CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Hepatitis C Virus Screening, Testing, and Diagnosis in Adults

Updates, Authorship, and Related Guidelines

Date of current publication	January 12, 2023
Highlights of changes, additions, and updates in the January 12, 2023 edition	• Text added on dried blood spot (DBS) analysis for HCV RNA diagnostic testing. • Note: The NYSDOH AI guideline Treatment of Chronic HCV with Direct-Acting Antivirals (July 2017 through October 2020) was replaced with 3 guidelines: 1) Hepatitis C Virus Screening, Testing and Diagnosis in Adults; 2) Pretreatment Assessment in Adults With Chronic Hepatitis C Virus Infection; and 3) Treatment of Chronic Hepatitis C Virus Infection in Adults
Intended users	New York State clinicians who provide medical care for adults who may require treatment for HCV
Lead author	Joshua S. Aron, MD
Writing group	Christine A. Kerr, MD; David E. Bernstein, MD; Colleen Flanigan, RN, MS; Christopher J. Hoffmann, MD, MPH; Charles J. Gonzalez, MD
Author and writing group conflict of interest disclosures	None
Date of original publication	January 12, 2023
Committee	Hepatitis C Virus (HCV) Guideline Committee
Developer and funder	New York State Department of Health AIDS Institute (NYSDOH AI)
Development process	See Supplement: Guideline Development and Recommendation Ratings
Related NYSDOH AI guidelines	• PEP to Prevent HIV Infection • Pretreatment Assessment in Adults With Chronic Hepatitis C Virus Infection • Treatment of Chronic Hepatitis C Virus Infection in Adults

Hepatitis C Virus Screening, Testing, and Diagnosis in Adults

Date of current publication: January 12, 2023
Lead author: Joshua S. Aron, MD
Writing group: Christine A. Kerr, MD; David E. Bernstein, MD; Colleen Flanigan, RN, MS; Christopher J. Hoffmann, MD, MPH; Charles J. Gonzalez, MD
Committee: Hepatitis C Virus (HCV) Guideline Committee
Date of original publication: January 12, 2023

Contents

Purpose of This Guideline

This guideline on testing for and diagnosis of chronic hepatitis C virus (HCV) infection was developed by the New York State Department of Health AIDS Institute (NYSDOH AI) to guide primary care providers and other practitioners in New York State in identifying individuals with chronic HCV infection for treatment. The guideline aims to achieve the following goals:

- Increase compliance with the 2014 New York State public health law that requires that an HCV screening test be offered to every individual born between 1945 and 1965 who receives healthcare services from a physician, physician assistant, or nurse practitioner in a primary care or inpatient hospital setting.
- Promote universal HCV testing in adults (≥18 years old).
- Promote HCV testing in patients who are planning to get pregnant or are currently pregnant, for each pregnancy.
- Increase the number of people in New York State with chronic HCV who are diagnosed and referred for HCV treatment.
- Provide evidence-based clinical recommendations to support the goals of the New York State Hepatitis C Elimination Plan (NY Cures HepC).

Rationale

HCV infection in the United States: First isolated in 1989, hepatitis C virus (HCV) is the most common chronic bloodborne infection in the United States [Armstrong, et al. 2006; Chen and Morgan 2006]. Injection drug use is associated with the highest risk of contracting HCV [Alter 1999]. HCV is also transmitted through infected blood or organs before 1992,

infected blood products before 1987, perinatal exposure (also known as vertical transmission), sexual exposure, and needlesticks or other blood exposures in healthcare settings [CDC 1998]. For more information, see the guideline section Who to Test for HCV Infection > Risk Factors.

It has been estimated that between 2013 and 2016, approximately 4 million adults (1.7%) in the United States had positive HCV antibody test results indicating past or current infection, and approximately 2.4 million adults (1.0%) had positive HCV RNA test results indicating current infection [Hofmeister, et al. 2019]. HCV prevalence in the United States varies widely and is influenced by the opioid epidemic and injection drug use [Liang and Ward 2018]. In a study performed in 4 urban U.S. emergency departments (EDs) between 2015 and 2016, 1,315 participants (9.2%) had positive HCV antibody test results; of those, 693 (62%) had positive HCV RNA test results [Galbraith, et al. 2020]. In a retrospective cohort study from an ED serving Appalachia, 3,665 participants (10.5%) had positive HCV antibody test results; of those, 1,601 (50.3%) had positive HCV RNA test results [Moore, et al. 2021].

In the most recent report available, the U.S. Centers for Disease Control and Prevention reported 137,713 new cases of chronic HCV infection nationwide in 2018, with 63.1% among males and 36.9% among females [Ryerson, et al. 2020]. People born between 1945 and 1965 accounted for 36.3% of newly reported chronic HCV cases in 2018; those born between 1966 and 1980 accounted for 23.1%, and those born between 1981 and 1996 accounted for 36.5% [Ryerson, et al. 2020]. These data demonstrate a decrease in the age of HCV cases reported from earlier peaks among people born between 1945 and 1965. This decrease was also observed in New York State (excluding New York City) and in New York City in 2020 [NYSDOH 2022; NYCDOHMH 2021]. See Table 1, below.

Table 1: Newly Diagnosed Cases of HCV in New York State and New York City [a]

New York State [NYSDOH 2022] [b]	**New York City** [NYCDOHMH 2021]
• 154,804 cases reported from 2001 to 2020 • 2020 cases: 4,126 reported – 27% (1,105) of cases reported from the 1945 to 1965 birth cohort, with 70% male and 30% female – 26% (1,078) of cases reported age <30 years, with 58% in males and 42% in females	• 174,399 cases reported from 2001 to 2020 • 2020 cases: 2,995 reported – 32% (906) of cases reported from the 1945 to 1965 birth cohort, with 556 (62%) in males and 337 (37%) in females (3 unknown) – 13% (386) of cases reported age <30 years, with 229 (59%) in males, 150 (39%) in females, 2 (<1%) in transgender individuals, and 5 (1%) unknown

Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; HCV, hepatitis C virus.

Notes:

a. Cases meeting the CDC case definition for acute or chronic (New York State) or chronic (New York City) confirmed or probable cases of HCV, including perinatal hepatitis C. There may be duplication of individuals both within and between the New York State and City HCV surveillance systems, and the total cases reported in this table should not be interpreted as numbers of unique individuals reported with HCV.
b. Excluding New York City.

HCV-related morbidity and mortality: Chronic HCV infection drives the development of hepatocellular carcinoma (HCC) by inducing fibrosis and cirrhosis [El-Serag 2012]. Approximately 25% to 30% of people with untreated chronic HCV infection will develop cirrhosis within 20 to 30 years, with progression occurring more quickly in men and among individuals who use alcohol, acquire HCV infection after age 40, or have HIV/HCV coinfection [Klevens, et al. 2016; Younossi, et al. 2015]. Among individuals with cirrhosis, >25% will develop end-stage liver disease or HCC, resulting in death without a liver transplant [Klevens, et al. 2012].

Treatment with direct-acting antivirals (DAAs) is associated with reduced risk of HCC among individuals without cirrhosis [Carrat, et al. 2019; Kanwal, et al. 2017]. However, 2 studies among individuals with cirrhosis or elevated FIB-4 who were successfully treated for HCV with DAAs found that the risk of HCC did not regress after years of follow-up (means 2.9 and 5.4 years) and that cirrhosis was strongly associated with HCC risk [Kanwal, et al. 2020; Ioannou, et al. 2019]. In a study among 1,717 participants in Texas, the most common risk factors for cirrhosis and HCC shifted from active viral hepatitis to resolved or treated viral hepatitis and alcoholic and nonalcoholic fatty liver disease (NAFLD) [El-Serag, et al. 2020]. Significant racial and ethnic differences were observed in the distribution of risk factors, with a high prevalence of metabolic syndrome and NAFLD in Hispanic individuals and a high prevalence of alcoholic liver disease and heavy alcohol use in Black individuals [El-Serag, et al. 2020].

Access to care: The availability of safe and effective oral DAAs has revolutionized HCV treatment and made cure possible for many patients. However, treatment requires diagnosis and access to and engagement in care. NYS is actively seeking to identify people with chronic HCV infection and link them to treatment before irreversible liver damage occurs and, on a public health level, to eliminate HCV in the state (see New York State Hepatitis C Elimination). People with HCV infection may face significant barriers to accessing care in clinical settings, including lack of health insurance, physical disability, ongoing substance use, mental health disorders, and housing instability. Locating HCV screening sites in various community-based organizations, such as syringe-exchange programs, sexually transmitted infection clinics, and local health departments is integral to providing HCV screening, treatment, and education in diverse settings.

Who to Test for HCV Infection

☑ RECOMMENDATIONS

Routine Testing

- Clinicians should perform HCV screening at least once for all patients ≥18 years old who are not known to have HCV infection. (A2)
- Clinicians should repeat HCV screening in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy. (B3)
  - See the NYSDOH AI guideline Treatment of Chronic Hepatitis C Virus Infection in Adults > HCV Testing and Management in Pregnant Adults.
- Clinicians should perform *repeat* HCV testing based on individual exposure to the following risk factors, at least once if risk exposure is episodic and annually if ongoing:
  - Injection (A1) or intranasal (A2) drug use
  - Hemodialysis (A1)
  - HIV infection diagnosis (A1)
  - Sex partner(s) with HCV infection (A2)
  - Tattoo, piercing, or acupuncture obtained in a nonsterile setting (A2)
  - Incarceration (A2)
  - Unexplained liver disease or abnormal transaminase levels (A1)
- Clinicians should recommend *repeat* HCV testing *at least annually* to MSM and others who are not known to have HCV infection and:
  - Engage in receptive anal sex and other behaviors that may tear mucous membranes (A2)
  - Have multiple sex partners (A2)
  - Are taking PrEP to prevent HIV acquisition (A3)
  - Are transgender women (B3)
  - Engage in sex while using recreational mind-altering substances, particularly methamphetamine (A2)
  - Have been diagnosed with another STI within the previous 12 months (A2)

Potential Exposure to HCV in an Occupational Setting: See the NYSDOH AI guideline PEP to Prevent HIV Infection > Management of Potential Exposure to Hepatitis C Virus.

Abbreviations: HCV, hepatitis C virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

HCV Screening

HCV testing should be performed *at least once in* all individuals ≥18 years old, regardless of risk factors [Schillie, et al. 2020; U.S. Preventive Services Task Force 2020]. In the United States, chronic infection with HCV is highly prevalent, but approximately 50% of people with HCV may not be aware of their infection [CDC 2019; Hofmeister, et al. 2019; Kim, et al.

2019]. Reliable testing to identify HCV and pharmacologic treatment to cure the disease are available, and universal testing in individuals ≥18 years old was demonstrated to be cost-effective compared with cohort- and risk-based testing, mainly by reducing cirrhosis- and liver-related mortality [Barocas, et al. 2018].

In addition to universal, one-time testing for adults, HCV testing should be performed in all patients who are planning to get pregnant or are currently pregnant, with each pregnancy (see the NYSDOH AI guideline Treatment of Chronic Hepatitis C Virus Infection in Adults > HCV Testing and Management in Pregnant Adults). HCV testing should also be performed in patients reporting a potential exposure to HCV (see the NYSDOH AI guideline PEP to Prevent HIV Infection > Management of Potential Exposure to Hepatitis C Virus).

Repeat HCV testing should be performed based on individual patient risk factors and how often risk factors are present (see guideline section Risk Factors, below).

As part of HCV screening and diagnosis, a series of serologic and virologic tests are used, including laboratory-based antibody tests, point-of-care rapid HCV antibody tests for initial screening, and laboratory-based HCV RNA tests for HCV diagnosis (see guideline section HCV Testing Sequence and Diagnosis).

☆ NEW YORK STATE LAW

- Clinicians must offer an HCV screening test to every individual born between 1945 and 1965. If an individual accepts the offer and the test is reactive, the clinician must offer the individual follow-up healthcare (including an HCV RNA test) or refer the individual to a healthcare provider who can provide follow-up healthcare.

Risk Factors

Perinatal transmission: A 2011 meta-analysis estimated that the risk of perinatal (vertical) HCV infection among subjects with HCV antibody-reactive and HCV RNA detectable test results without HIV was 5.8%; for those with HIV, it was 10.8% [Arshad, et al. 2011]. Factors associated with an increased risk of perinatal transmission include HIV/HCV coinfection and high maternal HCV viral load [Benova, et al. 2014; Arshad, et al. 2011].

Injection or intranasal drug use: Sharing injection drug use (IDU) equipment is an efficient method of transmitting HCV. In the United States, a reduction in new HCV infections between 1992 and 2009 was attributed to expansions of syringe-access programs, safer injection practices among people who inject drugs, and increased enrollment in drug treatment programs [Klevens, et al. 2012]. However, HCV prevalence among individuals who inject drugs entering substance use treatment in New York City (n = 1,535) was 67% (95% confidence interval, 66% to 70%) during the period from 2006 to 2013 and was not significantly different from that observed from 2000 to 2001 [Jordan, et al. 2015].

The demographics of IDU include many young people living in suburban and rural regions [Klevens, et al. 2012]. Adolescents and young adults may advance to IDU after first becoming addicted to prescription oral opioids [Liang and Ward 2018; Mateu-Gelabert, et al. 2015]. Reports from several states (including New York State) underscore the importance of awareness of HCV risk among adolescents and young adults and of offering HCV screening to this population [Zibbell, et al. 2015; CDC 2012; CDC(a) 2011; CDC(b) 2011; Pollini, et al. 2011; CDC 2008].

Among noninjecting drug users, sharing oral and nasal drug use equipment has been associated with an increased risk of HCV infection [Macias, et al. 2008; Neaigus, et al. 2007; Koblin, et al. 2003]. In addition, blood and HCV RNA have been confirmed in the nasal secretions and drug-sniffing paraphernalia of intranasal drug users with HCV infection [Aaron, et al. 2008]. In a systematic review of 28 studies on the prevalence of HCV in noninjecting drug users who smoked, sniffed, or snorted heroin, powder or crack cocaine or methamphetamine, investigators found HCV prevalence rates ranging from 2.3% to 35.3% [Stern, et al. 2008; Scheinmann, et al. 2007].

Sexual transmission: Because many people with HCV have a history of drug use, estimation of sexual transmission is a challenge [Tohme and Holmberg 2010]. Sexual transmission of HCV among monogamous heterosexual couples is infrequent. The estimated maximum prevalence of HCV infection among sex partners of individuals with chronic HCV infection was only 1.2%, and the maximum incidence of HCV transmission through sexual contact was 0.07% per year or approximately 1 per 190,000 sexual contacts [Terrault, et al. 2013]. Sexual transmission risk increases with multiple partners, STI diagnosis, HIV diagnosis, and exposure to blood [Tohme and Holmberg 2010]. Several reports have demonstrated isolated outbreaks of sexual HCV transmission among MSM with HIV who engage in receptive anal intercourse [Wandeler, et al. 2012; CDC(b) 2011; Urbanus, et al. 2009; van de Laar, et al. 2009]. In a report from New York City on sexual transmission among MSM with HIV and no previous history of IDU, new HCV infections were highly

correlated with engaging in receptive anal intercourse, engaging in sex while using methamphetamine, or participating in group sex [CDC(b) 2011].

PrEP: Individuals may have higher than average rates of baseline risk and ongoing risk of HCV acquisition with ongoing IDU and condomless sexual behavior. In a 2020 study of 350 men taking PrEP, 4.2% tested positive for HCV infection. Risk factors associated with HCV infection were engaging in receptive condomless anal sex with casual partners, having an anal STI, IDU, and sharing straws when snorting drugs [Hoornenborg, et al. 2020; Hoornenborg, et al. 2017]. Another study representing 304 person-years of PrEP use reported an annual incidence rate of 0.7 per 100 patient-years among individuals who were initially not infected with HCV and did not report IDU [Volk, et al. 2015]. A report evaluated 14 MSM without HIV taking PrEP who were diagnosed with HCV infection from 2013 to 2018. Most participants were asymptomatic for HCV, and most reported increases in sexual and drug use behaviors that put them at increased risk of exposure to HCV and bacterial STIs. These findings underline the need for consistent HCV screening and expanded prevention messages among MSM taking PrEP [Price, et al. 2019].

Transgender women: In 1 study of 571 transgender women in New York City, rates of HCV infection varied from 3.6% among White transgender women to 15.7% among Hispanic transgender women [Nuttbrock and Hwahng 2017]. Using data collected from the U.S. Centers for Disease Control and Prevention's National HIV Behavioral Surveillance survey and respondent-driven sampling, investigators identified 201 transgender women in San Francisco, California, between June 2019 and February 2020. Of these, 48 were HCV seropositive, and 6.0% were HCV RNA-positive [Hernandez, et al. 2021]. Older age and history of IDU were identified as risk factors for HCV infection. However, HCV and other STI screening rates among transgender women remain low. In a retrospective, multisite study of gender-identity clinics in New York City, only 27% of participants were screened for HCV at baseline [Mangla, et al. 2017].

History of incarceration: Incarcerated populations are a significant but declining portion of the HCV epidemic in the United States [Alvarez, et al. 2014; Varan, et al. 2014; Larney, et al. 2013]. A study from 2009 to 2013 at 2 maximum-security prisons in New York State estimated an HCV prevalence of 10.1%; IDU, having a partner who injected drugs, and HIV diagnosis were most strongly associated with HCV infection [Alvarez, et al. 2014].

Exposure to blood in a healthcare setting: The average incidence of anti-HCV seroconversion after unintentional needlesticks or sharps exposures from a source with HCV infection is 1.8% [CDC 1998]. Healthcare-related transmission of HCV is documented infrequently in the United States [Tomkins, et al. 2012; Henderson 2003]. In 2014, 1% of reported acute HCV cases that included information on exposure type were considered to be occupationally acquired [CDC(b) 2017].

Hemodialysis: In the United States between 2014 and 2015, 36 cases of acute HCV infection in 19 different hemodialysis clinics in 8 states were reported [CDC 2016]. The CDC and the National Kidney Foundation recommend HCV antibody screening for patients receiving chronic hemodialysis at admission, followed by screening every 6 months thereafter [KDIGO 2018; CDC(a) 2017; CDC 2016].

Receipt of blood transfusion or organ transplant before 1992 or clotting factor concentrates from human plasma before 1987: Donor screening for HCV infection and inactivation procedures for pooled plasma and plasma derivative products have virtually eliminated the risk of HCV transmission through blood products in the United States [CDC 1998; Watson, et al. 1992].

Tattoos, piercings, or acupuncture obtained in nonsterile settings: Tattoos or piercings obtained in nonsterile settings, and especially those obtained during incarceration, have been associated with HCV infection, even after controlling for IDU and transfusion before 1992 [Carney, et al. 2013; Tohme and Holmberg 2012]. Low levels of HCV RNA have been detected on acupuncture needles from individuals known to have HCV infection [Lemos, et al. 2014], although acupuncture has not been established as a confirmed route of transmission.

HIV infection: HCV infection is common among individuals with HIV because the routes of acquisition are similar. For decades, IDU has been recognized as the main risk factor for HIV/HCV coinfection, but an increasing number of sexually transmitted HCV infections have been documented in MSM with HIV [Breskin, et al. 2015; Fierer and Factor 2015; Hagan, et al. 2015]. In a study among MSM with HIV in Europe, Australia, and Canada, HCV incidence significantly increased from 1990 to 2006 [van de Laar, et al. 2009]. Analyses of data from the Multicenter AIDS Cohort Study in the United States and a cohort of MSM with HIV in San Diego, California, demonstrated a similar rise in HCV incidence among MSM [Witt, et al. 2013]. In a New York City study of 54,488 MSM diagnosed with HIV between 2000 and 2015 who did not use injection drugs, 2,762 (5.1%) were diagnosed with HCV after being diagnosed with HIV [Gabai, et al. 2020; Chaillon, et al. 2019].

In MSM with HIV, sexual acts that may tear mucous membranes, sex while using methamphetamines, and having other STIs have been associated with HCV infection [Fierer and Factor 2015; Hagan, et al. 2015].

Unexplained liver disease or abnormal transaminase levels: In a study among patients seen by primary care providers, alanine transaminase levels of 50 to 100 IU/L were associated with HCV prevalence 10-fold higher than in the general population, whereas hepatitis B virus prevalence was not increased [Helsper, et al. 2012].

HCV Testing Sequence and Diagnosis

☑ RECOMMENDATIONS

HCV Antibody Testing

- Clinicians should perform HCV screening using either a laboratory-based HCV antibody test or a point-of-care rapid antibody test. (A1)

HCV RNA Testing

- If the HCV antibody test result is positive, clinicians should perform an HCV RNA test. (A1) Some laboratories perform reflex testing and automatically test for HCV RNA after a positive HCV antibody result.
- If the HCV antibody test result is negative and acute HCV infection is suspected, clinicians should perform an HCV RNA test. (A1)
- In patients with a history of a positive HCV antibody test result, clinicians should perform an HCV RNA test (not an HCV antibody test) for screening. (A1)

Testing After Known HCV Exposure

- After a known HCV exposure, which generally occurs in an occupational setting, clinicians should perform a baseline HCV antibody test, and if positive, an HCV RNA test and liver function tests, including a liver enzyme test. (A2)

Acute HCV

- Clinicians should suspect acute HCV infection if a patient has detectable HCV RNA in the absence of a positive antibody test or a documented negative HCV antibody test result within the previous 6 months and a newly positive HCV antibody test result. (A3)
- Clinicians should perform laboratory screening for HIV, HAV, and HBV infections in all patients with possible acute HCV infection, given the similar risk factors for acquisition. (A3)
- Clinicians should repeat HCV antibody and RNA tests 24 weeks after exposure to assess for spontaneous HCV clearance or chronic HCV infection; earlier testing may be indicated for patients at increased risk of transmitting HCV to others. (A3)

Chronic HCV

- If HCV RNA is detected after a positive HCV antibody test result, the patient has confirmed chronic HCV infection and clinicians should evaluate for treatment. (A2)

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

☆ NEW YORK STATE LAW

- Clinicians must report all suspected or confirmed cases of HCV infection, specifying acute or chronic, to the local health department of the area where the individual resides, in full compliance with New York State laws and regulations (see NYSDOH Communicable Disease Reporting).

HCV Antibody Testing

HCV antibody testing is the first step in identifying whether a patient has been exposed to the virus [CDC 2013]. For more information, see U.S. Centers for Disease Control and Prevention Testing Recommendations for Hepatitis C Virus Infection.

HCV antibody testing performed by laboratories uses enzyme immunoassay (EIA) or chemiluminescent immunoassay (CIA or CMIA). Currently available FDA-approved HCV immunoassays have a sensitivity of approximately 99% even when used in low-prevalence populations [Abdel-Hamid, et al. 2002; Colin, et al. 2001; Gretch 1997; Lee, et al. 1995].

Reflex testing is an automatic HCV RNA test of the same specimen performed after a positive HCV antibody test. This testing provides confirmation or exclusion of active infection with a single laboratory test order, eliminating the need for the patient to return for follow-up testing and expediting linkage to care for those who have HCV (see Table 2: Interpretation of HCV Test Results, below). Knowledge of the laboratory's HCV reflex testing procedures is necessary, including the availability of reflex testing and, if available, whether it is performed automatically or must be requested. Information on the availability of HCV antibody screening with reflex to HCV RNA analysis should be available in the laboratory's test menu along with any special specimen collection instructions for reflex testing (i.e., 2 separate blood tubes). If reflex testing is not available, confirmatory HCV RNA testing should be performed as soon as possible after a reactive HCV antibody test result is received.

A rapid, point-of-care HCV antibody screening test is also available; this test can be performed with a finger-stick blood sample and produce results within 20 to 40 minutes. The sensitivity and specificity of this test is equivalent to traditional EIA tests [Lee, et al. 2010]. The NYSDOH Hepatitis C Screening Program and others use this simple and convenient testing method outside of traditional healthcare settings in drug treatment centers, syringe-exchange programs, and other community-based locations. The short testing process means the test can be performed and the result given while the patient is still present. If the patient is HCV antibody positive, a follow-up appointment for confirmatory HCV RNA testing can be made or, in some locations, dried blood spot (DBS) testing can be offered (see guideline section HCV RNA Testing, below).

If the HCV antibody test is negative, the immunocompetent patient does not have chronic HCV infection; ongoing individual risk factors will determine the need for future screening and the need for ongoing education about risk-reduction strategies. However, a false-negative antibody test result may occur in patients who may have been exposed to the virus within the previous 6 months and may be experiencing acute HCV infection (see the guideline section Acute HCV Infection, below) [Nastouli, et al. 2009]. HCV RNA is usually detectable within days to 2 weeks after exposure [Maheshwari and Thuluvath 2010; Wang, et al. 2002], whereas it may take 2 to 6 months for HCV antibodies to be detectable ("window period;" for a graphic description of the window period, please see the Association of Public Health Laboratories Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories). False-negative antibody test results may also occur in patients who are immunocompromised because of advanced HIV infection, use of immunosuppressive therapy, long-term hemodialysis, or other conditions [Larouche, et al. 2012; Thomson, et al. 2009]. In these patients, confirmatory HCV RNA testing should be performed.

If the HCV antibody test is positive, confirmatory HCV RNA testing should be performed [Moorman, et al. 2017; Freiman, et al. 2016]. It is important to inform patients that a reactive HCV antibody test result does not confirm active HCV infection.

HCV RNA Testing

U.S. Food and Drug Administration (FDA)-approved HCV RNA tests are available at many laboratories and should be the primary choice for HCV RNA testing whenever possible. All FDA-approved HCV RNA tests are ultrasensitive, with a lower limit of detection ranging from 3.4 to 15 IU/mL. Additionally, several are approved to provide both a qualitative (diagnostic) and quantitative (viral load monitoring) result. These tests can identify the presence of virus as early as 2 weeks post-exposure, rather than the 8 to 24 weeks needed for HCV antibodies to develop [Kamili, et al. 2012]; see FDA: Hepatitis C. All of the FDA-approved HCV RNA tests can be performed on serum or plasma samples. This offers some flexibility regarding specimen collection, but the requirement for venipuncture can be challenging in some individuals and settings and may create a barrier to obtaining confirmation of active HCV infection.

DBS analysis to detect and measure HCV RNA has been used to facilitate HCV diagnosis and management outside of the United States, primarily in rural or resource-limited sites where it may be difficult to transport serum samples that require an intact cold chain [Parr, et al. 2018; Lange, et al. 2017; Greenman, et al. 2015]. Although fingerstick blood collection may be a desirable alternative to venipuncture for some patients who wish to avoid phlebotomy, there are no FDA-approved HCV RNA tests for DBS or any fingerstick-collected blood specimen. Therefore, use of DBS for HCV RNA testing is limited. Importantly, use of DBS specimens reduces the sensitivity of HCV RNA testing. The lower limit of detection is typically 1 to 2 logs higher for DBS methods than for standard HCV RNA tests that use serum or plasma. This reduced sensitivity could negatively affect HCV RNA detection during the early stage of infection when HCV viral load can fluctuate widely. Although a positive HCV RNA result on a DBS sample confirms active infection, some ambiguity may remain if the

result is negative. If a DBS sample produces a negative HCV RNA result and the care provider remains concerned about the presence of active HCV infection, a standard HCV RNA test should be obtained.

The New York State Department of Health Wadsworth Center Laboratory has developed a DBS method for qualitative HCV RNA diagnostic testing (i.e., to confirm active infection); it is not validated for quantitative HCV RNA testing (i.e., viral load for treatment monitoring). The limit of detection of the Wadsworth Center Laboratory DBS HCV RNA test is 250 IU/mL (compare to ~4 IU/mL for serum and plasma). This DBS method is intended for patients participating in HCV rapid testing programs for whom venipuncture is not an option, and fingerstick collection is the most feasible way to obtain HCV RNA testing and confirm active HCV infection. HCV rapid testing providers in New York State that need DBS HCV RNA testing for their patients may be able to access this testing from the Wadsworth Center Laboratory (see Hepatitis C Dried Blood Spot Testing in NYS).

If HCV RNA is not detected after a positive antibody test, then 1) the patient had previous exposure to HCV but has cleared the virus and does not have active HCV infection, or 2) the result of the HCV antibody test was falsely reactive. In these patients, ongoing HCV screening should occur based on individual risk factors. Because the presence of HCV antibodies can be lifelong, detection of current HCV infection in patients with positive HCV antibody test results requires HCV RNA testing. Repeat HCV antibody testing is not useful in patients with previously reactive antibody tests.

If HCV RNA is detected after a positive HCV antibody test result, the patient has confirmed HCV infection and should be evaluated for treatment of chronic or acute HCV infection. It is important to advise all patients with HCV viremia that they may be infectious and should take precautions to avoid transmitting HCV to others.

→ KEY POINTS

- The presence of HCV antibodies alone may not indicate active HCV infection.
- In patients with a history of a reactive HCV antibody test result, subsequent screening requires an HCV RNA test, not an HCV antibody test, to detect infection.
- HCV antibodies do not prevent future HCV infections; prevention measures are needed for individuals with ongoing risk factors.

Table 2: Interpretation of HCV Test Results [a]

Anti-HCV	HCV RNA	Interpretation	Response
Positive	Detected	Acute or chronic HCV infection	Evaluate for treatment.
Positive	Not detected	• Resolution of HCV by spontaneous or treatment-related clearance, *or* • HCV infection during period of intermittent viremia, *or* • False-positive antibody screening result	• Perform HCV RNA testing based on risk factors. • Repeat HCV RNA testing if acute exposure is known or suspected.
Negative	Detected	• Early acute HCV infection, *or* • Chronic HCV infection in immunosuppressed patients	• Evaluate for treatment if patient has risk factors. • Repeat testing if patient has no risk factors or exposure and a false-positive result is suspected.
Negative	Unknown	Presumed absence of HCV infection if the HCV RNA testing was not performed or the status is unknown	Perform HCV antibody testing based on risk factors.

Abbreviation: HCV, hepatitis C virus.

Note:

a. Adapted from [CDC 2013]. For more information about interpreting HCV test results, see the Association of Public Health Laboratories Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories.

Acute HCV Infection

The acute phase is considered the first 6 months of HCV infection. Approximately 65% to 75% of individuals with acute HCV infection are asymptomatic [Marcellin 1999]. When symptoms are present, they last a few weeks to months after exposure and may range from clinical hepatitis with jaundice, choluria (tea-colored urine), steatorrhea, and abdominal pain to vague, nonspecific symptoms, such as fatigue, anorexia, low-grade fever, myalgias, arthralgia, mood disturbances, and nausea or vomiting [Loomba, et al. 2011; Gerlach, et al. 2003; Marcellin 1999]. As a result, in the absence of a clearly defined risk factor for transmission, acute HCV infection is rarely diagnosed. During acute HCV infection, serum aminotransferase levels vary and may be normal or up to 20 times the upper limit of normal [Maheshwari, et al. 2008].

An estimated 20% to 45% of individuals with HCV infection will clear the virus spontaneously, generally within 12 to 16 weeks [Kamal 2008]. Approximately 11% of those who remain viremic 6 months after infection will eventually experience spontaneous clearance [Seeff 1997]. Predictors of spontaneous clearance include female sex, age <40 years, IL28B CC genotype (highest incidence in East and South Asian and European individuals, lowest in Black individuals), symptomatic infection (jaundice), and a competent immune system (no immunosuppressive therapy or uncontrolled HIV) [Grebely, et al. 2014]. Because both aminotransferases and HCV viral load may fluctuate during the acute phase, durable spontaneous clearance, if it occurs, is not expected until 24 weeks after inoculation or exposure. Following spontaneous clearance, patients will remain antibody positive.

→ KEY POINTS

- The timing of HCV treatment is determined with respect to the likelihood of spontaneous clearance and patient or care provider concerns regarding risk of transmission.
- Patient education should include the following information:
  - If patients have acute HCV infection, they may be infectious and should take precautions to avoid transmitting HCV to others.
  - HCV infection may clear spontaneously (i.e., without treatment).
  - Treatment options are available if HCV infection is established.

Given the excellent response rates with current direct-acting antiviral (DAA) therapy, there is no clear advantage to treating HCV infection in the acute phase [Naggie, et al. 2017]. It is reasonable to wait a minimum of 24 weeks to repeat HCV RNA and antibody tests to assess for spontaneous clearance or confirm infection. In some circumstances, clinicians and their patients may decide to initiate therapy sooner; however, if patients have an increased risk of transmitting HCV, are men with HIV who have sex with men, or use injection drugs, a minimum of 12 to 16 weeks is needed to assess for spontaneous clearance before initiation of therapy. Other factors influencing decisions to initiate early treatment may be lack of access to healthcare, concerns for delay due to family planning, and known cirrhosis or preexisting liver disease. The recommended DAA regimens used in these situations are the same as those indicated for chronic HCV therapy.

It is important to educate patients with potential acute HCV infection about the possibility of spontaneous clearance, the need to avoid or minimize hepatotoxic drugs (including alcohol), and the need to take precautions to prevent HCV transmission to others (see patient education information at NYSDOH AI Hepatitis C Educational Materials).

All Recommendations

☑ ALL RECOMMENDATIONS: HEPATITIS C VIRUS SCREENING, TESTING, AND DIAGNOSIS IN ADULTS

Routine Testing

- Clinicians should perform HCV screening at least once for all patients ≥18 years old who are not known to have HCV infection. (A2)
- Clinicians should repeat HCV screening in all patients who are planning to get pregnant (A2) or are currently pregnant (B3), and screening should be repeated with each pregnancy. (B3)
  - See the NYSDOH AI guideline Treatment of Chronic Hepatitis C Virus Infection in Adults > HCV Testing and Management in Pregnant Adults.
- Clinicians should perform *repeat* HCV testing based on individual exposure to the following risk factors, at least once if risk exposure is episodic and annually if ongoing:
  - Injection (A1) or intranasal (A2) drug use
  - Hemodialysis (A1)
  - HIV infection diagnosis (A1)
  - Sex partner(s) with HCV infection (A2)
  - Tattoo, piercing, or acupuncture obtained in a nonsterile setting (A2)
  - Incarceration (A2)
  - Unexplained liver disease or abnormal transaminase levels (A1)
- Clinicians should recommend *repeat* HCV testing *at least annually* to MSM and others who are not known to have HCV infection and:
  - Engage in receptive anal sex and other behaviors that may tear mucous membranes (A2)
  - Have multiple sex partners (A2)
  - Are taking PrEP to prevent HIV acquisition (A3)
  - Are transgender women (B3)
  - Engage in sex while using recreational mind-altering substances, particularly methamphetamine (A2)
  - Have been diagnosed with another STI within the previous 12 months (A2)

Potential Exposure to HCV in an Occupational Setting: See the NYSDOH AI guideline PEP to Prevent HIV Infection > Management of Potential Exposure to Hepatitis C Virus.

HCV Antibody Testing

- Clinicians should perform HCV screening using either a laboratory-based HCV antibody test or a point-of-care rapid antibody test. (A1)

HCV RNA Testing

- If the HCV antibody test result is positive, clinicians should perform an HCV RNA test. (A1) Some laboratories perform reflex testing and automatically test for HCV RNA after a positive HCV antibody result.
- If the HCV antibody test result is negative and acute HCV infection is suspected, clinicians should perform an HCV RNA test. (A1)
- In patients with a history of a positive HCV antibody test result, clinicians should perform an HCV RNA test (not an HCV antibody test) for screening. (A1)

Testing After Known HCV Exposure

- After a known HCV exposure, which generally occurs in an occupational setting, clinicians should perform a baseline HCV antibody test, and if positive, an HCV RNA test and liver function tests, including a liver enzyme test. (A2)

☑ ALL RECOMMENDATIONS: HEPATITIS C VIRUS SCREENING, TESTING, AND DIAGNOSIS IN ADULTS

Acute HCV

- Clinicians should suspect acute HCV infection if a patient has detectable HCV RNA in the absence of a positive antibody test or a documented negative HCV antibody test result within the previous 6 months and a newly positive HCV antibody test result. (A3)
- Clinicians should perform laboratory screening for HIV, HAV, and HBV infections in all patients with possible acute HCV infection, given the similar risk factors for acquisition. (A3)
- Clinicians should repeat HCV antibody and RNA tests 24 weeks after exposure to assess for spontaneous HCV clearance or chronic HCV infection; earlier testing may be indicated for patients at increased risk of transmitting HCV to others. (A3)

Chronic HCV

- If HCV RNA is detected after a positive HCV antibody test result, the patient has confirmed chronic HCV infection and clinicians should evaluate for treatment. (A2)

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

References

Aaron S, McMahon JM, Milano D, et al. Intranasal transmission of hepatitis C virus: virological and clinical evidence. *Clin Infect Dis* 2008;47(7):931-34. [PMID: 18764772] https://pubmed.ncbi.nlm.nih.gov/18764772

Abdel-Hamid M, El-Daly M, El-Kafrawy S, et al. Comparison of second- and third-generation enzyme immunoassays for detecting antibodies to hepatitis C virus. *J Clin Microbiol* 2002;40(5):1656-59. [PMID: 11980937] https://pubmed.ncbi.nlm.nih.gov/11980937

Alter MJ. Hepatitis C virus infection in the United States. *J Hepatol* 1999;31 Suppl 1:88-91. [PMID: 10622567] https://pubmed.ncbi.nlm.nih.gov/10622567

Alvarez KJ, Befus M, Herzig CT, et al. Prevalence and correlates of hepatitis C virus infection among inmates at two New York State correctional facilities. *J Infect Public Health* 2014;7(6):517-21. [PMID: 25182508] https://pubmed.ncbi.nlm.nih.gov/25182508

Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006;144(10):705-14. [PMID: 16702586] https://pubmed.ncbi.nlm.nih.gov/16702586

Arshad M, El-Kamary SS, Jhaveri R. Hepatitis C virus infection during pregnancy and the newborn period--are they opportunities for treatment? *J Viral Hepat* 2011;18(4):229-36. [PMID: 21392169] https://pubmed.ncbi.nlm.nih.gov/21392169

Barocas JA, Tasillo A, Eftekhari Yazdi G, et al. Population-level outcomes and cost-effectiveness of expanding the recommendation for age-based hepatitis C testing in the United States. *Clin Infect Dis* 2018;67(4):549-56. [PMID: 29420742] https://pubmed.ncbi.nlm.nih.gov/29420742

Benova L, Mohamoud YA, Calvert C, et al. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis* 2014;59(6):765-73. [PMID: 24928290] https://pubmed.ncbi.nlm.nih.gov/24928290

Breskin A, Drobnik A, Pathela P, et al. Factors associated with hepatitis C infection among HIV-infected men who have sex with men with no reported injection drug use in New York City, 2000-2010. *Sex Transm Dis* 2015;42(7):382-86. [PMID: 26222751] https://pubmed.ncbi.nlm.nih.gov/26222751

Carney K, Dhalla S, Aytaman A, et al. Association of tattooing and hepatitis C virus infection: a multicenter case-control study. *Hepatology* 2013;57(6):2117-23. [PMID: 23315899] https://pubmed.ncbi.nlm.nih.gov/23315899

Carrat F, Fontaine H, Dorival C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet* 2019;393(10179):1453-64. [PMID: 30765123] https://pubmed.ncbi.nlm.nih.gov/30765123

CDC. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease *MMWR Recomm Rep* 1998;47(Rr-19):1-39. [PMID: 9790221] https://pubmed.ncbi.nlm.nih.gov/9790221

CDC. Use of enhanced surveillance for hepatitis C virus infection to detect a cluster among young injection-drug users--New York, November 2004-April 2007. *MMWR Morb Mortal Wkly Rep* 2008;57(19):517-21. [PMID: 18480744] https://pubmed.ncbi.nlm.nih.gov/18480744

CDC. Notes from the field: hepatitis C virus infections among young adults--rural Wisconsin, 2010. *MMWR Morb Mortal Wkly Rep* 2012;61(19):358. [PMID: 22592276] https://pubmed.ncbi.nlm.nih.gov/22592276

CDC. Testing for HCV infection: an update of guidance for clinicians and laboratorians. *MMWR Morb Mortal Wkly Rep* 2013;62(18):362-65. [PMID: 23657112] https://pubmed.ncbi.nlm.nih.gov/23657112

CDC. CDC urging dialysis providers and facilities to assess and improve infection control practices to stop hepatitis C virus transmission in patients undergoing hemodialysis. *Am J Transplantation* 2016;16(5):1633-34. https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.13811

CDC. Viral hepatitis surveillance—United States, 2017 2019 Nov 14. https://www.cdc.gov/hepatitis/statistics/2017surveillance/index.htm [accessed 2022 Jul 15]

CDC(a). Hepatitis C virus infection among adolescents and young adults: Massachusetts, 2002-2009. *MMWR Morb Mortal Wkly Rep* 2011;60(17):537-41. [PMID: 21544042] https://pubmed.ncbi.nlm.nih.gov/21544042

CDC(a). Dialysis safety: guidelines, recommendations and resources. 2017 Dec 18. https://www.cdc.gov/dialysis/guidelines/ [accessed 2022 Jul 15]

CDC(b). Sexual transmission of hepatitis C virus among HIV-infected men who have sex with men--New York City, 2005-2010. *MMWR Morb Mortal Wkly Rep* 2011;60(28):945-50. [PMID: 21775948] https://pubmed.ncbi.nlm.nih.gov/21775948

CDC(b). Viral hepatitis: statistics and surveillance. 2017 May 11. https://www.cdc.gov/Hepatitis/Statistics/index.htm [accessed 2022 Jul 15]

Chaillon A, Sun X, Cachay ER, et al. Primary incidence of hepatitis C virus infection among HIV-infected men who have sex with men in San Diego, 2000-2015. *Open Forum Infect Dis* 2019;6(4):ofz160. [PMID: 31041355] https://pubmed.ncbi.nlm.nih.gov/31041355

Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *Int J Med Sci* 2006;3(2):47-52. [PMID: 16614742] https://pubmed.ncbi.nlm.nih.gov/16614742

Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. *J Viral Hepat* 2001;8(2):87-95. [PMID: 11264728] https://pubmed.ncbi.nlm.nih.gov/11264728

El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142(6):1264-73.e1. [PMID: 22537432] https://pubmed.ncbi.nlm.nih.gov/22537432

El-Serag HB, Kanwal F, Feng Z, et al. Risk factors for cirrhosis in contemporary hepatology practices-findings from the Texas Hepatocellular Carcinoma Consortium Cohort. *Gastroenterology* 2020;159(1):376-77. [PMID: 32234536] https://pubmed.ncbi.nlm.nih.gov/32234536

Fierer DS, Factor SH. Defining the scope of sexually transmitted hepatitis C virus epidemic among HIV-infected men who have sex with men in New York City. *Sex Transm Dis* 2015;42(7):400-401. [PMID: 26222756] https://pubmed.ncbi.nlm.nih.gov/26222756

Freiman JM, Tran TM, Schumacher SG, et al. Hepatitis c core antigen testing for diagnosis of hepatitis C virus infection: a systematic review and meta-analysis. *Ann Intern Med* 2016;165(5):345-55. [PMID: 27322622] https://pubmed.ncbi.nlm.nih.gov/27322622

Gabai CM, Moore MS, Penrose K, et al. Hepatitis C infection among men who have sex with men living with HIV in New York City, 2000-2015. *Sex Transm Infect* 2020;96(6):445-50. [PMID: 31801894] https://pubmed.ncbi.nlm.nih.gov/31801894

Galbraith JW, Anderson ES, Hsieh YH, et al. High prevalence of hepatitis c infection among adult patients at four urban emergency departments - Birmingham, Oakland, Baltimore, and Boston, 2015-2017. *MMWR Morb Mortal Wkly Rep* 2020;69(19):569-74. [PMID: 32407307] https://pubmed.ncbi.nlm.nih.gov/32407307

Gerlach JT, Diepolder HM, Zachoval R, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. *Gastroenterology* 2003;125(1):80-88. [PMID: 12851873] https://pubmed.ncbi.nlm.nih.gov/12851873

Grebely J, Page K, Sacks-Davis R, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology* 2014;59(1):109-20. [PMID: 23908124] https://pubmed.ncbi.nlm.nih.gov/23908124

Greenman J, Roberts T, Cohn J, et al. Dried blood spot in the genotyping, quantification and storage of HCV RNA: a systematic literature review. *J Viral Hepat* 2015;22(4):353-61. [PMID: 25367722] https://pubmed.ncbi.nlm.nih.gov/25367722

Gretch DR. Use and interpretation of HCV diagnostic tests in the clinical setting. *Clin Liver Dis* 1997;1(3):543-57, vi. [PMID: 15560057] https://pubmed.ncbi.nlm.nih.gov/15560057

Hagan H, Jordan AE, Neurer J, et al. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive men who have sex with men. *AIDS* 2015;29(17):2335-45. [PMID: 26258525] https://pubmed.ncbi.nlm.nih.gov/26258525

Helsper C, van Essen G, Frijling BD, et al. Follow-up of mild alanine aminotransferase elevation identifies hidden hepatitis C in primary care. *Br J Gen Pract* 2012;62(596):e212-16. [PMID: 22429439] https://pubmed.ncbi.nlm.nih.gov/22429439

Henderson DK. Managing occupational risks for hepatitis C transmission in the health care setting. *Clin Microbiol Rev* 2003;16(3):546-68. [PMID: 12857782] https://pubmed.ncbi.nlm.nih.gov/12857782

Hernandez CJ, Trujillo D, Sicro S, et al. High hepatitis C virus seropositivity, viremia, and associated risk factors among trans women living in San Francisco, California. *PLoS One* 2021;16(3):e0249219. [PMID: 33784365] https://pubmed.ncbi.nlm.nih.gov/33784365

Hofmeister MG, Rosenthal EM, Barker LK, et al. Estimating prevalence of hepatitis C virus infection in the United States, 2013-2016. *Hepatology* 2019;69(3):1020-31. [PMID: 30398671] https://pubmed.ncbi.nlm.nih.gov/30398671

Hoornenborg E, Coyer L, Boyd A, et al. High incidence of HCV in HIV-negative men who have sex with men using pre-exposure prophylaxis. *J Hepatol* 2020;72(5):855-64. [PMID: 31862485] https://pubmed.ncbi.nlm.nih.gov/31862485

Hoornenborg E, Krakower DS, Prins M, et al. Pre-exposure prophylaxis for MSM and transgender persons in early adopting countries. *AIDS* 2017;31(16):2179-91. [PMID: 28991023] https://pubmed.ncbi.nlm.nih.gov/28991023

Ioannou GN, Beste LA, Green PK, et al. Increased risk for hepatocellular carcinoma persists up to 10 years after HCV eradication in patients with baseline cirrhosis or high FIB-4 scores. *Gastroenterology* 2019;157(5):1264-78.e4. [PMID: 31356807] https://pubmed.ncbi.nlm.nih.gov/31356807

Jordan AE, Des Jarlais DC, Arasteh K, et al. Incidence and prevalence of hepatitis C virus infection among persons who inject drugs in New York City: 2006-2013. *Drug Alcohol Depend* 2015;152:194-200. [PMID: 25891230] https://pubmed.ncbi.nlm.nih.gov/25891230

Kamal SM. Acute hepatitis C: a systematic review. *Am J Gastroenterol* 2008;103(5):1283-97; quiz 1298. [PMID: 18477352] https://pubmed.ncbi.nlm.nih.gov/18477352

Kamili S, Drobeniuc J, Araujo AC, et al. Laboratory diagnostics for hepatitis C virus infection. *Clin Infect Dis* 2012;55(Suppl 1):s43-48. [PMID: 22715213] https://pubmed.ncbi.nlm.nih.gov/22715213

Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology* 2017;153(4):996-1005.e1. [PMID: 28642197] https://pubmed.ncbi.nlm.nih.gov/28642197

Kanwal F, Kramer JR, Asch SM, et al. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. *Hepatology* 2020;71(1):44-55. [PMID: 31222774] https://pubmed.ncbi.nlm.nih.gov/31222774

KDIGO. Hepatitis C in CKD. 2018 Oct. https://kdigo.org/guidelines/hepatitis-c-in-ckd/ [accessed 2022 Jul 15]

Kim HS, Yang JD, El-Serag HB, et al. Awareness of chronic viral hepatitis in the United States: an update from the National Health and Nutrition Examination Survey. *J Viral Hepat* 2019;26(5):596-602. [PMID: 30629790] https://pubmed.ncbi.nlm.nih.gov/30629790

Klevens RM, Canary L, Huang X, et al. The burden of hepatitis C infection-related liver fibrosis in the United States. *Clin Infect Dis* 2016;63(8):1049-55. [PMID: 27506688] https://pubmed.ncbi.nlm.nih.gov/27506688

Klevens RM, Hu DJ, Jiles R, et al. Evolving epidemiology of hepatitis C virus in the United States. *Clin Infect Dis* 2012;55(Suppl 1):s3-9. [PMID: 22715211] https://pubmed.ncbi.nlm.nih.gov/22715211

Koblin BA, Factor SH, Wu Y, et al. Hepatitis C virus infection among noninjecting drug users in New York City. *J Med Virol* 2003;70(3):387-90. [PMID: 12767001] https://pubmed.ncbi.nlm.nih.gov/12767001

Lange B, Roberts T, Cohn J, et al. Diagnostic accuracy of detection and quantification of HBV-DNA and HCV-RNA using dried blood spot (DBS) samples - a systematic review and meta-analysis. *BMC Infect Dis* 2017;17(Suppl 1):693. [PMID: 29143616] https://pubmed.ncbi.nlm.nih.gov/29143616

Larney S, Kopinski H, Beckwith CG, 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):1215-24. [PMID: 23504650] https://pubmed.ncbi.nlm.nih.gov/23504650

Larouche A, Gaetan G, El-Bilali N, et al. Seronegative hepatitis C virus infection in a child infected via mother-to-child transmission. *J Clin Microbiol* 2012;50(7):2515-19. [PMID: 22535990] https://pubmed.ncbi.nlm.nih.gov/22535990

Lee SR, Wood CL, Lane MJ, et al. Increased detection of hepatitis C virus infection in commercial plasma donors by a third-generation screening assay. *Transfusion (Paris)* 1995;35(10):845-49. [PMID: 7570915] https://pubmed.ncbi.nlm.nih.gov/7570915

Lee SR, Yearwood GD, Guillon GB, et al. Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection. *J Clin Virol* 2010;48(1):15-17. [PMID: 20362493] https://pubmed.ncbi.nlm.nih.gov/20362493

Lemos MA, Jr., Silva JB, Braga AC, et al. Acupuncture needles can carry hepatitis C virus. *Infect Control Hosp Epidemiol* 2014;35(10):1319-21. [PMID: 25203197] https://pubmed.ncbi.nlm.nih.gov/25203197

Liang TJ, Ward JW. Hepatitis C in injection-drug users - a hidden danger of the opioid epidemic. *N Engl J Med* 2018;378(13):1169-71. [PMID: 29601263] https://pubmed.ncbi.nlm.nih.gov/29601263

Loomba R, Rivera MM, McBurney R, et al. The natural history of acute hepatitis C: clinical presentation, laboratory findings and treatment outcomes. *Aliment Pharmacol Ther* 2011;33(5):559-65. [PMID: 21198704] https://pubmed.ncbi.nlm.nih.gov/21198704

Macias J, Palacios RB, Claro E, et al. High prevalence of hepatitis C virus infection among noninjecting drug users: association with sharing the inhalation implements of crack. *Liver Int* 2008;28(6):781-76. [PMID: 18312289] https://pubmed.ncbi.nlm.nih.gov/18312289

Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. *Lancet* 2008;372(9635):321-32. [PMID: 18657711] https://pubmed.ncbi.nlm.nih.gov/18657711

Maheshwari A, Thuluvath PJ. Management of acute hepatitis C. *Clin Liver Dis* 2010;14(1):169-76; x. [PMID: 20123448] https://pubmed.ncbi.nlm.nih.gov/20123448

Mangla N, Mamun R, Weisberg IS. Viral hepatitis screening in transgender patients undergoing gender identity hormonal therapy. *Eur J Gastroenterol Hepatol* 2017;29(11):1215-18. [PMID: 28857896] https://pubmed.ncbi.nlm.nih.gov/28857896

Marcellin P. Hepatitis C: the clinical spectrum of the disease. *J Hepatol* 1999;31 Suppl 1:9-16. [PMID: 10622554] https://pubmed.ncbi.nlm.nih.gov/10622554

Mateu-Gelabert P, Guarino H, Jessell L, et al. Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *J Subst Abuse Treat* 2015;48(1):13-20. [PMID: 25124258] https://pubmed.ncbi.nlm.nih.gov/25124258

Moore JD, Galbraith J, Humphries R, et al. Prevalence of hepatitis c virus infection identified from nontargeted screening among adult visitors in an academic Appalachian regional emergency department. *Open Forum Infect Dis* 2021;8(8):ofab374. [PMID: 34381848] https://pubmed.ncbi.nlm.nih.gov/34381848

Moorman AC, Drobenuic J, Kamili S. Prevalence of false-positive hepatitis C antibody results, National Health and Nutrition Examination Study (NHANES) 2007-2012. *J Clin Virol* 2017;89:1-4. [PMID: 28171829] https://pubmed.ncbi.nlm.nih.gov/28171829

Naggie S, Holland DP, Sulkowski MS, et al. Hepatitis C virus postexposure prophylaxis in the healthcare worker: why direct-acting antivirals don't change a thing. *Clin Infect Dis* 2017;64(1):92-99. [PMID: 27682067] https://pubmed.ncbi.nlm.nih.gov/27682067

Nastouli E, Thomson EC, Karayiannis P, et al. Diagnosing acute hepatitis C in HIV-infected patients: nucleic acid testing compared with antibody and antigen-antibody detecting methods. *J Clin Virol* 2009;44(1):78-80. [PMID: 18986830] https://pubmed.ncbi.nlm.nih.gov/18986830

Neaigus A, Gyarmathy VA, Zhao M, et al. Sexual and other noninjection risks for HBV and HCV seroconversions among noninjecting heroin users. *J Infect Dis* 2007;195(7):1052-61. [PMID: 17330797] https://pubmed.ncbi.nlm.nih.gov/17330797

Nuttbrock LA, Hwahng SJ. Ethnicity, sex work, and incident HIV/STI among transgender women in New York City: a three year prospective study. *AIDS Behav* 2017;21(12):3328-35. [PMID: 27501810] https://pubmed.ncbi.nlm.nih.gov/27501810

NYCDOHMH. Hepatitis A, B and C in New York City: 2020 annual report. 2021 Nov 15. https://www1.nyc.gov/assets/doh/downloads/pdf/cd/hepatitis-abc-annual-report-2020.pdf [accessed 2022 Aug 23]

NYSDOH. Unpublished data. 2022 [accessed 2022 Aug 25]

Parr JB, Lodge EK, Holzmayer V, et al. An efficient, large-scale survey of hepatitis C viremia in the Democratic Republic of the Congo using dried blood spots. *Clin Infect Dis* 2018;66(2):254-60. [PMID: 29048459] https://pubmed.ncbi.nlm.nih.gov/29048459

Pollini RA, Banta-Green CJ, Cuevas-Mota J, et al. Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Subst Abuse Rehabil* 2011;2(1):173-80. [PMID: 23293547] https://pubmed.ncbi.nlm.nih.gov/23293547

Price JC, McKinney JE, Crouch PC, et al. Sexually acquired hepatitis C infection in HIV-uninfected men who have sex with men using preexposure prophylaxis against HIV. *J Infect Dis* 2019;219(9):1373-76. [PMID: 30462305] https://pubmed.ncbi.nlm.nih.gov/30462305

Ryerson AB, Schillie S, Barker LK, et al. Vital signs: newly reported acute and chronic hepatitis C cases - United States, 2009-2018. *MMWR Morb Mortal Wkly Rep* 2020;69(14):399-404. [PMID: 32271725] https://pubmed.ncbi.nlm.nih.gov/32271725

Scheinmann R, Hagan H, Lelutiu-Weinberger C, et al. Non-injection drug use and hepatitis C virus: a systematic review. *Drug Alcohol Depend* 2007;89(1):1-12. [PMID: 17174481] https://pubmed.ncbi.nlm.nih.gov/17174481

Schillie S, Wester C, Osborne M, et al. CDC recommendations for hepatitis C screening among adults - United States, 2020. *MMWR Recomm Rep* 2020;69(2):1-17. [PMID: 32271723] https://pubmed.ncbi.nlm.nih.gov/32271723

Seeff LB. Natural history of hepatitis C. *Hepatology* 1997;26(3 Suppl 1):21s-28s. [PMID: 9305659] https://pubmed.ncbi.nlm.nih.gov/9305659

Stern RK, Hagan H, Lelutiu-Weinberger C, et al. The HCV Synthesis Project: scope, methodology, and preliminary results. *BMC Med Res Methodol* 2008;8:62. [PMID: 18789163] https://pubmed.ncbi.nlm.nih.gov/18789163

Terrault NA, Dodge JL, Murphy EL, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: the HCV Partners Study. *Hepatology* 2013;57(3):881-89. [PMID: 23175457] https://pubmed.ncbi.nlm.nih.gov/23175457

Thomson EC, Nastouli E, Main J, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. *AIDS* 2009;23(1):89-93. [PMID: 19050390] https://pubmed.ncbi.nlm.nih.gov/19050390

Tohme RA, Holmberg SD. Is sexual contact a major mode of hepatitis C virus transmission? *Hepatology* 2010;52(4):1497-1505. [PMID: 20635398] https://pubmed.ncbi.nlm.nih.gov/20635398

Tohme RA, Holmberg SD. Transmission of hepatitis C virus infection through tattooing and piercing: a critical review. *Clin Infect Dis* 2012;54(8):1167-78. [PMID: 22291098] https://pubmed.ncbi.nlm.nih.gov/22291098

Tomkins SE, Elford J, Nichols T, et al. Occupational transmission of hepatitis C in healthcare workers and factors associated with seroconversion: UK surveillance data. *J Viral Hepat* 2012;19(3):199-204. [PMID: 22329374] https://pubmed.ncbi.nlm.nih.gov/22329374

U.S. Preventive Services Task Force. Hepatitis C virus infection in adolescents and adults: screening. 2020 Mar 2. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening [accessed 2022 Jul 15]

Urbanus AT, van de Laar TJ, Stolte IG, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *AIDS* 2009;23(12):F1-7. [PMID: 19542864] https://pubmed.ncbi.nlm.nih.gov/19542864

van de Laar T, Pybus O, Bruisten 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):1609-17. [PMID: 19422083] https://pubmed.ncbi.nlm.nih.gov/19422083

Varan AK, Mercer DW, Stein MS, et al. Hepatitis C seroprevalence among prison inmates since 2001: still high but declining. *Public Health Rep* 2014;129(2):187-95. [PMID: 24587554] https://pubmed.ncbi.nlm.nih.gov/24587554

Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a cinical practice setting. *Clin Infect Dis* 2015;61(10):1601-3. [PMID: 26334052] https://pubmed.ncbi.nlm.nih.gov/26334052

Wandeler G, Gsponer T, Bregenzer A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. *Clin Infect Dis* 2012;55(10):1408-16. [PMID: 22893583] https://pubmed.ncbi.nlm.nih.gov/22893583

Wang TY, Kuo HT, Chen LC, et al. Use of polymerase chain reaction for early detection and management of hepatitis C virus infection after needlestick injury. *Ann Clin Lab Sci* 2002;32(2):137-41. [PMID: 12017194] https://pubmed.ncbi.nlm.nih.gov/12017194

Watson HG, Ludlam CA, Rebus S, et al. Use of several second generation serological assays to determine the true prevalence of hepatitis C virus infection in haemophiliacs treated with non-virus inactivated factor VIII and IX concentrates. *Br J Haematol* 1992;80(4):514-18. [PMID: 1581236] https://pubmed.ncbi.nlm.nih.gov/1581236

Witt MD, Seaberg EC, Darilay A, 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. [PMID: 23532480] https://pubmed.ncbi.nlm.nih.gov/23532480

Younossi ZM, Otgonsuren M, Henry L, et al. Inpatient resource utilization, disease severity, mortality and insurance coverage for patients hospitalized for hepatitis C virus in the United States. *J Viral Hepat* 2015;22(2):137-45. [PMID: 24813350] https://pubmed.ncbi.nlm.nih.gov/24813350

Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged </=30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. *MMWR Morb Mortal Wkly Rep* 2015;64(17):453-58. [PMID: 25950251] https://pubmed.ncbi.nlm.nih.gov/25950251

Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B. Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.