Viral Hepatitis

Laboratory Support of Diagnosis and Management

Table of Contents

CLINICAL BACKGROUND

Hepatitis (inflammation of the liver) can be caused by medications, viruses, and other diseases. Viral hepatitis is a common form that affects roughly 1% to 2% of the United States population[1]; causes include the hepatitis viruses, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV), and varicella zoster virus (VZV). This Clinical Focus discusses the hepatitis viruses.

Five hepatitis viruses have been well characterized: hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV).

- HAV, HBV, and HCV are the most frequent causes of viral hepatitis in the United States (**Table 1**).
- HDV infection is rare in the United States, except among HBV-infected individuals.
- HEV is considered an uncommon form of viral hepatitis in the developed world and is not discussed further in this Clinical Focus.

Clinical manifestations vary widely between different forms of viral hepatitis, as summarized below and in **Table 2**.

- HAV is highly contagious and usually manifests as acute infection in adults but is usually asymptomatic in children.[2] It is a self-limiting disease, has no chronic carrier state, and seldom causes serious sequelae, although some patients may develop acute fulminant liver failure.[2]
- HBV and HCV manifest as acute or asymptomatic disease, but often establish chronic infection resulting in substantial morbidity and mortality. Chronic infection with HBV or HCV may lead to liver cirrhosis and hepatocellular carcinoma (HCC).
- HDV is a "defective" virus in that it can replicate only in the presence of HBV. HBV/HDV coinfection (simultaneous acquisition of HBV and HDV) and superinfection (acquisition of HDV by a person with chronic HBV infection) significantly increase the severity of disease relative to HBV infection alone.[3,4,5] Acute HBV/HDV coinfection may be severe, but it tends to resolve

Table 1. Incidence and Prevalence of Viral Hepatitis in the United States

Virus	New Infections[a]	Chronically Infected People[a]
HAV	2,500	NA
HBV	19,200	0.8-2.2 million
HCV	30,500	2.7-3.9 million
HDV	Unknown	Rare in United States[b]
HEV	Unknown[c]	NA

NA, not applicable.
[a] 2014 estimate[1,6,7]
[b] Risk is elevated in individuals with chronic HBV infection and risk factors such as intravenous drug use.[3,8]
[c] US seroprevalence, indicating past exposure, is 21%.[9]

Table 2. Clinical Spectrum of Viral Hepatitis

Virus	Transmission Route	Incubation Period	Mortality[1]	Likelihood of Chronic Disease[10-12]	Associated with HCC
HAV	Fecal-oral	2-6 wk	1%	None	No
HBV	Parenteral, perinatal, sexual	4-26 wk	1%-2% (3,000/y)	5%	Yes
HCV	Parenteral, perinatal, sexual	2-23 wk	1%-5% (12,000/y)	50%-85%	Yes
HDV	Parenteral, sexual, perinatal	6-26 wk	2%-20%	90% in superinfection[a]	Yes[b]
HEV[6]	Fecal-oral	2-9 wk	1%[c]	Rare[c]	No

HCC, hepatocellular carcinoma.
[a] Higher in immunocompromised patients.
[b] Requires coinfection with HBV. Simultaneous infection with HBV is associated with severe acute disease and low likelihood of chronic infection (<5%); superinfection with HBV carries high likelihood of fulminant disease (2%-20%), chronic HDV infection (up to 80%), and cirrhosis (60%-70%), and may progress to hepatocellular carcinoma (HCC).
[c] 10%-30% in pregnant women.[2]

spontaneously. In contrast, HBV/HDV superinfection has a high likelihood of progressing to chronic infection.

Timely diagnosis of all forms of viral hepatitis is useful for preventing transmission (especially in the case of fecal-orally transmitted viruses) and understanding outbreak patterns. Prompt and accurate diagnosis of chronic HBV and HCV is needed to avoid complications and spread of the virus. In addition, treatment and vaccination options depend on the specific viral cause. Treatment for HAV is supportive, whereas specific antiviral therapies are available for HBV and HCV infection. Vaccines are available for HAV and HBV.

Laboratory testing can help evaluate many aspects of hepatitis virus infection and management. This Clinical Focus provides an overview of indications for testing, available tests, and information to assist in test interpretation.

The tables and figures are provided for informational purposes only and are not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, current guidelines, and assessment of the patient.

INDIVIDUALS SUITABLE FOR TESTING

A summary of individuals who are suitable for screening and diagnostic testing is provided in **Table 3**. Additionally, patients with diagnosed viral hepatitis may be candidates for ongoing monitoring with chemistry, serologic, and molecular tests.

TEST AVAILABILITY

Quest Diagnostics offers a variety of serologic and molecular assays for diagnosing different forms of viral hepatitis, selecting treatment, monitoring disease course, determining treatment response, and identifying candidates for HAV and HBV vaccination (**Table 4**). Information about specific tests and panels can be found in the Appendix.

TEST SELECTION AND INTERPRETATION

Reviewing the potential route of transmission (**Table 2**) and patient characteristics (**Table 3**) can help in appropriate test selection. In some cases, multiple tests may be required to characterize an individual's viral hepatitis infection (**Figure 1**). The sections below summarize the use and interpretation of some of the major tests available for diagnosis and disease management. Interpretations of individual tests are summarized in **Table 5**; however, results of an individual test cannot be interpreted in isolation, particularly for HBV infection.

Hepatitis A Virus (HAV)

Clinical indications for HAV testing include flu-like symptoms and either jaundice or an alanine aminotransferase (ALT) level >400 IU/L. HAV IgM antibody is the preferred test for diagnosis of acute HAV infection because it rises early (5-10 days after onset of symptoms) and persists only 3 to 12 months. On the other hand, HAV IgG antibody titer rises later in the course of infection and can persist for a lifetime.[13] An HAV

Table 3. Individuals Suitable for Screening or Diagnostic Laboratory Testing[11,14,15]

Risk Group	HAV	HBV	HCV	HDV
Individuals with clinical symptoms or elevated liver enzyme levels	•	•	•	
Individuals born in highly or moderately endemic areas		•	•	
Children of immigrants from highly endemic areas (if the children were not vaccinated as infants)		•	•	
Individuals with HIV or HCV infection	•[a]	•		
Household and sexual contacts of infected persons		•	•	
Pregnant women[b]		•		
Children born to infected women		•	•	
Intravenous drug users (current or past)		•	•	
Men who have sex with men		•	•	
Healthcare workers after exposure to blood borne pathogen[c]		•	•	
Individuals receiving immunosuppressive therapy, including recipients of organ transplants or cancer chemotherapy		•	•	
Hemodialysis patients		•	•	
Individuals born 1945 through 1965 (baby boomer population)[d]			•	
Individuals who received a transfusion before 1992 or clotting factor concentrates produced before 1987			•	
Individuals who have received an unregulated tattoo or piercing or used drugs intranasally			•	
Individuals who have a history of sexually transmitted infections or participate in high-risk sexual activities		•	•	
Inmates of correctional facilities		•	•	
Individuals with chronic HBV infection	•[a]			•[e]

[a] Assess immunity prior to HAV vaccination.
[b] HCV testing is also indicated for pregnant women at high risk for HCV infection.
[c] HBV testing for immunity may be desirable prior to vaccinating healthcare workers.
[d] The Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force recommends one-time HCV antibody testing for all individuals born 1945 through 1965.[16,17] This group accounts for up to 75% of adult HCV cases in the United States. Those with positive antibody results should be tested using an HCV nucleic acid test to determine whether there is active infection.
[e] If HDV coinfection or superinfection is clinically suspected.

total antibody test detects both IgG and IgM; when used in combination with the HAV IgM antibody test, it is an effective way to determine current or previous infection and test for immunity before vaccination. Follow-up testing in patients with acute HAV infection focuses on evaluation of liver function and monitoring infection for resolution (**Figure 1**).

Positive HAV IgM antibody test results indicate that the patient has a current or recent HAV infection. The presence of HAV total antibody in the absence of HAV IgM indicates previous infection or immunity against HAV infection. In an infant less than 18 months of age, a positive antibody test result may indicate passive transfer of maternal antibody. Negative results most likely indicate absence of infection. False-negative antibody results may occur in acute disease prior to seroconversion and in patients with a suppressed or nonfunctioning immune system. Thus, a negative HAV IgM result does not exclude the possibility of infection.

Table 4. Clinical Needs Addressed by Available Laboratory Tests[a]

Clinical Need	HAV	HBV	HCV	HDV
Screen, diagnose, or assess prognosis	•	•	•	•
Assess liver damage		•	•	
Determine disease status (acute vs chronic)		•	•	
Determine need for treatment		•	•	
Select appropriate therapy		•	•	
Determine response to therapy		•	•	
Determine cause of therapeutic resistance		•	•	
Document resolution of infection	•	•	•	•
Determine immune status	•	•		
Epidemiology		•		

[a] A dot (•) indicates that laboratory testing is available to meet the stated clinical need for the designated type of viral hepatitis.

Hepatitis B Virus (HBV)

Diagnosis of Acute HBV Infection

Similar to HAV, clinical indications for testing for acute HBV infection include flu-like symptoms and either jaundice or an ALT level >400 IU/L. Hepatitis B surface antigen (HBsAg) and core IgM antibody (HBcAb IgM) are present in acute infections. Thus, tests for these markers are used to diagnose acute HBV infection.

A positive test result for HBsAg indicates that the patient has a current HBV infection and is infectious. A positive result for HBcAb IgM indicates an acute, rather than chronic, infection. Other markers that may be positive during an acute infection include total HBcAb, HBV DNA, and HBeAg (**Table 6**). In an infant <18 months of age, a positive antibody test result may indicate passive transfer of maternal antibody.

Negative HBsAg and HBcAb IgM antibody results most likely indicate absence of infection. False-negative antibody results may occur in acute disease (prior to seroconversion) and in patients with a suppressed or nonfunctioning immune system. Thus, a negative result does not rule out infection. If clinical suspicion is high, negative results may be followed up with testing for HBV DNA or by retesting at a subsequent date. A negative HBV DNA result indicates absence of current infection. In rare cases, a negative HBV DNA test result could reflect a viral load below the assay's limit of detection.

Diagnosis of Chronic HBV Infection

In patients with acute hepatitis B, markers of active HBV infection should be tested 6 months after initial diagnosis to document resolution or chronic infection (**Figure 1**). Certain individuals without documented acute hepatitis B should also be screened for chronic HBV infection (**Table 3**); similar to testing for acute HBV infection, the HBsAg assay is used to test for chronic HBV infection in these individuals.[18]

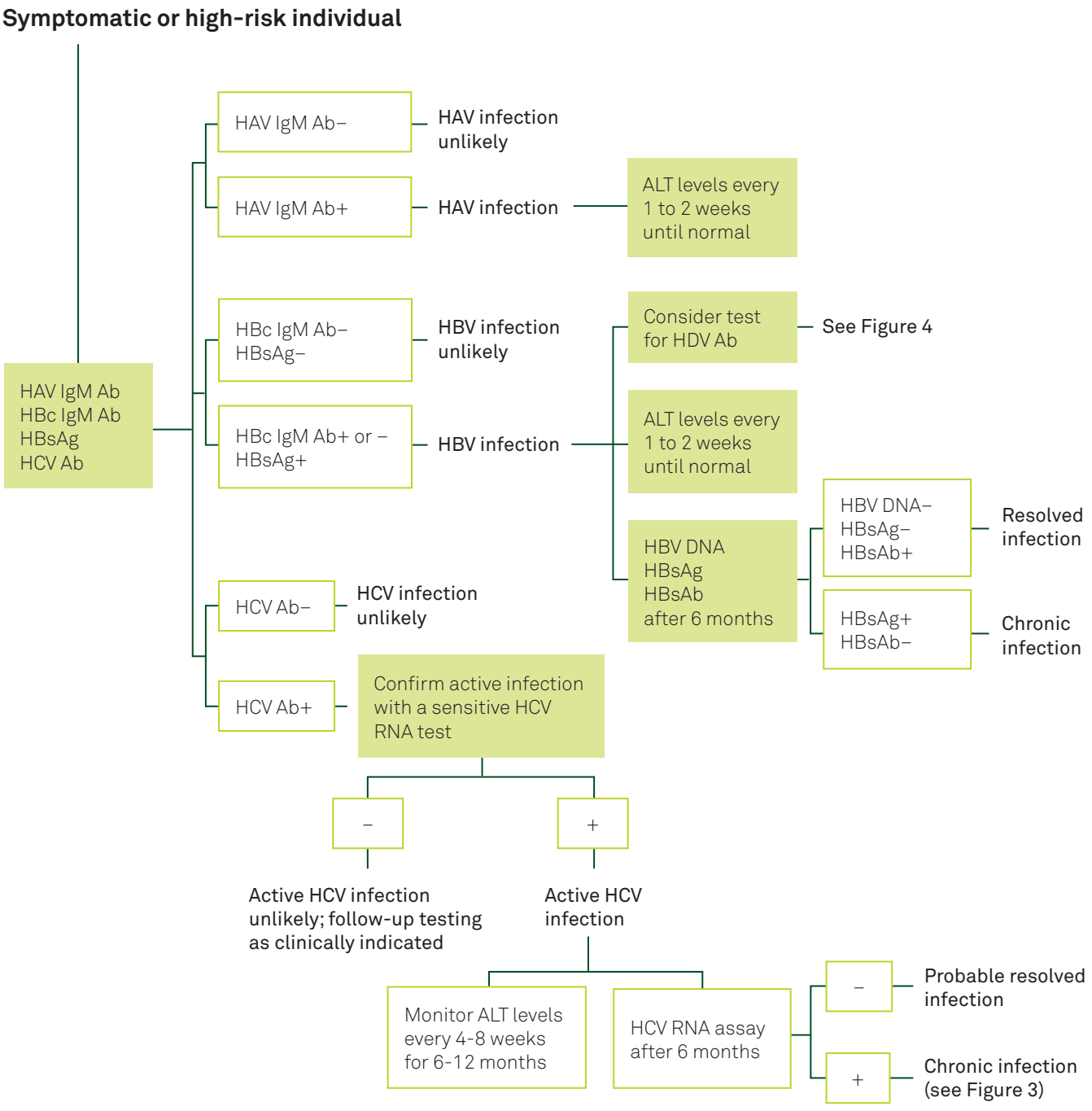
In patients with previously documented HBV infection, chronic HBV infection is marked by the presence of HBsAg and/or HBV DNA >6 months after the initial diagnosis.[18-20] In patients without a previously documented infection, chronic HBV infection is marked by the absence of HBcAb IgM and the presence of HBsAg, HBV DNA, or HBeAg (**Table 6**).[19] The absence of HBsAg is consistent with the absence of current infection.

Decision to Treat

Therapy for chronic HBV infection is focused on minimizing illness and death.[21] Part of the decision to treat is based on the phase of the disease (**Table 7**).[21] Seroconversion from HBeAg-positive to hepatitis B envelope antibody (HBeAb)-positive, which occurs towards the end of the immune-active phase, is also an important marker of disease status and usually indicates a good outcome.

In general, guidelines from the American Association for the Study of Liver Disease (AASLD) recommend antiviral therapy

Figure 1. Diagnosis and Monitoring of Hepatitis



ALT indicates alanine aminotransferase; HAV, hepatitis A virus; HBc IgM Ab, hepatitis B core IgM antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; and HDV, hepatitis D virus.

This figure was developed by Quest Diagnostics and is based in part on references 7, 10, and 11. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, current guidelines, and assessment of the patient.

Table 5. Interpretation of Individual Test Results in the Diagnosis of Acute and Chronic Viral Hepatitis

Marker	Interpretation
HAV	
HAV IgM	Presence indicates current or recent infection. A negative result indicates absence of infection.
HAV total Ab	Presence of total (IgM and IgG) HAV antibody in the absence of HAV IgM antibody indicates immunity against HAV infection.
HBV	
HBsAg	Presence indicates that a person has HBV infection and is infectious.
HBcAb, total	Presence indicates past or current HBV infection.
HBcAb IgM	Presence usually indicates HBV infection within the preceding 4 to 6 months (ie, acute infection).
HBeAb	Presence indicates resolving infection or response to therapy.
HBeAg	Presence indicates active viral replication and high infectivity
HBsAb	Presence indicates resolution and immunity against HBV infection or response to vaccination.
HBV DNA	Presence indicates current infection.
HDV	
HDV Ab, total	Presence coincident with the presence of HBsAg indicates past or current HBV/HDV coinfection or superinfection.
HDV IgM	Presence coincident with the presence of HBsAg indicates past or current HBV/HDV coinfection or superinfection. A negative result coincident with the presence of HDV total antibody indicates resolved infection.
HCV	
HCV Ab	Presence (with detectable HCV RNA) indicates current infection. A positive result coincident with a negative HCV RNA test may indicate a resolved infection or a false-positive antibody screening test.
HCV RNA	Presence indicates current infection. A negative result indicates absence of current infection.

for patients in the active phases of infection (HBeAg-positive immune-active and HBeAg-negative immune reactivation). Laboratory tests for ALT, HBV DNA, and HBeAg can help identify the phase of HBV infection and thus indicate if therapy is appropriate (**Table 7**).[21] ALT measurements can be used to monitor patients in whom treatment is not recommended.[15,21]

Therapy Selection, Monitoring, and Discontinuation

The 2 main types of therapy for chronic hepatitis B infection are pegylated-interferon (peg-IFN) and nucleos(t)ide analogs (NAs). Laboratory testing should not be the sole factor used to determine which therapy to use, but it can help identify likelihood of success for some patients. If peg-IFN is being

Table 6. Interpretation of Hepatitis B Markers[10,18]

Marker	HBV Infection Status				
	Susceptible to Infection	Immune Due to Vaccination	Immune Due to Infection	Acute	Chronic
HBsAg	-	-	-	+	+
HBsAb	-	+	+	-	-
HBc total Ab	-	-	+	+	+
HBc IgM Ab	-	-	-	+	-
HBV DNA	-	-	-[a]	+	+

[a] Very low levels may be detected with highly sensitive assays.

Table 7. HBV Phase and Treatment Recommendations

Phase	HBeAg	ALT	HBV DNA	Liver Histology	Antiviral Therapy
Immune-tolerant	Positive	Normal	Typically >1 million IU/mL	Inflammation and fibrosis minimal	Not recommended[a] (unless certain conditions are met[b])
Immune-active (immune-clearance)	Positive	Elevated	≥20,000 IU/mL	Inflammation or fibrosis moderate to severe	Recommended
Inactive (low replication)	Negative	Normal	Undetectable or low (<2,000 IU/mL)	Necroinflammation minimal; fibrosis variable	Not recommended unless patient has cirrhosis[c]
Immune-reactivation	Negative	Elevated	≥2,000 IU/mL	Inflammation or fibrosis moderate to severe	Recommended

[a] Monitor ALT every 6 months for transition to other phases.
[b] Treat with antiviral therapy if patient 1) has decompensated cirrhosis or 2) is >40 years of age and liver biopsy indicates significant necroinflammation or fibrosis.
[c] If not treated, monitor ALT every 3 months for a year; if normal, decrease frequency to 6 to 12 months.[15]

considered, genotype testing can indicate the likelihood of success: loss of HBeAg and HBsAg is more likely in patients with genotypes A and B compared to those with other genotypes.[21] Therapy selection can also be informed by identification of a coinfection with HIV and/or HDV. Peg-IFN should be used in patients with HDV coinfection, and therapy must be coordinated in HIV coinfected individuals since many anti-HBV drugs also have anti-HIV activity.[21]

Once a patient begins treatment, response to therapy can be measured using a variety of laboratory tests.

- ALT: falling levels during treatment are consistent with treatment response.
- HBeAg: loss of HBeAg in HBeAg-positive patients is an indicator of treatment response.
- HBsAg and HBsAb: clearance of HBsAg and the concurrent acquisition of HBsAb indicates resolution of infection. Though most treated patients develop HBsAb, only 0.5% of patients achieve clearance of HBsAg; these patients have better survival rates and are less likely to have hepatic decompensation.[21]
- Quantitative HBsAg: some studies have shown that quantitative HBsAg testing can indicate response to therapy (**Table 8**).[22-24]
- Quantitative HBV DNA: assays can help monitor response to therapy and predict the emergence of resistance to antiviral agents. Decreasing HBV DNA levels over time indicate that therapy is working. Conversely, a large increase in HBV DNA levels can indicate the emergence of resistance (virological breakthrough) in patients treated with NAs.[21] Results can also be used to guide changes in drug selection after therapy initiation: a change in regimen may be appropriate for patients who do not achieve a primary response (ie, patients with less than a 2-log decrease in HBV DNA within 6 months) when being treated with a NA .[18]
- HBV genotype and mutations: testing can detect the emergence of mutations associated with resistance to antiviral drugs. Although increasing levels of HBV DNA in patients receiving antiviral therapy is suggestive of drug resistance, confirmatory testing for resistance-associated mutations (**Table 9**) can help differentiate primary nonresponse from breakthrough infection.[18] The presence of resistance-associated mutations in patients with virologic breakthrough or rebound suggests the need to add or replace an antiviral drug in the regimen.[1]
- CBC, TSH, creatine kinase, etc: tests can help monitor potential adverse effects. For specific information on tests needed to monitor each therapy, see AASLD guidelines.[21]

Even if a patient responds to therapy, determining the appropriate time to discontinue a therapeutic regimen can be difficult. The preferred duration of peg-IFN therapy is 48 weeks, but the duration of NA therapy depends on the phase of the infection, HBV DNA levels, and the presence or absence of cirrhosis. Thus, testing for HBeAg, HBeAb, ALT, and HBV DNA

Table 8. Likelihood of HBV Therapy Response Based on HBsAg Levels[22-24]

Treatment	Serum HBeAg	Quantitative HBsAg Levels (HBV genotype)	Therapy Response
Peg-IFN	Positive	No decline (A or D) or >20,000 IU/mL (B or C) after 12 weeks of therapy	Unlikely
		≤20,000 IU/mL after 12 weeks of therapy	More likely[a]
	Negative	No decline and <2 log HBV DNA decline after 12 weeks of therapy	Unlikely[b]
Nucleos(t)ide analogs	Positive	Low baseline	Likely
		Steep decline during therapy	Likely
		Low at end of therapy	Likely (sustained)
	Negative	Low	Likely (sustained)

HBV indicates hepatitis B virus; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; Peg-IFN, pegylated interferon.
[a] 22% to 45% of patients vs only 6% of patients with >20,000 IU/mL.[24]
[b] Based on a study that included 7 such patients; none achieved sustained response.[23]

can help with the decision to discontinue NA treatment and help monitor patients once treatment stops (**Figure 2**).

Resolution of Chronic HBV Infection

In patients with a known history of HBV infection or the presence of HBcAb and/or HBsAb, the disappearance of HBsAg and HBV DNA along with persistently normal ALT levels indicates resolution of infection. Some individuals have detectable DNA after disappearance of HBsAg. While this may not be associated with active disease in immunocompetent individuals, it may represent treatment failure or failure of natural immunity when HBsAb is absent. HBV DNA-positive individuals may be at risk for recurrent HBV disease, cirrhosis, and HCC. Additionally, HBV DNA-positive organ donors could potentially transmit the infection to organ transplant recipients.

Vaccination

HBV vaccination is generally recommended for patients with negative results for both HBsAg and HBsAb. Those with negative HBsAg and positive HBsAb already have immunity due to past (resolved) infection or vaccination and need not be vaccinated.[18]

Hepatitis C Virus (HCV)

Screening and Diagnosis of HCV Infection

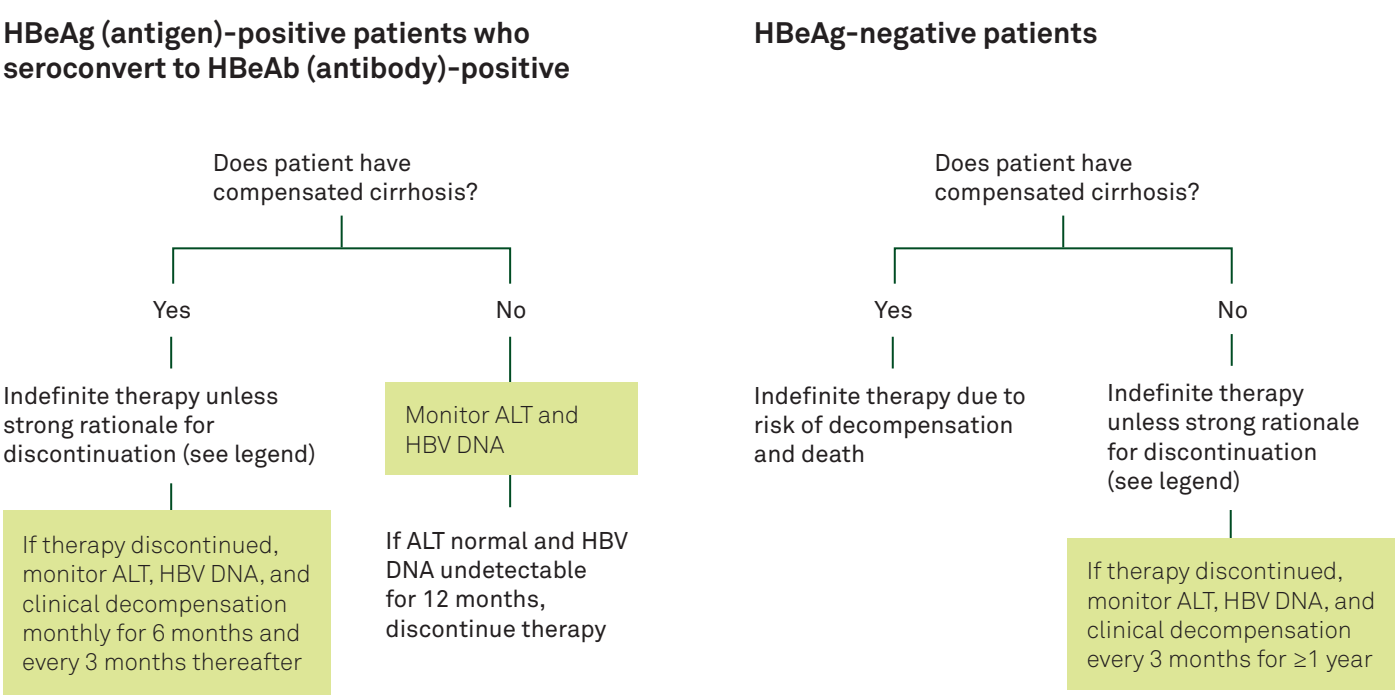
Certain individuals should be screened for HCV infection (**Table 3**). Some individuals (eg, intravenous drug users and HIV-infected men who have sex with men) should be tested annually.[11] When HCV infection is identified, it is considered acute during the first 6 months.[11] Six months after initial diagnosis, a patient should be tested for active HCV infection to document resolution of acute infection or presence of chronic infection (**Figure 1**).

Table 9. HBV DNA Polymerase Gene Mutations Associated with Resistance to Nucleos(t)ide Analogs[25]

Therapy	A181T/V	L180M + M204V	M204I	M204V	N236T	Other
Adefovir	•	±	±	±	•	
Entecavir		±	±	±		•[a]
Lamivudine	±	•	•	•		•[a]
Tenofovir					±	
Telbivudine		•	•			•[a]

A dot (•) indicates the variant confers resistance; ± indicates intermediate or reduced susceptibility.
[a] 2 combinations of mutations also confer resistance: 1) L180M + M204V/I ± I169T ± V174L ± M250V; 2) L180M + M204V/I ± T184G ± S202I/G.

Figure 2. Criteria to Discontinue Therapy for Chronic Hepatitis B Virus (HBV) Infection



Discontinuation of therapy should include consideration of risks and benefits, including virological collapse, hepatic decompensation, liver cancer, death, burden of therapy (eg, financial costs), and preferences of patient or provider.

Individuals with persistent viremia (failure to achieve undetectable levels of HBV DNA after 96 weeks and/or the decline of HBV DNA plateauing) should continue nucleos(t)ide analog therapy, regardless of ALT levels. If virological breakthrough (HBV DNA increase by >1 log compared to nadir or HBV DNA ≥100 IU/mL when previously undetectable) occurs, consider switching therapy or adding a second antiviral drug.

This figure was developed by Quest Diagnostics based in part on reference 21. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, current guidelines, and assessment of the patient.

HCV antibody immunoassays are used as the initial test for diagnosing HCV infection, because such assays have high sensitivity, wide availability, and lower cost. However, antibody tests cannot differentiate between current and past infection; an RNA test is needed for that purpose. Hepatitis C virus RNA tests are used to confirm infection in antibody-positive individuals. They are also used to diagnose infection prior to seroconversion. Unlike antibody tests, which are not positive until 4 to 10 weeks after virus acquisition, RNA tests can detect HCV 2 to 3 weeks after infection is initiated. An RNA method is also the test of choice to diagnose HCV infection in immunocompromised individuals.[14]

Results of antibody and RNA tests can be used together to indicate infection status or history.

- A reactive, or so called "positive," HCV antibody test result with a positive HCV RNA test indicates active infection.
- A positive HCV antibody test result with a negative HCV RNA test result may indicate a resolved infection. It could also indicate a false-positive antibody screening assay, which is more likely in people at low risk of HCV acquisition. Testing with another HCV antibody assay can be considered to differentiate resolved HCV infection from a biologic false-positive antibody test. In an infant less than 18 months of age, a positive antibody test result with a negative RNA test result may indicate passive transfer of maternal antibody.
- A nonreactive HCV antibody test result could be a false-negative result if seroconversion has not occurred.

Therefore, negative results should be followed up with a repeat antibody test or an HCV RNA test if the patient has a history of exposure within the previous 6 months.

Decision to Treat

Therapy for chronic HCV infection focuses on eradicating viral infection and preventing complications such as HCC, cirrhosis, and liver failure. Treatment is generally recommended for all patients with chronic HCV infection and a life expectancy ≥12 months. Initiation of therapy is most urgent in patients with certain conditions (eg, advanced fibrosis or compensated cirrhosis).[14]

The stage of fibrosis may be useful for prognosis or to help prioritize who should be treated if resources are limited. A biopsy is the historic "gold standard" for assessing fibrosis, but the procedure carries a moderate risk of complications and is subject to sampling error. Imaging and predictive models that incorporate serum markers are noninvasive options that may be useful to assess the likelihood of advanced fibrosis. One such model, the FibroTest-ActiTest, is based on serum levels of α2-macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, gamma glutamyl transferase (GGT), and ALT, along with age and sex. A fibrosis score is calculated and equated to a Metavir stage (ie, F0 to F4), reflecting the level of fibrosis. Additionally, a necroinflammation activity score is calculated and equated to a Metavir grade (ie, A0 to A3), reflecting liver inflammation. The lowest and highest scores may obviate the need for a biopsy, while intermediary scores should be interpreted in the patient's overall clinical context.

Treatment Selection

Baseline testing is recommended prior to treatment in order to assess severity of liver disease and select the most appropriate therapy (**Table 10**).[11] The large number of tests can be facilitated by the use of panels (**Appendix**; **Figure 3**).

Many licensed treatment options are available, including direct-acting antivirals (DAAs), peg-IFN, ribavirin, and various combinations. The AASLD guidelines provide thorough recommendations about selecting an appropriate therapeutic regimen.[11] Selection depends mainly on 1) previous treatment status (treatment-naïve vs treatment-experienced), 2) cirrhosis status (without vs compensated vs decompensated), and 3) HCV genotype (genotypes 1 through 6). Laboratory testing can directly assess HCV genotype to help with treatment selection.

For some genotypes (1a or 3), testing for resistance-associated substitutions (RASs) can further guide treatment selection. However, routine baseline testing for RASs prior to treatment is not recommended. The following exceptions are noted by AASLD and selected drug package inserts:

- The *NS3* Q80K substitution is associated with a lower response rate in individuals with genotype 1a and cirrhosis when treated with sofosbuvir plus simeprevir. At this time, sofosbuvir plus simeprevir is not recommended as therapy for individuals who have cirrhosis, genotype 1a, and the Q80K polymorphism.[14]
- Baseline testing for RASs is recommended for patients with genotype 1a who are being considered for treatment with elbasvir plus grazoprevir; presence of a mutation can inform therapy duration and regimen.[26]
- Clinical studies indicate that lower sustained virological response (SVR) rates are associated with RASs in patients with genotype 3 HCV: SVR rates are lower when the *NS5A* substitution Y93H is present in patients who are treated with sofosbuvir plus daclatasvir or a sofosbuvir plus velpatasvir fixed-dose combination.[27,28]

Host factors can also influence the effectiveness of certain therapies in certain patients. Individuals with an *IL28B* CT or TT genotype have worse rates of SVR to interferon/ribavirin therapy than those with the CC genotype.[29-31] In addition to *IL28B* genotype, a pair of polymorphisms (rs1127354 and rs7270101) in the inosine triphosphatase gene (*ITPA*) may play a role in HCV treatment selection or dosing. Patients whose *ITPA* variants are associated with the lowest *ITPA* activity have the lowest likelihood of having ribavirin-induced anemia[32]; those with genotype 1 infection,[33] but not those with type 2 or 3 infection,[34] are also less likely to require a ribavirin dose reduction. Assessment of anemia risk in combination with clinical evaluation may help determine the frequency of monitoring for anemia in patients receiving ribavirin. Although ribavirin-associated anemia may lead to dose reduction, *ITPA* variants have not been associated with the likelihood of SVR.[33,34]

Treatment Response

After treatment is initiated, measurement of HCV viral load at specified time intervals helps predict the likelihood of SVR and guide treatment decisions (**Table 10**).[35,36] The same quantitative test method should be used each time to avoid technology-related variability.

HCV viral load measurement at week 4 can help assess treatment response and adherence to therapy. Patients without cirrhosis typically have an undetectable level at this time. If HCV RNA is still detectable, the measurement may be

Table 10. Laboratory Testing Recommended for HCV Antiviral Therapy[11]

Test	Baseline	During treatment, week				After treatment
		4	8	12	24	
Advanced fibrosis evaluation (liver biopsy, imaging, and/or noninvasive markers, such as FibroTest™)	•					6 months after
Estimated glomerular filtration rate (eGFR)	•[a]	•[b]				
Complete blood count	•[a]	•[b]				
Serum creatinine		•[b]				
HCV genotype/subtype	•					
Hepatic function panel[c]	•[a]	•[b,d]	•[e]	•[e]		
Quantitative HCV viral load	•[f]	•[g]				12 weeks after (also consider testing at end of treatment and 24 weeks)
Thyroid-stimulating hormone[h]	•[a]			•	•	

Other baseline tests

- HAV (patients suspected of acute hepatitis)
- HBsAg[i], anti-HBs, anti-HBc (total)
- HBV DNA[i]
- HIV (and other coinfections and conditions that may accelerate liver fibrosis)
- Prothrombin time with international normalized ratio (INR)[a]
- Serum pregnancy test[j]
- Testing for the presence of HCV resistance-associated variants (RAV), as clinically indicated

[a] <12 weeks before therapy.
[b] Or as clinically indicated.
[c] Includes levels of albumin, ALT, alkaline phosphatase, aspartate aminotransferase, and bilirubin (direct and total).
[d] If ALT increases 10-fold increase, discontinue therapy.
[e] Those receiving EBR/GZR-Zepatier.
[f] Exception: when quantitative HCV viral load will affect therapy duration.
[g] If HCV viral load is detectable at week 4, repeat test at week 6; if viral load increases >10-fold, discontinue therapy.
[h] Patients on interferon.
[i] If HBsAg is positive, HBV DNA should be tested prior to direct-acting antiviral therapy. Patients with low or undetectable HBV DNA levels should be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV DNA, and those patients with HBV DNA levels meeting treatment criteria should initiate HBV therapy. Info from hcvguidelines.org.
[j] Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) RBV treatment for women of childbearing potential, and for female partners of men who receive RBV treatment.

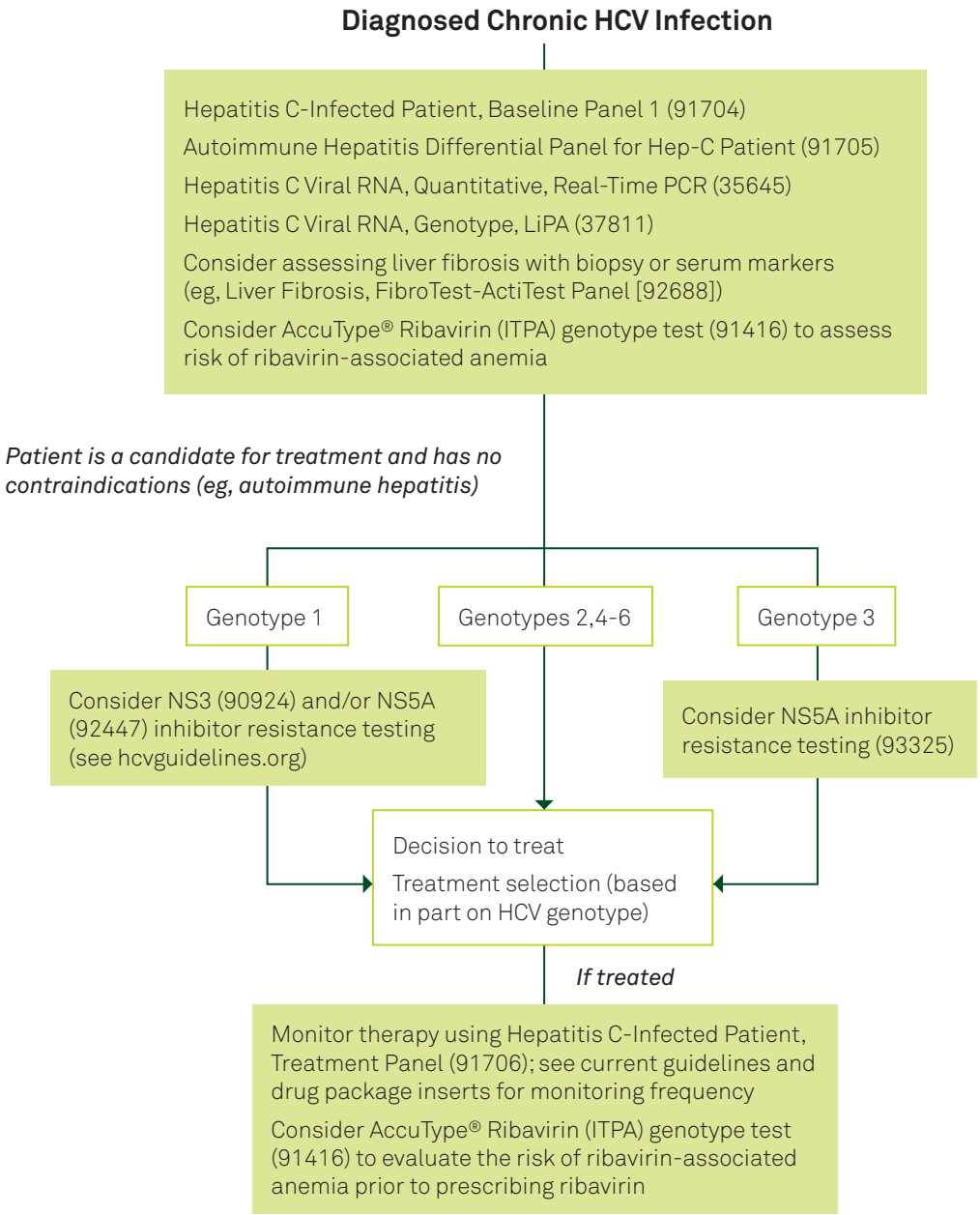
repeated 2 weeks later, at week 6. If the viral load increases by more than 1 $\log_{10}$ IU/mL during that interval, treatment should be discontinued.[14]

Absence of detectable HCV RNA at the end of treatment indicates a treatment response. Since DAAs are effective in most patients, viral load measurement at end of treatment is optional; however, viral load testing should be done 12 weeks after completion of therapy to ensure SVR. Testing again at ≥24 weeks after end of treatment may be considered.[14]

If there is a lack of response (or an insufficient response) as measured by HCV RNA levels, *NS3* sequence analysis may be used to detect mutations associated with resistance to *NS3* protease inhibitors, including boceprevir, telaprevir, and simeprevir. The emergence of RASs in patients with genotype 1a or 1b HCV infection may result in DAA resistance and failure of the therapeutic regimen.

Sequence analysis of the *NS5A* and *NS5B* genes can be used to detect mutations associated with resistance to *NS5A*

Figure 3. Management of Chronic Hepatitis C Virus (HCV) Infection



Serum markers (eg, Liver Fibrosis, FibroTest-ActiTest Panel [92688]) may be helpful in assessing the presence of advanced fibrosis but have limitations that should be taken into account when interpreting results.[35,36] Patients who are not selected for therapy should continue to be monitored; biopsy may be warranted in those with evidence of progressive liver disease.

This figure was developed by Quest Diagnostics based in part on references 35-37. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, current guidelines, and assessment of the patient.

inhibitors (eg, daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir) and the *NS5B* inhibitor sofosbuvir.[14,38-42] When an *NS5A* inhibitor is being considered for retreatment, pretreatment testing for resistance to *NS5A* inhibitors is recommended for patients with cirrhosis or patients who are in need of urgent retreatment.[11]

Resolution of Chronic HCV Infection

HCV resolution is indicated by repeatedly negative HCV RNA test results. Undetectable HCV RNA for ≥12 weeks after completion of therapy indicates SVR.[11] The HCV antibody, on the other hand, is not a good indicator of infection resolution since it will persist. Note also that the presence of HCV antibody does not protect against reinfection.

Hepatitis D Virus (HDV)

HDV occurs only as a coinfection or superinfection with active HBV infection. When HDV infection is suspected in HBV-positive individuals, laboratory testing can be used for diagnosis, differentiating coinfection from superinfection, and determining if the HDV infection is active or resolved (**Figure 4**). The total HDV antibody assay is generally the initial test.

- Positive total HDV antibody results, in the presence of HBsAg, indicate past or current HBV/HDV coinfection or superinfection.
- Negative total HDV antibody results are consistent with the absence of HDV infection.
- In the presence of positive total HDV antibody results, negative HDV IgM results indicate resolved infection.

Positive HDV antibody results may be followed by HDV RNA testing for confirmation of current infection.[12]

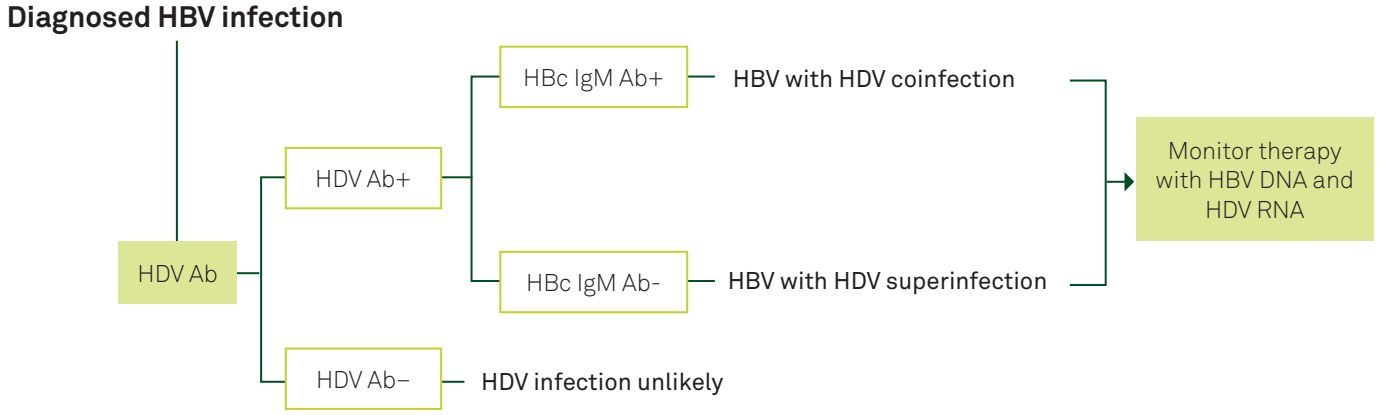
- Positive HDV RNA results in patients with HDV antibodies indicate active infection, whereas negative results indicate resolved infection.
- HDV RNA testing may also be useful in HBsAg-positive/HDV Ab-negative individuals if coinfection or superinfection is strongly suspected.

HDV and HBc IgM antibody testing can be used to differentiate coinfection and superinfection. Prognosis and management depends on the type of infection in a particular patient.[12]

- In acute HDV infection (usually coinfection) both HDV IgM and IgG can be positive, but IgM predominates. In chronic HDV infection (usually superinfection), both IgM and IgG levels are typically high and long-lasting.
- HBc IgM is a marker of acute infection, which is usually associated with coinfection. Thus, if positive, coinfection is more likely than superinfection.

HDV antibody and HDV RNA become undetectable within months after resolution.

Figure 4. Diagnosis and Management of Hepatitis D Virus (HDV) Infection



HBc IgM Ab indicates hepatitis B core IgM antibody; HBV, hepatitis B virus; HDV, hepatitis D virus.

This figure was developed by Quest Diagnostics and is based in part on reference 12. It is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, current guidelines, and assessment of the patient.

APPENDIX

Laboratory Tests for Viral Hepatitis

Test Codes	Test	Clinical Application
Viral Hepatitis Screening Panels		
10306(X)[a,b]	Hepatitis Panel, Acute with Reflex to Confirmation Includes HAV IgM, HBsAg w/rfl confirmation, HBcAb, HCV Ab w/rfl HCV RNA.	Screen for acute hepatitis caused by hepatitis A, B, or C
6462(X)[a,b]	Hepatitis Panel, General Includes total HAV Ab, qualitative HBsAb, HBsAg w/ rfl confirmation, HBcAb, HCV Ab w/rfl HCV RNA.	Detect hepatitis caused by hepatitis A, B, or C
Hepatitis A Virus (HAV)		
512(X)	Hepatitis A Antibody (IgM)	First-line diagnostic test for acute HAV infection
508(X)	Hepatitis A Antibody, Total	Screen for immunity prior to vaccination
36504(X)[a,b]	Hepatitis A Antibody, Total with Reflex to IgM	Indicate prior or acute infection with, or immunization to, HAV
Hepatitis B Virus (HBV)		
17378(X)	Donor, Hepatitis B Core Total Antibody	Screen for HBV infection in donors of human cells, tissues, and tissue-based products
17375(X)[b]	Donor, Hepatitis B Surface Antigen with Reflex to Confirmation	Screen for HBV infection in donors of human cells, tissues, and tissue-based products
499(X)	HBV Surface Antibody, Qualitative	Indicate resolved infection or vaccine response
4848(X)	Hepatitis B Core Antibody (IgM)	First-line diagnostic test for acute HBV infection Indicate recent infection (within preceding 4-6 months)
501(X)	Hepatitis B Core Antibody, Total	Indicate current or prior infection
37676(X)[b]	Hepatitis B Core Antibody, Total with Reflex to IgM	Indicate current or prior infection; differentiate recent infection (within preceding 4-6 months) from chronic or prior infection
7105(X)[a]	Hepatitis B Immunity Panel Includes HBcAb and HBsAb, qualitative	Indicate immunity to HBV
8475(X)	Hepatitis B Surface Antibody, Quantitative	Indicate immunity post-infection, vaccination, or HBIG
37132(X)	Hepatitis B Surface Antibody Quantitative, Liver Transplant	Assess HBV immunoglobulin pre- and post-infusion of HBIG
498(X)[b]	Hepatitis B Surface Antigen with Reflex to Confirmation	First-line diagnostic test for HBV infection Indicates chronic hepatitis when still positive 6 months after diagnosis of HBV infection
94333(X)	Hepatitis B Surface Antigen, Quantitative, Monitoring	Determine HBV infection phase and prognosis; monitor therapy response

(Continued)

APPENDIX *(Continued)*

Laboratory Tests for Viral Hepatitis

Test Codes	Test	Clinical Application
8369(X)[c]	Hepatitis B Virus DNA, Quantitative Real-Time PCR	Determine need to treat chronic HBV infection Indicator of chronic hepatitis when still positive 6 months after diagnosis of acute HBV infection Monitor response to therapy Demonstrate viral replication in patients with mutant HBV (eg, HBeAg- and HBeAb+ individuals) Predict likelihood of response to therapy Indicate emergence of resistant variants during antiviral therapy Linear range: 20-170,000,000 IU/mL
16694(X)[b]	Hepatitis B Virus DNA, Quantitative PCR with Reflex to HBV Genotype	Determine need to treat chronic HBV infection Predict likelihood of response to therapy Detect HBV mutations associated with resistance to antiviral agents Identify HBV genotype (A–H) for epidemiologic and prognostic purposes Detect mutations in precore and basal core promoter regions, which may influence immune response and outcome
10529(X)[d]	Hepatitis B Virus Drug Resistance, Genotype, and BCP/Precore Mutations	Detect (HBV mutations associated with resistance to antiviral agents Identify HBV genotype (A–H) for epidemiologic and prognostic purposes Detect mutations in precore and basal core promoter regions, which may influence immune response and outcome
556(X)	Hepatitis Be Antibody	Indicate convalescence/treatment response
555(X)	Hepatitis Be Antigen	Indicate active viral replication and high infectivity Assess likelihood of chronic hepatitis and HBV carriage
27(X)[a]	Hepatitis Be Panel Includes HBeAg, HBeAb.	Indicate likelihood of chronic infection Indicate response to therapy and level of infectivity (disappearance of HBeAg and appearance of HBeAb)
Hepatitis C Virus (HCV)		
90251(X)[d,e,f]	AccuType® IL28B	Predict response to interferon therapy in patients with genotype 1 HCV infection
91416(X)[d,e]	AccuType® Ribavirin (ITPA)	Assess risk for ribavirin-induced anemia in patients treated for HCV infection Help establish frequency of monitoring in patients being treated with ribavirin
93305(X)[c]	Donor, Hepatitis C Antibody (Anti-HCV)	Screen for HCV infection in donors of human cells, tissues, and tissue-based products
8472(X)[b]	Hepatitis C Antibody with Reflex to HCV RNA, Quantitative Real-Time PCR	Diagnose HCV infection Establish baseline viral load for treatment monitoring

(Continued)

APPENDIX *(Continued)*

Laboratory Tests for Viral Hepatitis

Test Codes	Test	Clinical Application
91704(X)[a,c]	Hepatitis C-Infected Patient, Baseline Panel 1 Includes hepatic function panel; CBC (includes differential and platelet counts); creatinine; HBsAb (qualitative); HAV, total Ab; HBsAg w/rfl confirmation; HBcAb, total; HIV-1/2 Ab w/rfl, HCV RNA genotype, LiPA.	Assess risk from underlying medical conditions and comorbid infections prior to initiation of HCV therapy Establish baseline laboratory parameters in order to define changes during therapy Determine HCV genotype to guide treatment selection and duration of therapy
91707(X)[a,b]	Hepatitis C-Infected Patient, Baseline Panel 2 Includes hepatic function panel; CBC (includes differential and platelet counts); creatinine; HIV-1/2 Ab w/rfl; HCV genotype, LiPA.	Assess risk from underlying medical conditions and comorbid infections prior to, during, and after initiation of HCV therapy
91706(X)[a]	Hepatitis C-Infected Patient, Treatment Panel Includes CBC (with differential and platelet counts); creatinine; ALT; quantitative HCV RNA, real-time PCR.	Assess response to therapy and adverse effects
92447(X)[d]	Hepatitis C Viral RNA Genotype 1 NS5A Drug Resistance	Detect mutations associated with NS5A inhibitor resistance or failure Guide selection of therapy in patients with HCV genotype 1 infection
92204(X)[d]	Hepatitis C Viral RNA Genotype 1 NS5B Drug Resistance	Identify resistance-associated mutation as potential cause of NS5B inhibitor (sofosbuvir) failure
93325(X)[d]	Hepatitis C Viral RNA Genotype 3 NS5A Drug Resistance	Detect mutations associated with NS5A inhibitor resistance or failure Guide selection of therapy in patients with HCV genotype 3 infection
37811(X)[d]	Hepatitis C Viral RNA Genotype, LiPA®	Predict likelihood of therapeutic response Determine the duration of treatment
93871(X)[b,d]	Hepatitis C Viral RNA Genotype,LiPA® with Reflex to HCV NS5A Drug Resistance	Genotype used to guide treatment selection and duration. If genotype is 1a, reflex to NS5A drug resistance test (92447)
90924(X)[d]	Hepatitis C Viral RNA NS3 Drug Resistance	Detect NS3 mutations associated with resistance to NS3 protease inhibitors, including boceprevir, telaprevir, and simeprevir Detect the NS3 Q80K polymorphism associated with a lower SVR rate for pegylated interferon, ribavirin, and simeprevir treatment regimens for HCV genotype 1a
35645(X)	Hepatitis C Viral RNA, Quantitative Real-Time PCR	Confirm active HCV infection and establish baseline viral load Assess prognosis (prior to the initiation of therapy) Monitor response to therapy Test for recurrence or reinfection Linear range: 15-100,000,000 IU/mL LOD: 10-13 IU/mL

(Continued)

APPENDIX *(Continued)*

Laboratory Tests for Viral Hepatitis

Test Codes	Test	Clinical Application
37273(X)[d]	Hepatitis C Viral RNA, Qualitative TMA	Diagnose acute infection Confirm EIA diagnosis of acute or chronic infection Differentiate between resolved and active infection Demonstrate resolution of infection Test for recurrence or reinfection LOD = 5.3 IU/mL
11348(X)[b,c]	Hepatitis C Viral RNA, Quantitative Real-Time PCR with Reflex to Genotype, LiPA®	Confirm active infection and establish baseline viral load. Genotype used to guide treatment selection and duration Linear range: 15-100,000,000 IU/mL Perform only for baseline evaluation. If baseline RNA already measured, order genotype LiPA only
93873(X)[b,c]	Hepatitis C Viral RNA, Quantitative Real-Time PCR with Reflexes	Confirms active infection and establishes baseline viral load. If viral load is >300 IU/mL, reflex to genotyping test (37811). Genotype used to guide treatment selection and duration. If genotype is 1a, reflex to NS5A drug resistance test (92447)
10051(X)[b]	Hepatitis C Viral RNA, Quantitative, Real-Time PCR with Reflex to Qualitative TMA	All indications listed for qualitative HCV RNA assay (test code 37237) above Establish baseline viral load Predict response to antiviral therapy Differentiate lack of therapeutic response from partial therapeutic response Linear range: 15-100,000,000 IU/mL (if <15 IU/mL, reflex to qualitative TMA assay)
92688(X)[g]	Liver Fibrosis, FibroTest-ActiTest Panel	Assist with noninvasive evaluation of liver fibrosis in patients with HCV infection
Hepatitis D Virus (HDV)		
4990(X)[d]	Hepatitis D Virus (HDV) Antibody, Total	Diagnose HDV infection in patients with fulminant hepatic failure or known previous HBV infection
35664(X)	Hepatitis D Virus (HDV) IgM Antibody, EIA	Detect HDV infection in patients with fulminant hepatic failure or known previous HBV infection, including those with reactive HDV total antibody results and suggestive clinical features but negative HDV RNA results[12]
34469(X)[d]	Hepatitis D Virus RNA, Qualitative Real-Time PCR	Confirm HDV infection in individuals with reactive HDV antibody results[13] Diagnose HDV infection in symptomatic, HBsAg-positive, HDV antibody-negative individuals with suggestive clinical features Test for resolution
Additional Tests		
823(X)	Alanine Aminotransferase (ALT)	Diagnose and manage certain liver diseases (eg, viral hepatitis, cirrhosis)
6399(X)	CBC (includes differential and platelet counts)	Assess risk from underlying medical conditions and comorbid infections (eg, anemia, leukemia, inflammatory processes) prior to, during, and after initiation of HCV therapy

(Continued)

APPENDIX *(Continued)*

Laboratory Tests for Viral Hepatitis

Test Codes	Test	Clinical Application
375(X)	Creatinine	Assess risk from underlying medical conditions and comorbid infections (eg, renal damage) prior to, during, and after initiation of HCV therapy
396(X)	hCG, Qualitative, Urine	Determine if patient is pregnant
8396(X)	hCG, Total, Quantitative	Determine if patient is pregnant
10256(X)	Hepatic function panel Includes total protein (test code 754[X]), albumin (test code 223[X]), globulin (calculated), albumin/globulin ratio (calculated), total bilirubin (test code 287[X]), direct bilirubin (test code 285[X]), indirect bilirubin (calculated), alkaline phosphatase (test code 234[X]), AST (test code 822[X]), ALT (test code 823[X])	Assess risk from underlying medical conditions and comorbid infections prior to, during, and after initiation of HCV therapy
91431(X)	HIV-1/2 Antigen and Antibodies, Fourth Generation, with Reflexes	Diagnose underlying HIV-1/2 infection
8847(X)	Prothrombin Time with INR	Assess liver function

HBIG, hepatitis B immune globulin.
Refer to the Quest Diagnostics Test Center (QuestDiagnostics.com/TestCenter) for additional testing options.
[a] Components of panels may be ordered separately.
[b] Reflex tests are performed at an additional charge and are associated with additional CPT codes.
[c] The analytical performance characteristics of this assay have been determined by Quest Diagnostics. The modifications have not been cleared or approved by the FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
[d] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
[e] Additional assistance in interpretation of results is available from our Genetic Counselors by calling 1-866-GENE-INFO (866-436-3463).
[f] This test is performed pursuant to a license agreement with Roche Diagnostics, Inc.
[g] Biopsy to assess liver fibrosis has been recommended if needed to assist with prognosis or treatment decisions.[26,28] Although noninvasive assessment of fibrosis can be used, it is not considered a replacement for biopsy in routine practice.

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