein, 2008a); (Zarski, 1998). Owing to overlapping risk factors for these infections and additional benefits of their identification and treatment, persons with HCV should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard assays for screening (Moyer, 2013); (Centers for Disease Control and Prevention [CDC], 2008); (http://www.aafp.org/afp/2008/0315/p819.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm) and counseled on how to reduce their risk of acquiring these infections, including through HBV vaccination (see below).

Patients with obesity and metabolic syndrome having underlying insulin resistance are more prone to have nonalcoholic fatty liver disease, which is a risk factor for 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 25 kg/m^2 or higher or 30 kg/m^2 or higher, respectively) should be counseled regarding strategies to reduce weight and improve insulin resistance via diet, exercise, and medical therapies (Musso, 2010); (Shaw, 2006). Patients with HCV infection and hyperlipidemia or cardiovascular comorbidities may also benefit from various hypolipidemic drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease (Lewis, 2007). Therefore, these agents should not be withheld in 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 that can assist with treatment and monitoring plans. The Metavir fibrosis score (F0-F4) and Ishak fibrosis score (0-6) are commonly used to score the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation, or of hepatic steatosis, and help exclude 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 a liver-directed physical exam (normal in most patients), routine blood tests (eg, serum alanine aminotransferase [ALT] and aspartate aminotransferase [AST], albumin, bilirubin, international

normalized ratio levels, and complete blood cell counts with platelets), serum fibrosis marker panels, liver imaging (eg, ultrasound, computed tomography scan), and transient elastography. Simple blood tests (eg, serum AST-to-platelet ratio index [APRI]), (Wai, 2003); (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri) FIB-4, (Sterling, 2006) and 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, which is associated with a greater likelihood of developing future hepatic complications in untreated patients (Chou, 2013); (Rockey, 2006). Liver elastography can provide 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 section When and In Whom to Initiate Therapy. Because persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require more frequent follow-up; these persons should also avoid hepatotoxic drugs (eg, excessive acetaminophen [ie, >2 g/d] or certain herbal supplements) or nephrotoxic drugs (eg, nonsteroidal antiinflammatory drugs) and receive ongoing imaging surveillance for liver cancer and gastroesophageal varices (Sangiovanni, 2006); (Fontana, 2010). Persons with cirrhosis are also more susceptible to invasive pneumococcal infection (Marrie, 2011) and should receive pneumococcal vaccination (Centers for Disease Control and Prevention [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 the sharing of needles and other infected implements. Recently, epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008). **Testing and Linkage to Care 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.

Recommendation for Linkage to Care

- **All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management.**
  Rating: Class IIa, Level C

Improvement in identification of current (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 practitioner 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 (stage F3 or above on Metavir scale), 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 practitioner assessment and delays in linkage to care can result in negative health outcomes. Further, 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, and 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 practitioner-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 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 the use of illicit drugs. Based on data from IFN-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 these barriers are listed in **Testing and Linkage to Care Table 3**. One strategy that addresses several barriers is colocalization or integrated care of HCV screening, evaluation, and treatment with other medical or social services. Colocalization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities and programs providing needle exchange, substance abuse treatment, and methadone maintenance) but is not uniformly available (Islam, 2012); (Stein, 2012); (Bruggmann, 2013). 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 an SVR, 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 [http://echo.unm.edu]) 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 (ie, gastroenterology, infectious diseases, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV infection treatment in populations that might have otherwise remained untreated. The short duration of therapy and few serious adverse events related to the new hepatitis C medications present an opportunity to expand the number of mid-level practitioners and primary care physicians 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 test and care programs have identified the use of patient navigators or care coordinators to be an important intervention in overcoming challenges to 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.

Changes made on July 6, 2016.