

What's New — May 2010 Update

Significant revisions include the following:

- An annual HCV antibody test is now recommended for HIV-infected patients who have continued high-risk behaviors but are seronegative for HCV; such individuals include:
 - Injection drug users
 - Men who have sex with men without barrier protection
 - Anyone with multiple sexual partners
- Quantitative HCV RNA viral load testing is now recommended for HIV-infected patients:
 - To confirm a reactive HCV ELISA antibody screen
 - To exclude HCV infection in those who are seronegative for HCV but have risk factors for HCV exposure and unexplained liver disease, including increased serum liver enzymes
- A table has been added that lists the tests for measuring HCV RNA (see Table 1)
- Figure 1. *HCV Testing Algorithm for HIV-Infected Patients* has been updated
- Assessment for anti-HCV therapy is now recommended for HIV-infected patients with acute HCV infection (see Section VI. B. *Assessment for Treatment of Acute HCV Infection*)
- Sections on assessment of mental health disorders and alcohol and substance use have been added (see Sections V. F. *Assessment for Mental Health Disorders* and G. *Assessment for Alcohol and Substance Use*)
- A new section has been added on ongoing evaluation of patients when anti-HCV therapy is deferred (see Section VII)
- A new section has been added that outlines baseline assessments and counseling at initiation of therapy (see Section VIII)
- Consultation with a psychiatrist is now recommended when prescribing anti-HCV therapy for HIV-infected patients with mental health disorders
- Figure 2. *Initial Anti-HCV Therapy for HIV/HCV Co-infected Patients* has been updated and now recommends determining whether or not to continue anti-HCV treatment after week 12 by assessing for virologic response according to quantitative HCV RNA
- A table has been added that outlines strategies for managing side effects of anti-HCV therapy (see Table 7)

I. INTRODUCTION

Hepatitis C virus (HCV) is a common cause of death from liver disease among the HIV-infected population.¹ Approximately 15% to 30% of people with HIV are estimated to be co-infected with HCV in the United States.² The rate is much higher among patients infected with HIV through injection drug use (approximately 70% to 90%) or individuals with hemophilia who received factor concentrates before 1987.³ Data collected from the ACTG A5001 cohort demonstrate that HIV/HCV co-infected patients visit the emergency department more frequently, are hospitalized more often, and have longer hospital stays than HIV mono-infected patients.⁴ Other studies have established HCV-related end-stage liver disease as a leading cause of in-hospital mortality among HIV-infected patients.⁵⁻⁷

Therapy for HCV has become increasingly successful. However, anti-HCV therapy is complex, particularly in the presence of HIV, and requires many treatment considerations, as well as careful monitoring.

Key Point:

The similar routes of exposure for HIV and HCV place patients with either infection at risk for HIV/HCV co-infection.

II. NATURAL HISTORY OF HEPATITIS C VIRUS

HCV and HIV are both RNA viruses but belong to different viral families (*Flaviviridae* and *Retroviridae*, respectively) and have very different life cycles.⁸ Like HIV, HCV mutates frequently, establishing a genetically diverse population of viral quasi-species within each infected host. This genetic diversity is at least partly responsible for the ability of HCV to evade the body's immune defenses and establish chronic infection. Unlike HIV, HCV RNA replicates in the cytoplasm of its host cell, the hepatocyte. This mode of genetic replication prevents incorporation of the HCV genome into the hepatocyte, enabling possible clearance of HCV from plasma and eradication of infection.

A. Acute HCV Infection

Acute HCV disease is often asymptomatic, with 25% to 35% of HCV mono-infected patients developing only mild constitutional symptoms or jaundice. Symptoms may be even milder or occur less frequently in HIV-infected patients. This lower incidence of symptomatic presentation in HIV-infected patients has been attributed in part to a weaker immune response compared with HCV mono-infected patients. Patients who experience symptoms, which are suggestive of a stronger immune response, have demonstrated better clinical outcomes in comparison with patients who are asymptomatic during acute HCV infection.⁹

The acute phase is defined as the first 6 months of HCV infection. During this time, serum alanine aminotransferase (ALT) levels frequently rise, fluctuate, and fall again, which indicates recovery from the acute phase. Estimates of spontaneous HCV clearance without treatment are 15% to 45% in non-HIV-infected adults and 11.5% in HIV-infected adults.¹⁰ Likelihood of HCV clearance among HIV-infected individuals is diminished in patients with lower CD4 cell counts, especially CD4 <200 cells/mm³.¹¹ Treatment of acute HCV infection in HIV-infected adults is supported by a 60% to 70% sustained virologic response rate.¹²

B. Chronic HCV Infection

Chronic infection arises in individuals who do not clear the virus during acute infection. Two-thirds of patients with chronic infection develop persistent or fluctuating serum ALT elevations, which are indicative of active liver inflammation. Because serum ALT levels may normalize intermittently, a single normal serum ALT level does not indicate that liver damage is absent. In contrast to many other liver diseases, the degree of ALT elevation in HCV-infected individuals frequently fails to correlate with the degree of liver inflammation observed on liver biopsy.

Key Point:

Up to 30% of patients with either HCV mono-infection or HIV/HCV co-infection may have persistently normal liver chemistries but still have significant liver disease.¹³

1. Histologic Damage in Chronic HCV Infection

Chronic HCV infection can cause inflammatory infiltration, particularly of the portal tracts, as well as both focal and bridging necrosis and fibrosis. Typically, chronic HCV infection results in a lymphocyte-predominant inflammatory infiltrate in the portal tracts and peri-portal regions of the liver. Inflammation may activate hepatic stellate cells to produce collagen. This, in turn, leads to the deposition of fibrous tissue first in the portal tracts and then in peri-portal regions. In more advanced stages of fibrosis, bridging fibrosis between portal tracts is present, and, in more advanced cirrhosis, fibrotic nodules are also present.

2. Cirrhosis and Hepatocellular Carcinoma in HCV Infection

Approximately 10% to 15% of patients with HCV infection will progress to cirrhosis after 20 years of infection.¹³ After development of cirrhosis from HCV, hepatocellular carcinoma (HCC) occurs at an estimated rate of 0% to 3% per year. The incidence of HCC from any cause of cirrhosis in the United States increased from 1.6 per 100,000 in 1975 to 4.9 per 100,000 in 2005; among black men, the incidence was 7.0 per 100,000 in 2005.¹⁴

Key Point:

Progression to cirrhosis occurs more quickly in men, in patients who use alcohol, in those who acquire HCV after 40 years of age, and in HIV/HCV co-infected patients.¹³

C. HCV Genotypes

HCV exists in 6 known genotypes and over 50 genotypic subtypes. Approximately 70% of patients with HCV in the United States are infected with genotypes 1 and 4, with genotypic subtype 1a being more common than subtype 1b. Ninety-one percent of HCV-infected non-Hispanic blacks were infected with genotype 1 in the third National Health and Nutrition Examination Survey (NHANES III).¹⁵ Although there are no known differences in clinical course among the various genotypes and subtypes, genotypes 1 and 4 are known to have a poorer response to interferon-based therapy than genotypes 2 and 3.

III. ROUTES OF TRANSMISSION OF HEPATITIS C VIRUS

A. Parenteral Transmission

Parenteral transmission is the primary route for HCV infection. Injection drug use accounts for at least 60% of all new infections in the United States. In some populations of injecting drug users, >80% have been infected with HCV; however, lower prevalence has been found in other populations, particularly among young users.¹⁶ Patients should be advised to avoid sharing any injection or drug preparation equipment. Although HCV transmission may be reduced through cleansing shared syringes with bleach and water between uses,¹⁷ HCV can also be transmitted through the use of other equipment, including cookers (metal bottle caps), water for dissolving drugs and rinsing syringes, cotton for filtering the solution, and tourniquets.

The risk for HCV infection from injury with an HCV-contaminated needle is 1.8%.¹³ For information regarding management of occupational exposure to HCV, refer to [HIV Prophylaxis Following Occupational Exposure](#).

B. Sexual Transmission

The efficiency of sexual transmission of HCV is much lower than HIV or other sexually transmitted viruses. However, isolated outbreaks of perimucosal HCV transmission have been reported among HIV-infected men who have sex with men (MSM).¹⁸⁻²³ In the setting of the following risk factors, HCV transmission was increased among HIV-infected MSM compared with non-HIV-infected MSM: sharing drugs via anal or intranasal routes; unprotected anal intercourse and anal/oral (“rimming”) or anal/hand contact (“fisting”); and the presence of other sexually transmitted infections (STIs).

Among non-HIV-infected, monogamous, heterosexual couples who are discordant for HCV, the risk for sexual HCV transmission is estimated to be 0% to 0.6% annually.¹³ Limited data suggest that the presence of HIV does not increase the risk of sexual HCV transmission amount heterosexual couples.²⁴ Some studies have shown that long-term, monogamous partners of HCV-infected individuals (>10 years) have slightly higher rates of HCV infection than the general population; however, the rate remains low (1.5%).^{25,26}

Key Point:

Guidelines indicating that barrier protection may not be necessary between HCV-discordant sexual partners apply only in the setting of HCV mono-infection and **do not** apply in the setting of HIV/HCV co-infection.

C. Perinatal Transmission

Maternal-fetal transmission of HCV in mono-infected women with detectable HCV RNA at delivery is approximately 4% to 7%. However, HIV co-infection increases the risk for perinatal transmission to 20%.¹³

For more information regarding perinatal transmission among HIV-infected patients, see *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*.

D. Nonsexual Household Transmission

Nonsexual household transmission is rare in the United States, although it has been known to occur, probably through inadvertent exposure to blood or infectious body fluids.

IV. SCREENING AND DIAGNOSIS OF HEPATITIS C VIRUS

A. Screening for HCV Infection

RECOMMENDATIONS:

Clinicians should screen all HIV-infected patients for anti-HCV antibodies at baseline. (AII)

HIV-infected patients who are seronegative for HCV but have continued high-risk behaviors should be screened at least annually for HCV. Individuals at high risk include injection drug users (AII), men who have sex with men without barrier protection (AII), or anyone with multiple sexual partners (AIII).

The high rate of HIV/HCV co-infection and the similar routes of transmission of both viruses underscore the importance of screening all HIV-infected patients for anti-HCV antibodies at baseline. HIV-infected patients with continued high-risk behaviors who are seronegative for HCV at baseline should receive annual testing thereafter.

A number of tests are available for HCV screening. The most readily available is the ELISA for anti-HCV antibodies. These antibodies are not protective, serving instead as a marker of present or past disease. Seroconversion with the ELISA antibody test occurs in 50% of patients within 9 weeks of exposure, in 80% within 15 weeks of exposure, and in at least 97% within 6 months of exposure. In addition to currently available ELISAs, the FDA has recently approved a rapid HCV test, the OraQuick HCV Rapid Antibody Test, for patients at risk for HCV exposure. The ELISA tests are highly sensitive but relatively nonspecific, resulting in a low positive predictive value in low-prevalence populations.

B. Diagnosis of HCV Infection

RECOMMENDATIONS:

Clinicians should confirm a reactive HCV ELISA antibody test with a quantitative HCV RNA assay. (AI) Negative HCV RNA test results should be repeated after 3 to 6 months to confirm a negative result.

Clinicians should obtain a quantitative HCV RNA viral load assay in HIV-infected patients with risk factors for HCV exposure who have a negative HCV ELISA antibody test but unexplained liver disease, including increased serum liver enzymes. (AII)

Positive HCV ELISA screening results require confirmation by viral gene amplification techniques that are used to definitively diagnose HCV infection. HCV RNA is usually detectable within 1 to 2 weeks after exposure to the virus.

In chronically infected patients, HCV RNA may be detectable only intermittently; therefore, a single negative HCV RNA assay does not exclude chronic HCV infection. A follow-up HCV RNA test should be performed after 3 to 6 months to confirm a negative HCV RNA result. A positive result for HCV RNA is confirmation of active infection.

Key Points:

- Delayed or absent HCV seroconversion has been reported in HIV-infected patients²⁷; therefore, measurement of HCV RNA may be indicated in individuals with risk factors for HCV exposure who have a negative HCV antibody test but unexplained liver disease or elevated liver enzymes.
- The level of HCV RNA does not correlate with the severity of liver injury or fibrosis.

Although qualitative tests were previously more sensitive, the limit of detection for most quantitative HCV RNA assay is now sufficiently low to make the quantitative HCV RNA assay the preferred RNA test. Knowledge of the lower limits of detection of available diagnostic tests can enhance assessment of HCV RNA. A transcription-mediated assay (TMA) is a newer isothermic amplification technology that is similar to a qualitative RNA. Table 1 lists the tests for measuring HCV RNA. Figure 1 provides an algorithm for screening and diagnosis of HCV infection.

TABLE 1
AVAILABLE TESTS FOR MEASURING HCV RNA

Type of Test ^a	Method (Manufacturer)	Dynamic Range ^b	FDA Approval Status
VERSANT HCV RNA 3.0	bDNA (Siemens)	615 to 7.7×10^6 IU/mL ^c	Approved
COBAS AmpliPrep/ COBAS TaqMan HCV Test	Real-time RT-PCR (Roche)	43 to 6.90×10^7	Approved
RealTime HCV	Real-time RT-PCR (Abbott)	12 to 1×10^8 IU/mL	Submitted
COBAS Amplicor HCV Monitor	RT-PCR (Roche)	600 to 5×10^5 IU/mL ^d	Approved
Amplicor HCV Monitor Test, v2.0	RT-PCR (Roche)	600 to 8.5×10^5 IU/mL ^d	Approved

ASR, analyte-specific reagent; bDNA, branched chain DNA; qPCR, quantitative PCR.

^a Only quantitative tests are shown because qualitative tests are no longer indicated for clinical use.

^b Results may vary at the lower limit of detection depending on the laboratory performing the test.

^c Siemens reports results in both IUs and copies/mL.

^d According to Conformité Européenne (CE) marking.

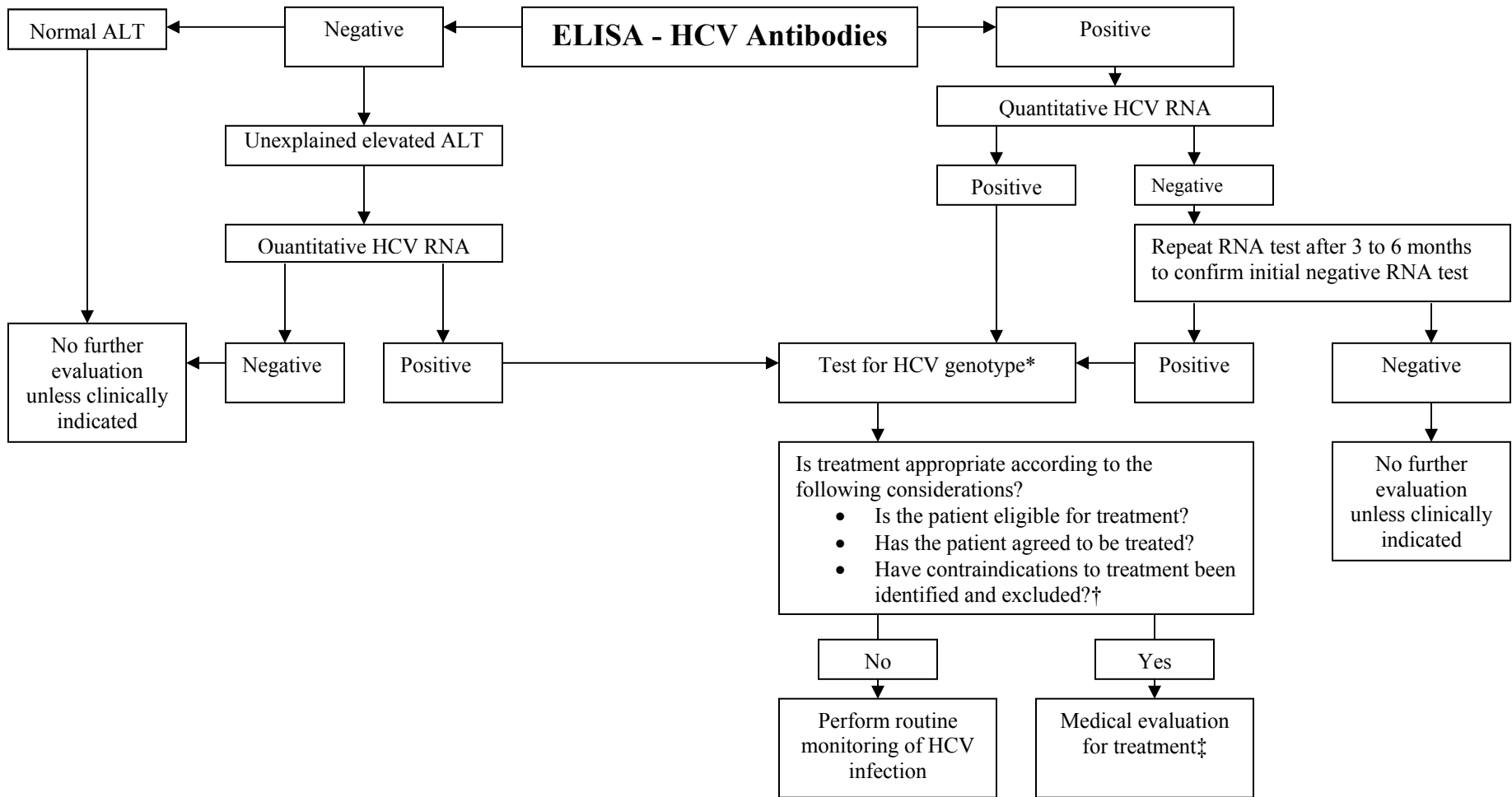


Figure 1. Hepatitis C Virus Testing Algorithm for HIV-Infected Patients *HCV genotypic testing may not be necessary for patients in whom HCV treatment is contraindicated due to non-modifiable contraindications, such as hypersensitivity to either interferon or ribavirin, hemoglobinopathies (e.g., thalassemia major and sickle cell anemia), unstable angina or unstable cardiac arrhythmias, and hepatic decompensation. †Some contraindications would not prevent anti-HCV therapy after they are appropriately addressed (see Table 2). ‡The medical evaluation for treatment should be performed in consultation with a clinician experienced in the treatment of HCV or a hepatologist (also see Figure 2).

V. EVALUATION AND INITIAL MANAGEMENT OF CONFIRMED HEPATITIS C INFECTION

RECOMMENDATIONS:

As part of the baseline evaluation of HIV/HCV co-infected patients, clinicians should (AII):

- Obtain laboratory measurements, including a complete blood count, serum AST and ALT, bilirubin, prothrombin time, and serum albumin
- Determine the patient's HCV genotype
- Assess for signs and symptoms of liver disease
- Assess for alcohol and substance use
- Screen for immunity to hepatitis A and B viruses

A. Laboratory Measurements

Higher serum ALT and AST levels are, to some degree, predictive of more rapid disease progression; however, significant liver disease may occur even in the presence of persistently normal levels.²⁸ Bilirubin, albumin, and prothrombin time are useful tests for evaluation of advanced liver disease. For HCV RNA, the same laboratory should be used for subsequent testing because of the inter-laboratory variation of quantitative HCV RNA assay results.

B. Genotypic Testing

Because patients with HCV genotypes 1 and 4 are known to have a poorer response to interferon-based therapy than genotypes 2 and 3, genotypic testing can guide treatment considerations, such as likelihood of treatment response and dose and length of treatment.

Key Point:

HCV genotypic testing is not necessary for patients in whom HCV treatment is contraindicated due to non-modifiable contraindications, such as hypersensitivity to interferon or ribavirin, hemoglobinopathies (e.g., thalassemia major and sickle cell anemia), unstable angina, unstable cardiac arrhythmias, and hepatic decompensation.

C. Assessment for Fibrosis, Cirrhosis, and Hepatocellular Carcinoma

1. Fibrosis

Liver biopsy is the most specific test for defining the extent of liver pathology induced by HCV infection. It may be used to predict an individual's long-term prognosis. Typically, liver biopsy reports will describe the degrees of inflammation and fibrosis. Several indices have been developed and validated to describe inflammation and fibrosis. The Batts-Ludwig scoring system²⁹ assesses the degrees of inflammation (grade) and fibrosis (stage) on a scale of 1 to 4 and is commonly used in the clinical setting. The Ishak or Metavir scoring system is also valid and is used in many of the clinical trials that study liver biopsy material.

The decision to treat HIV/HCV co-infected patients is often based on biopsy, particularly for patients with genotype 1 or 4; however, it is not required to treat HCV and, in some cases, may not be preferred. For example, patients with hemophilia require transjugular liver biopsies, and either the patient or the provider may not wish to proceed with this intervention. A patient's decision to decline liver biopsy should not preclude treatment for HCV when it is otherwise indicated.

Key Point:

Liver biopsy is used primarily to guide the decision to treat but may not be necessary in patients who are not being considered for treatment or who will be treated regardless of biopsy result.

2. Cirrhosis

Ultrasound of the liver can sometimes detect cirrhosis and steatosis. Liver stiffness measurements and calculations of a fibrosis score from noninvasive tests, such as FibroTest and FibroSure, are available in the United States. These tests use a combination of serum biochemical markers to predict the degree of hepatic fibrosis.³⁰ The AST/platelet ratio index is an easily calculated index used as a predictor of the presence or absence of significant fibrosis on liver biopsy in patients with chronic HCV. In one study, this index accurately distinguished significant from insignificant fibrosis in 60% of patients.^{31,32} A technique used for calculating liver stiffness, known as elastography (FibroScan), has been studied for its potential as a sonography-based method for detecting liver fibrosis and cirrhosis.³³

3. Hepatocellular Carcinoma

Screening for HCC in persons with cirrhosis is most commonly performed with regular imaging by ultrasonography or CT scan, as well as with determination of serum α -fetoprotein (AFP). HCC is rare in HCV unless the patient has advanced fibrosis or cirrhosis. AFP testing alone has relatively low sensitivity and specificity for HCC, and the optimal interval for screening remains undetermined. However, evidence suggests that biannual AFP coupled with annual ultrasonography may be cost-effective in HCV-infected patients with cirrhosis.³⁴ If AFP is elevated, then a screening examination is no longer appropriate, and a diagnostic test is indicated. Both triple-phase CT scans and liver MRI offer greater sensitivity in finding and distinguishing among liver abnormalities.

D. Evaluation of Hepatitis A and B Status**RECOMMENDATIONS:**

As part of the baseline assessment, clinicians should ask HIV-infected patients about their HAV and HBV vaccination history and should:

- **Obtain HBV serologies: HBsAg, HBsAb, and HBcAb (IgG or total) (AII)**
- **Obtain Hepatitis A IgG (AII)**
- **Vaccinate those who are not immune to hepatitis A and/or B viruses (see [Hepatitis A Virus](#) and [Hepatitis B Virus](#)) (AII)**

Although hepatitis A virus (HAV) does not progress to a chronic infection, severe disease may develop in patients with underlying HCV. HIV/HCV/HBV tri-infection confers the risk for serious complications. Accordingly, HAV and HBV screening and vaccination should be performed according to current guidelines (see [Hepatitis A Virus](#) and [Hepatitis B Virus](#)).

E. Other Disease Screening

If clinically suspected, screening for the following diseases may be indicated in HIV/HCV co-infected patients (AII):

- Hemochromatosis: obtain percentage iron saturation with ferritin (uncommon in patients of African descent)
- Primary biliary cirrhosis: obtain anti-mitochondrial antibody
- Autoimmune hepatitis: obtain anti-nuclear antibody and anti-smooth muscle antibody
- α -1 anti-trypsin deficiency: obtain α -1 anti-trypsin level
- Wilson's Disease: obtain ceruloplasmin level
- Steatohepatitis: assess with liver biopsy (see Section V. C. *Assessment for Fibrosis, Cirrhosis, and Hepatocellular Carcinoma*)

F. Assessment for Mental Health Disorders

RECOMMENDATIONS:

Clinicians should perform the following:

- **Mental health screening in all HIV/HCV co-infected patients at baseline and at least annually according to standard guidelines for all HIV-infected patients** (see the [Mental Health Guidelines](#))
- **Depression screening at initiation of anti-HCV treatment and at least every 4 weeks thereafter during treatment** (see Section XII. *Treatment Monitoring of HIV/HCV Co-infected Patients*)

Screening for mental health disorders in HIV/HCV co-infected patients should be performed according to standard guidelines for all HIV-infected patients, regardless of whether or not the patient will receive anti-HCV therapy. Numerous studies have documented the association between interferon alfa and depression, with an estimated incidence between 20% and 40%; however, the prevalence of mental health disorders, and depression in particular, is increased in patients infected with HCV. The rate of depression in untreated HCV-infected patients may be as high as 25%,³⁵ demonstrating that HCV itself may also be a risk factor for depression. HCV commonly presents with symptoms of fatigue and malaise, which may mimic depression and complicate its diagnosis.

At present, insufficient data exist to determine the risk factors for developing depression during interferon treatment. Patients with a history of mental health disorders are at particular risk for mood alterations due to anti-HCV therapy.

Key Point:

A history of mental health disorders, such as depression, should not be regarded as a contraindication to therapy. However, clinicians who prescribe interferon alfa should consult with a psychiatrist when treating patients with a history of mental health disorders.

G. Assessment for Alcohol and Substance Use

RECOMMENDATIONS:

Clinicians should obtain an alcohol and substance use history for HIV/HCV co-infected patients. Patients with alcohol abuse or dependence should be referred for alcohol-dependency treatment. (AII)

Clinicians should educate HIV/HCV co-infected patients about the effects of alcohol, tobacco, and cannabis on the course of HCV infection. Patients who have other underlying liver disease should be advised to abstain from alcohol. (AII)

Numerous studies indicate that patients with HCV and heavy alcohol intake have increased progression of hepatic fibrosis and increased risk for cirrhosis, HCC, and death.^{36,37} Although some studies suggest that light to moderate consumption may contribute to progression, this has not been clearly shown.³⁸ The National Institute on Alcohol Abuse and Alcoholism defines moderate alcohol use for most adults as up to two drinks per day for men and one drink per day for women and older people. One drink equals one 12-ounce bottle of beer or wine cooler, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits. For more information regarding alcohol dependence in HIV-infected patients, see [Clinical Management of Alcohol Use and Abuse in HIV-Infected Patients](#).

Most hepatologists recommend abstinence from alcohol in patients who are infected with HCV. All patients with HCV infection who use alcohol should be educated about the effects of alcohol on the course of HCV infection. Abstinence in heavy drinkers with HCV is associated with improvement in chemical markers, as well as decreased HCV RNA levels.^{39,40} Patients with alcohol abuse or dependence should be referred for alcohol-dependency treatment.

Smoking tobacco is a risk factor for hepatoma and is a predictor for the progression of fibrosis in persons with HCV.⁴¹ Daily cannabis use may increase the risk for progression to moderate to severe fibrosis by up to 7-fold compared with non-daily use in HCV-infected patients.⁴² However, weekly or monthly cannabis use does not significantly increase risk for progression of fibrosis compared with rare or no use.

Methamphetamine use promotes HCV replication in hepatic cells and, therefore, may contribute to HCV disease progression.⁴³ As with alcohol, abstinence from smoking and regular cannabis use, as well as abstinence from other substances, is recommended in individuals who are infected with HCV.

For more information regarding management of alcohol and substance use in HIV-infected patients, refer to the [Substance Use Guidelines](#).

VI. DECIDING WHETHER TO TREAT HCV IN HIV-INFECTED PATIENTS

When performing a medical evaluation for anti-HCV treatment in HIV/HCV co-infected patients, clinicians should consult with a hepatologist or other provider with experience in treating HCV. (AIII)

Clinicians should individualize the decision to treat HCV based on the following factors (AIII):

- **Contraindications and relative contraindications to therapy (see Table 2)**
- **Whether the patient has acute HCV**
- **Likelihood of response to treatment of chronic HCV (see Table 3)**
- **Likelihood of progression of fibrosis in the absence of treatment (see Table 3)**
- **Immune status**
- **Extent of liver damage**
- **HCV and HIV viral loads**
- **Risk for adverse effects of treatment**
- **Motivation for treatment and barriers to adherence to therapy**
- **CD4 count**

Patients with acute HCV who remain positive for HCV RNA 12 weeks after infection should be treated with combination pegylated interferon and ribavirin. (BIII)

Consideration of the factors used to guide the decision to treat HCV infection, including contraindications for HCV treatment, likelihood of progression of fibrosis without treatment, and the medical evaluation for potential anti-HCV treatment, should be in consultation with a hepatologist or other clinician with experience in HCV treatment.

A. Contraindications to Anti-HCV Therapy

RECOMMENDATIONS:

Clinicians should not prescribe anti-HCV treatment for HIV/HCV co-infected patients with any of the absolute contraindications listed in Table 2.

Clinicians should address any of the relative contraindications listed in Table 2 before prescribing anti-HCV therapy.

Among the considerations for anti-HCV therapy, assessment for contraindications to therapy is essential. Table 2 lists contraindications that would prevent initiation of anti-HCV treatment in HIV/HCV co-infected patients, as well as relative contraindications that, once addressed, would not affect the decision to treat.

TABLE 2
CONTRAINDICATIONS FOR HCV TREATMENT IN PATIENTS WITH HIV/HCV CO-INFECTION

Contraindications	Relative Contraindications
<ul style="list-style-type: none"> • Allergy to interferon/ribavirin • Patients on dialysis or with creatinine clearance <50 mL/min • Hemoglobinopathies (e.g., thalassemia major and sickle cell anemia) • Autoimmune hepatitis • Uncontrolled thyroid disease • Pregnant/nursing women, women unable to practice contraception, or men with pregnant partners • Current suicidal behavior or uncontrolled severe psychiatric illness • Severe cardiac disease (e.g., unstable angina, unstable arrhythmias) • Decompensated cirrhosis • Sarcoidosis or unexplained pulmonary infiltrates • Heart, lung, and kidney transplants • Neonates and infants • Patients receiving didanosine^a 	<ul style="list-style-type: none"> • Hb <10 g/dL^b • White blood cells <1500 cells/mm^{3b} • Platelets <90,000/mm³ • CD4 <100 cells/mm³ • Uncontrolled diabetes mellitus • Other autoimmune disorders (e.g., lupus, rheumatoid arthritis) • Ongoing heavy alcohol use^c • Active substance use if adherence to treatment is a concern^d • Untreated mental health disorder^e • Previous suicidal behavior^e

See package inserts for pegylated interferon and ribavirin for full details.

^a The combination of ribavirin and didanosine has demonstrated an increased risk for pancreatitis, lactic acidosis, hepatic decompensation, and death in patients with cirrhosis. Therefore, the combination is contraindicated.

^b These hematologic deficiencies can be corrected with hematopoietic growth factors. For example, patients receiving zidovudine may develop correctable granulocytopenia or severe anemia. Once corrected, such patients may be eligible for treatment.

^c Patients with alcohol dependence should be referred for alcohol-dependency treatment before initiation of anti-HCV therapy. For more information regarding alcohol dependence in HIV-infected patients, see [Clinical Management of Alcohol Use and Abuse in HIV-Infected Patients](#).

^d Active substance use is not a contraindication to anti-HCV treatment unless the clinician determines that it could interfere with adherence. Such a determination may be established on a case-by-case basis with the patient's adherence to HIV treatment as a guide.

^e Patients with a history of mental health disorders may safely complete a course of treatment if the disorder is in remission and there is sufficient interdisciplinary support.⁴⁴ Treatment of these individuals should be undertaken in consultation with a psychiatrist.

1. Untreated Mental Health Disorders

RECOMMENDATION:

When untreated mental health disorders are identified in HIV/HCV co-infected patients, clinicians should make appropriate referrals for mental health treatment before initiating anti-HCV therapy. (AII)

For patients with a suspected mental health disorder that is untreated, clinicians should refer the patient for mental health evaluation and treatment before consideration of anti-HCV therapy. See Section V. F. *Assessment for Mental Health Disorders*.

2. Heavy Alcohol and Substance Use

RECOMMENDATIONS:

Clinicians should screen patients for alcohol and substance use dependence before initiating anti-HCV treatment. (AII)

When untreated alcohol dependence is identified in HIV/HCV co-infected patients, clinicians should make appropriate referrals for substance-dependency treatment before initiating anti-HCV therapy. (AII)

One study found an inverse correlation between rates of response to interferon treatment and levels of alcohol intake during therapy.⁴⁵ Furthermore, there are reports of acute alcoholic hepatitis in several individuals consuming alcohol during interferon treatment.⁴⁶ Heavy drinkers are unlikely to achieve sustained virologic response (SVR). See Section V. G. *Assessment for Alcohol and Substance Use*.

Key Point:

Unlike heavy alcohol use, active substance use does not induce hepatotoxicity when combined with anti-HCV treatment. Active substance use, including injection drug use, is not a contraindication to anti-HCV treatment unless the clinician determines that it could interfere with adherence to treatment. Such a determination may be established on a case-by-case basis, using the patient's adherence to HIV treatment as a guide.

B. Assessment for Treatment of Acute HCV Infection

Treatment of acute infection is an important consideration for HIV-infected patients. The greater risk for chronic infection among HIV-infected patients co-infected with HCV, and the excellent treatment responses in mono-infected patients with acute HCV,¹² argue for consideration of anti-HCV therapy in HIV-infected patients who develop acute HCV. Good treatment responses have been seen even in patients infected with HCV genotypes 1 and 4. In general, if patients acutely infected with HCV are still positive for HCV RNA by 12 weeks after infection, treatment should be considered.

C. Assessment of Patients at Greatest Risk for Cirrhosis

Patients at greatest risk for progression to cirrhosis should be considered candidates for anti-HCV therapy (see Table 3). Patients who are most likely to progress to cirrhosis include those with persistently elevated serum ALT and those with a liver biopsy that reveals greater than stage 2 fibrosis (i.e., patients with at least periportal fibrosis on biopsy). However, because HIV itself is a risk factor for increased progression of HCV, serious consideration should be given to treatment of patients with minimal fibrosis or portal fibrosis (i.e., an Ishak score of F1). Table 4 outlines National Institutes of Health recommendations¹³ for HIV/HCV co-infected patients with minimal fibrosis or portal fibrosis.

TABLE 3 HCV TREATMENT CONSIDERATIONS FOR PATIENTS WITH HIV/HCV CO-INFECTION
<p>Factors associated with progression to cirrhosis without treatment</p> <ul style="list-style-type: none"> • Male sex • Alcohol use >30 g/day for men and >20 g/day for women • Infected at ≥40 years of age • Portal or bridging fibrosis or at least moderate inflammation or necrosis • HIV/HCV/HBV tri-infection • Elevated serum AST and ALT levels
<p>Factors associated with favorable response to therapy</p> <ul style="list-style-type: none"> • HCV genotype 2 or 3 and, to a lesser extent, genotype 4 (rather than 1a or 1b) • Low level of serum HCV RNA before treatment (<800,000 IU/mL) • Age <40 years • Duration of disease <5 years • Absence of cirrhosis or only minimal histologic evidence of fibrosis • Low concentrations of iron in liver tissue before treatment • Rapid clearance of HCV RNA • Abstinence from alcohol or avoidance of heavy alcohol use • Absence of hepatosteatosis • Insulin responsiveness
<p>HCV-induced extrahepatic disorders that indicate need for therapy</p> <ul style="list-style-type: none"> • Cryoglobulin vasculitis • Glomerulonephritis

TABLE 4 CURRENT TREATMENT GUIDELINES FOR PATIENTS WITH HIV/HCV CO-INFECTION*	
Patient Characteristics	Treatment Recommendations
Minimal fibrosis on liver biopsy	<ul style="list-style-type: none"> • Treat with pegylated interferon plus ribavirin if there are no contraindications <p style="text-align: center;"><i>or</i></p> <ul style="list-style-type: none"> • Observation, serial ALT and AST levels every 6 months, liver biopsy every 3 to 5 years
Persistent HCV viremia and liver biopsy showing portal or bridging fibrosis, compensated cirrhosis, or moderate inflammation or necrosis	Treat with pegylated interferon plus ribavirin if there are no contraindications (assess risks and benefits on a case-by-case basis)
Decompensated cirrhosis	Consider evaluation for liver transplant
* Decisions to treat should be individualized.	

D. ALT Levels in HIV/HCV Co-infected Patients

Patient motivation, age, duration of infection, degree of fibrosis, viral genotype, and HCV RNA may be considered when deciding whether to treat HIV-infected patients with normal ALT levels.⁴⁷ A higher prevalence of liver fibrosis has been found in HIV/HCV co-infected patients with a normal ALT, and in two studies, cirrhosis was found on liver biopsy in 12% to 14% of patients with a normal ALT.^{48,49} According to the 2007 updated recommendations from the HCV-HIV International Panel, co-infected patients with normal ALT levels should be considered for treatment if there are no contraindications.⁵⁰ Some experts consider increased ALT levels over baseline to be abnormal for HCV-infected patients, even when the increased levels are within the upper limit of normal.⁵¹

VII. ONGOING EVALUATION OF PATIENTS IN WHOM ANTI-HCV TREATMENT IS DEFERRED

RECOMMENDATIONS:

For patients in whom anti-HCV treatment is deferred, clinicians should:

- **Obtain serial ALT and AST levels every 6 months**
- **Consider obtaining a liver biopsy every 3 to 5 years to assess for disease progression (BIII)**
- **Perform ongoing patient education, including education regarding the hepatotoxic effects of alcohol and other substances (see Section V. G. *Assessment for Alcohol and Substance Use*) and prevention of HCV transmission (see Section XV. *Prevention of HCV Transmission and Re-infection*)**

Patients in whom anti-HCV treatment is deferred should receive serial ALT and AST levels every 6 months. However, liver biopsies showing portal or bridging fibrosis, or at least moderate inflammation or necrosis, are the best predictors of eventual cirrhosis. HCV viral load, serum transaminase levels (serum ALT, AST), and HCV genotype do not accurately predict the extent of liver damage, nor do they predict the likelihood of future progressive liver disease.

Significant progression of fibrosis has been observed in HIV/HCV co-infected patients. Up to two-stage increases via the Ishak fibrosis scoring system (0 to 6) have been observed in liver biopsies that were obtained approximately 3 years apart, even in patients who demonstrated mild liver disease at the initial biopsy.⁵² Therefore, repeat biopsy should be performed every 3 to 5 years to assess for disease progression in patients whose initial liver biopsy indicated that treatment was not required.

Key Point:

Even in patients who remain free of symptoms and whose liver chemistries remain normal, histologic damage still can occur.

VIII. BASELINE ASSESSMENTS AND COUNSELING AT INITIATION OF THERAPY

A. Laboratory Assessments

RECOMMENDATION:

Clinicians should obtain the following baseline assessments when the decision to initiate anti-HCV therapy has been made (AII):

- **Serum liver enzymes**
- **Complete blood count**
- **Thyroid-stimulating hormone**
- **Anti-nuclear antibody**
- **Glucose**
- **Quantitative HCV RNA in serum**
- **HCV genotype**
- **α -Fetoprotein (only if cirrhotic)**
- **Pregnancy testing for female patients of childbearing potential, as well as female partners of male patients, immediately prior to initiation of therapy**

B. Anti-HCV Treatment and Antiretroviral Therapy

RECOMMENDATIONS:

Clinicians should initiate or continue ART in HIV/HCV co-infected patients according to current ART guidelines (AIII), except for the following caveats:

- **The combined use of didanosine and ribavirin is contraindicated (AIII)**
- **The combination of zidovudine with interferon and ribavirin should be used with caution due to synergistic bone marrow suppressive effects (AIII)**
- **The combination of abacavir and ribavirin should be used with caution due to possible competitive inhibition between these agents (BIII)**

Growing evidence suggests that ART may improve clinical outcomes in HIV/HCV co-infected patients. Findings of the Swiss HIV Cohort Study and the Women’s Interagency HIV Study have shown that patients with HIV/HCV co-infection have an increased risk for progression to a new AIDS-defining event or death.^{53,54} Other reports have demonstrated an increased risk for opportunistic infections⁵⁵ and liver disease⁵⁶⁻⁵⁸ among HIV/HCV co-infected patients not receiving ARV treatment.

ART is not contraindicated in HIV/HCV co-infected patients. Co-infected patients should initiate or continue ART as indicated by current HIV treatment guidelines. However, the hepatotoxic effects of ARV agents or a hyperactive immune response precipitated by ART may accelerate HCV-induced liver damage, suggesting the possible benefit of treating HCV infection before initiating ART. In some settings, it may also be necessary to treat HCV before the patient is able to tolerate HIV therapy.⁵⁹

The adverse events associated with anti-HCV treatment in HIV/HCV co-infected patients are comparable with those seen in patients with HCV alone. However, the combination of anti-HCV treatment and ART in co-infected patients may lead to an increased incidence of metabolic complications and/or adverse drug interactions due to synergistic toxicity profiles.

Didanosine

Key Point:

The combination of didanosine and ribavirin is contraindicated. Several ongoing clinical trials have identified an increased risk for pancreatitis, lactic acidosis, hepatic decompensation, and death associated with the combination of ribavirin and didanosine in patients with cirrhosis. The combination of ribavirin and didanosine is known to raise intracellular levels of didanosine metabolites, which may be caused by the increased phosphorylation of didanosine by ribavirin and/or additive mitochondrial toxicity of these nucleoside analogs.⁶⁰

Zidovudine

Zidovudine can cause significant anemia and sometimes leukopenia, and the addition of interferon with ribavirin may exacerbate these complications. Hematopoietic growth factors may be required earlier in these patients, and, in general, this combination of drugs can be difficult for patients to tolerate and should be avoided if possible.⁶¹

Abacavir

Both abacavir and ribavirin are guanosine analogs and, theoretically, could competitively inhibit one another.^{62,63} One study involving 426 HIV/HCV co-infected patients receiving treatment for HCV infection found a 2-fold increased risk for HCV treatment failure by logistic regression analysis in patients also receiving abacavir.⁶² In another retrospective study, the use of abacavir with lamivudine as the NRTI backbone in HIV/HCV co-infected patients treated with pegylated interferon plus ribavirin was associated with a lower rate of SVR (29%) compared to a backbone of tenofovir plus lamivudine or emtricitabine (45%).⁶⁴ Additional studies are required to confirm these findings.

C. Contraception Counseling During Anti-HCV Therapy

RECOMMENDATION:

Clinicians should counsel female HIV/HCV co-infected patients and HIV/HCV co-infected male patients with female partners to use two effective methods of contraception to avoid pregnancy during ribavirin treatment and for 6 months afterward.

In addition to the regular use of condoms in the presence of HIV/HCV co-infection, patients receiving ribavirin and their partners should use a second effective method of contraception.

D. Prescribing Anti-HCV Therapy for Patients With a History of Mental Health Disorders

RECOMMENDATION:

Clinicians should prescribe interferon alfa in consultation with a psychiatrist when treating HIV/HCV co-infected patients with a history of mental health disorders, including depression.

Patients receiving effective treatment for mental health disorders may safely complete a course of anti-HCV therapy. However, the mental health disorder should be in remission, prescription of anti-HCV therapy should be in consultation with a psychiatrist, and sufficient interdisciplinary support should be available.⁴⁴ See Section V. F. *Assessment for Mental Health Disorders*.

E. Counseling Regarding Alcohol Use

RECOMMENDATION:

Clinicians should advise patients to abstain from alcohol and substance use during HCV antiviral therapy. (AII)

Patients who consume light or moderate amounts of alcohol should be advised to abstain from alcohol during antiviral therapy. A pre-treatment period of abstinence for these individuals is not necessary.⁶⁵

Although active substance use may diminish the efficacy of treatment, few studies address ongoing substance use during antiviral treatment among patients. The data that are available indicate that active and recent injection drug users can be treated successfully for HCV,^{66,67} and methadone and buprenorphine are not contraindications to treatment of HCV. Methamphetamine use has been shown to compromise the anti-HCV activity of interferon alfa.⁴³ See Section V. G. *Assessment for Alcohol and Substance Use*.

IX. TREATMENT REGIMENS FOR HEPATITIS C VIRUS IN HIV-INFECTED PATIENTS

RECOMMENDATIONS:

Pegylated interferon with ribavirin for 48 weeks is the standard recommended therapy for HIV/HCV co-infected patients with chronic HCV. (AI)

Weight-based ribavirin dosing is recommended in HIV/HCV co-infected patients with genotypes 1, 4, 5, and 6. (AI)

The primary goal of anti-HCV therapy for chronic HCV is eradication of HCV from the serum, as determined by undetectable HCV RNA. A secondary goal is reduction of hepatic inflammation/fibrosis with the expectation of decreased disease progression and subsequent reduction in HCC risk.

The most effective treatment for HCV infection is pegylated interferon with ribavirin. This form of interferon has covalently bound molecules of polyethylene glycol that slow the metabolism of interferon, thereby permitting a weekly dosing schedule, increased serum levels of interferon, and improved anti-HCV activity. Two approved forms of pegylated interferon are now available: alfa-2a and alfa-2b. Although the manner in which they are pegylated differs, clinical outcomes are similar. See Table 5 for dosing recommendations.

TABLE 5 COMPARISON DOSING WITH INTERFERON ALFA-2a and -2b		
	Pegylated interferon alfa-2b (Peg-Intron)	Pegylated interferon alfa-2a (Pegasys)
Interferon dosing	1.5 µg/kg SC weekly	180 µg SC weekly
Ribavirin dosing	Genotype 1 or 4: <75 kg: 400 mg + 600 mg PO bid (total daily dose of 1000 mg) ≥75 kg: 600 mg PO bid Genotype 2 or 3: 400 mg PO bid or same as above ⁶⁸	

Data from clinical trials have shown efficacy of pegylated interferon alone and as part of combination therapy with ribavirin 800 to 1000 mg/day in HIV/HCV co-infected patients. Three trials using the two different forms of pegylated interferon with ribavirin have confirmed that pegylated interferon plus ribavirin is superior compared with standard interferon plus ribavirin.⁶⁹⁻⁷¹ Appendix A provides a summary of data from clinical trials on anti-HCV therapy.

Treatment of Acute HCV Infection

SVR rates of 60% to 70% have been achieved in most studies when combination pegylated interferon and ribavirin were used for 24 weeks in patients with acute HCV mono-infection.¹² These data are from noncomparative studies, with the predominant risk group for HCV infection being men who have sex with men. The necessity of using ribavirin in addition to interferon has not been established for acute infection.

X. DURATION OF TREATMENT

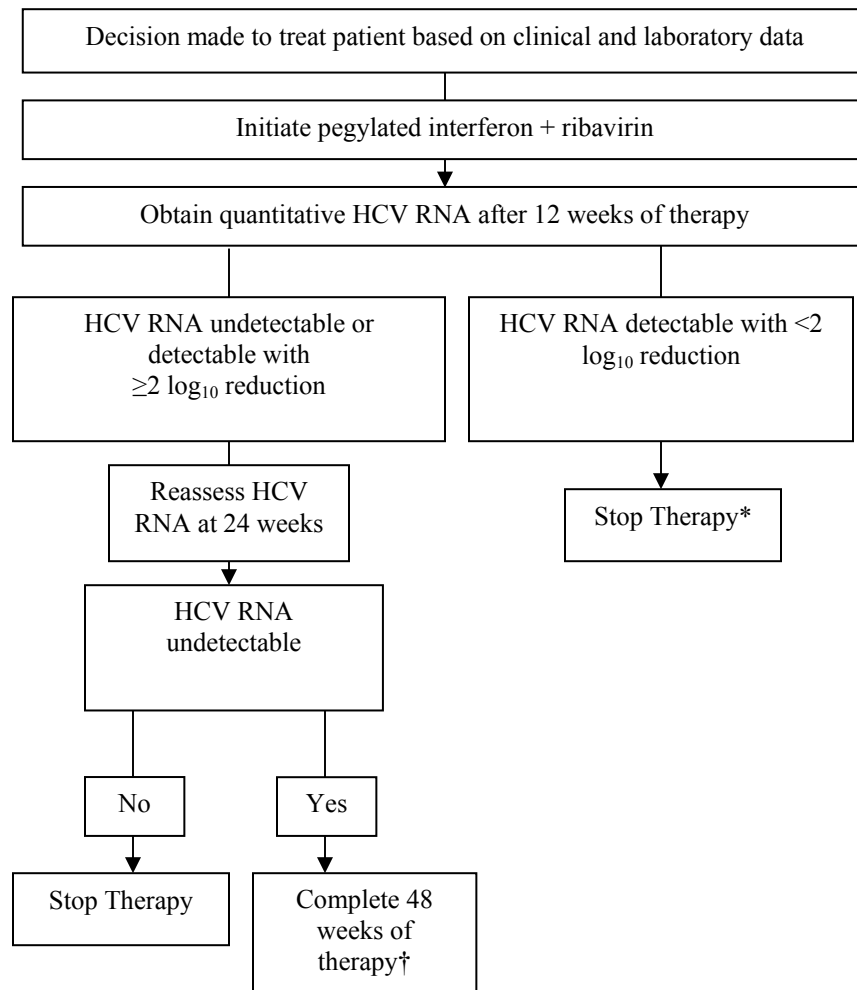
RECOMMENDATION:

Clinicians should consider discontinuation of treatment in patients whose ALT levels increase after 12 weeks of treatment; rising ALT levels during treatment may be an indication of treatment failure. (AIII)

The standard duration of therapy for co-infected patients is 48 weeks, even for patients with genotypes 2 and 3, because relapse rates have been found to be higher if treatment is given for only 24 weeks.⁷² However, after initiation of therapy, the decision to complete the full course of treatment is determined by the degree of change in HCV RNA at week 12 or 24 (see Figure 2). If serum ALT levels increase after initiation of treatment, then discontinuation of treatment may be warranted. Rising ALT levels during anti-HCV therapy may indicate treatment failure.

Although the optimal length of therapy has not yet been established for acute infection, the standard treatment duration for chronic infection may be a reasonable approach for acutely infected patients.

Figure 2. Initial Anti-HCV Therapy for HIV/HCV Co-infected Patients



* If ALTs have normalized or are continuing to improve, some experts would consider continuation of therapy, although this is not based on clinical trial evidence. A liver biopsy could be repeated to assess for histologic improvement.

† Forty-eight weeks is the standard recommended duration of therapy for all genotypes. According to HCV-HIV International Panel guidelines, discontinuation of treatment could be advised at 24 weeks in patients with HCV genotypes 2 or 3 who experience rapid virologic response under certain conditions (see Section X. A. *Shorter Courses of Therapy*). Otherwise, 48 weeks of therapy remains advisable.⁴⁰ Patients with genotypes 1 and 4 may demonstrate a better clinical outcome with a longer course of treatment (see Section X. B. *Longer Courses of Therapy*).

A. Shorter Courses of Therapy

Shorter courses of therapy have been studied in HCV mono-infected patients and, to a lesser extent, in HIV/HCV co-infected patients. These studies examined 4-week viral load responses; those who experienced rapid virologic response (RVR) by 4 weeks were candidates for a shorter treatment course, such as 24 weeks. Among the 389 HIV/HCV co-infected patients in the PRESCO trial (discussed in Appendix A), a 4-week RVR was the best predictor of an SVR. Among patients who received treatment for 24 to 48 weeks, an RVR had a 90% positive predictive value for SVR in patients with genotype 3, whereas the positive predictive value for SVR in patients with genotype 1 was 69%.⁷³ Similar findings were subsequently reproduced in a smaller study.⁷⁴

According to HCV-HIV International Panel guidelines, discontinuation of treatment could be advised at 24 weeks in the following patients with HCV genotypes 2 or 3 who experience rapid virologic response in the presence of *all* of the following conditions:

- HCV RNA is undetectable
- Weight-based ribavirin dosing has been prescribed
- The patient has adhered to treatment
- No advanced hepatic fibrosis is present

B. Longer Courses of Therapy

A subset of HCV-infected patients may benefit from longer therapy. However, the data demonstrating this possible benefit derive from studies involving HCV mono-infected patients with genotype 1 or 4 who did not have an RVR but who had the expected treatment response by week 24 of therapy. Among these patients, a benefit from longer courses of treatment was demonstrated. The greater rate of SVR occurred after 72 weeks of therapy instead of 48 weeks.^{75,76}

For HIV/HCV co-infected patients with genotype 1, the per-protocol analysis of the PRESCO trial did not demonstrate a significant difference in SVR rates among those with genotype 1 who were treated for either 48 or 72 weeks.⁷³ More studies are needed in HIV/HCV co-infected populations before current recommendations are likely to change. Potential obstacles to longer therapy include tolerability and adherence.

XI. IDENTIFICATION AND MANAGEMENT OF SIDE EFFECTS OF ANTI-HCV TREATMENT

RECOMMENDATIONS:

Clinicians should assess for possible side effects of anti-HCV treatment in HIV-infected patients (see Table 6).

Clinicians should educate HIV/HCV co-infected patients about strategies for managing side effects of anti-HCV therapy (see Table 7).

A. Mood Alterations With Anti-HCV Therapy

For patients who develop mood alterations, including depression, during interferon alfa therapy, most symptoms emerge by 8 weeks of treatment and appear to be dose-dependent. The side effects include fatigue, hypersomnia, irritability, emotional lability, social withdrawal, and impaired concentration (see Section V. F. *Assessment for Mental Health Disorders*).

Key Point:

The significant association between interferon alfa and depression underscores the importance of screening for depression at least every 4 weeks during anti-HCV therapy.⁷⁷ Simple screening techniques are provided in the Mental Health Guidelines [Depression and Mania in Patients With HIV/AIDS](#).

B. Other Side Effects of Anti-HCV Treatment

Interferon alfa has significant potential side effects, including flu-like symptoms, fatigue, alopecia, bone marrow suppression, and neuropsychiatric effects such as apathy, cognitive changes, irritability, depression, and suicide (see Table 6). In some patients, side effects are severe enough to require dose reductions or even discontinuation of treatment; however, some of these adverse effects may be treated with hematopoietic growth factors for bone marrow toxicity and with antidepressants for depression. Patients treated with interferon may also develop a paradoxical worsening of liver disease, possibly attributable to autoimmune processes, and fatal liver failure has occurred; however, this is a rare event and primarily occurs in patients with already-decompensated liver disease or those who have undergone transplantation.⁷⁸

TABLE 6 POSSIBLE SIDE EFFECTS OF TREATMENT FOR HEPATITIS C	
Interferon	Ribavirin
<ul style="list-style-type: none"> • Flu-like symptoms <ul style="list-style-type: none"> ○ Fatigue, myalgia, headache, low-grade fever (99-101.5°F) • Alopecia • Bone marrow suppression <ul style="list-style-type: none"> ○ Thrombocytopenia ○ Neutropenia ○ Anemia • Fatigue • Emotional lability • Depression/suicide • Insomnia • Anorexia/weight loss • Thyroid dysfunction <ul style="list-style-type: none"> ○ Hypothyroid ○ Hyperthyroid • Neuropathy • Injection site reactions • Paradoxical worsening of liver disease 	<ul style="list-style-type: none"> • Hemolytic anemia (dose-dependent) • Nausea • Cough, shortness of breath • Teratogenic effects • Rash, dry skin • Pruritus • Lactic acidosis • Pancreatitis

Table 7 provides strategies for managing side effects of anti-HCV therapy.

TABLE 7 STRATEGIES FOR MANAGING SIDE EFFECTS OF ANTI-HCV THERAPY
<ul style="list-style-type: none"> • Treatment of preexisting depressive symptoms before and during interferon therapy, as well as 6 to 12 months after interferon therapy, to avoid post-interferon therapy relapse* • Treatment of depressive symptoms that occur during interferon therapy, as well as continued treatment 6 to 12 months after interferon therapy completion, to avoid post-interferon therapy relapse* • Treatment of insomnia and anxiety as needed • Use of hematopoietic growth factors to manage bone marrow suppression as needed • Dose reduction of ribavirin and/or the use of recombinant erythropoietin to manage ribavirin-induced hemolytic anemia • Administration of the weekly injection of pegylated interferon at a time when side effects would cause the least disruption (e.g., on Friday night to mitigate side effects that could cause disruption during the work week) • Administration of acetaminophen or ibuprofen to alleviate symptoms, or for prophylactic use at the time of the injection and the following morning • Small, light meals and/or antiemetics • Regular light exercise • Adequate hydration
<p>*Treatment of depression in patients receiving interferon with selective serotonin reuptake inhibitors is generally safe and often effective (see Section V. F. <i>Assessment for Mental Health Disorders</i>).</p>

When side effects are intolerable and cannot be managed effectively, dose reduction or discontinuation of therapy may be necessary. Use of red blood cell or white blood cell hematopoietic growth factors, such as erythropoietin or granulocyte colony-stimulating factor, respectively, are commonly used to avoid dose reductions of anti-HCV therapy, because maintenance of therapeutic doses has demonstrated more favorable treatment responses.⁷⁹

XII. TREATMENT MONITORING OF HIV/HCV CO-INFECTED PATIENTS

RECOMMENDATIONS:

Clinicians should monitor anti-HCV treatment in HIV/HCV co-infected patients according to the assessments and schedules listed in Table 8.

A liver biopsy after eradication of HCV infection is not routinely indicated. (AIII)

HCV treatment should be monitored in HIV/HCV co-infected patients not only to determine whether the patient is responding to treatment but also to ensure that any complications associated with anti-HCV therapy are identified and addressed appropriately. Table 8 provides monitoring schedules for patients receiving anti-HCV therapy.

TABLE 8	
MONITORING OF HIV/HCV CO-INFECTED PATIENTS RECEIVING ANTI-HCV THERAPY	
Time Point	Recommended Laboratory Tests and Assessments
Baseline (at initiation of treatment)	<ul style="list-style-type: none"> • Obtain HIV viral load, CD4 count, CBC, chemistry panel, and quantitative HCV viral load, TSH • Perform pregnancy testing in female patients of childbearing potential, as well as female partners of male patients • Screen for comorbid disease/medications, alcohol and drug use, and depression • For patients with a history of depression, consider consultation with a psychiatrist for prophylactic antidepressant (see Section V. F. <i>Assessment for Mental Health Disorders</i>)
Week 1-2	<ul style="list-style-type: none"> • Obtain CBC with differential and LFTs
Week 4	<ul style="list-style-type: none"> • Obtain HCV quantitative viral load
Week 4 and every 4 weeks thereafter	<ul style="list-style-type: none"> • Obtain CBC and chemistry panel • Perform pregnancy testing in female patients of childbearing potential, as well as female partners of male patients, as long as ribavirin is administered and until 6 months after discontinuation • Evaluate for drug-drug interactions, mood alteration, and side effects
Week 12 and every 12 weeks thereafter	<ul style="list-style-type: none"> • Obtain HIV viral load, CD4 cell count, and quantitative HCV viral load • Screen for interferon-induced thyroid disease with TSH
Week 24 following therapy	<ul style="list-style-type: none"> • HCV quantitative viral load
CBC, complete blood count; TSH, thyroid-stimulating hormone.	

XIII. RETREATMENT OF HEPATITIS C VIRUS

Treatment failure with interferon (with or without ribavirin) is defined as failure to achieve an SVR by the end of treatment. Patients who fail interferon treatment are considered to be “non-responders.” The following factors may predict failure to achieve an SVR:

- Genotype 1
- Advanced fibrosis
- High baseline HCV viral load
- Age >40 years
- Longer duration of disease
- Standard versus pegylated interferon therapy
- Monotherapy versus combination therapy
- Short duration of treatment
- Black race (data suggest that weight-based dosing of ribavirin may improve outcome in this population⁸⁰)

Among non-responders previously treated with standard interferon with or without ribavirin, 20% to 28% may achieve an SVR of upon retreatment with pegylated interferon plus ribavirin.^{81,82} Patients with genotype 2 or 3 have better response rates upon retreatment than those with genotype 1. This does not mean, however, that retreatment should not be attempted for patients with genotype 1, especially if prior treatment did not include pegylated interferon with ribavirin. Long-term maintenance therapy with pegylated interferon does not appear to be effective in previous non-responders to anti-HCV therapy. Appendix B provides information regarding clinical trials of re-treatment in non-responders and relapsers.

XIV. TRANSPLANTATION IN HIV/HCV CO-INFECTED PATIENTS

RECOMMENDATION:

Clinicians should collaborate with transplantation programs to offer transplant as an option for HIV/HCV co-infected patients. (AIII)

Transplantation offers another treatment option for HCV mono-infected or HIV/HCV co-infected patients who are dying from liver failure. The 1- and 5-year survival rates for patients undergoing deceased donor transplant for non-cholestatic cirrhosis, a disease category that includes HCV-induced cirrhosis, are 87.1% and 73.4%, respectively.⁸³ Throughout the 1990s, concern about immunosuppression-related risks led to a virtual moratorium of organ transplant in HIV-infected individuals. In the early 2000s, liver transplants were performed in small numbers of carefully selected individuals with HIV infection. Small case reports suggested that the survival of HIV-infected individuals undergoing liver transplant might be comparable with that of non-HIV-infected liver recipients.^{84,85} However, a recent review of the database of United Network for Organ Sharing suggests otherwise. The outcome of liver transplant was studied in 30,520 non-HIV-infected patients and 138 HIV-infected patients undergoing liver transplant between 1997 and 2007. Two-year-survival was 81% for non-HIV-infected patients and 70% for HIV-infected patients ($p = .05$). For patients with HCV, 2-year survival was 79% for non-HIV-infected patients and 52% for HIV-infected patients ($p = .006$). None of the 24 patients with HIV infection who were negative for HCV died during follow-up.⁸⁶ These findings suggest that post-transplant survival rates may be diminished for HIV/HCV co-infected individuals.

XV. PREVENTION OF HCV TRANSMISSION AND RE-INFECTION

RECOMMENDATIONS:

Clinicians should:

- **Counsel HIV/HCV co-infected patients to avoid practices that transmit both HIV and HCV, including high-risk sexual practices, such as unprotected sex, and needle-sharing behaviors among injection drug users. (AII)**
- **Counsel active injection drug users to use new sterile equipment at all times, dispose of their syringes after one use, and clean their injection sites carefully with clean alcohol swabs. These patients should be urged to undergo treatment to reduce drug use (see [Working With the Active User](#)). (AIII)**
- **Advise household contacts of persons chronically infected with HCV to avoid sharing items that may be contaminated with blood, such as toothbrushes and razors. (AIII)**
- **Encourage uninfected, long-term sexual partners of persons co-infected with HCV and HIV to continue to follow safer-sex practices to prevent transmission of HIV and HCV. (AII)**

Behavioral health counseling is critical for preventing HIV and HCV transmission. Patients with previously resolved HCV infection should also be informed of the risk for re-infection. Antibody to HCV will stay positive for life, even after successful anti-HCV therapy, but does not confer any protective immunity. Re-infection would be documented by a recurrence of HCV viremia.

For a table of the elements that should be included in behavioral health counseling, refer to Table 4 of [Primary Care Approach to the HIV-Infected Patient](#). For information regarding occupational or non-occupational post-exposure management, refer to [HIV Prophylaxis Following Occupational Exposure](#) and [HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault](#).

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FURTHER READING

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APPENDIX A

CLINICAL TRIAL RESULTS FOR HCV THERAPY

TABLE 1	
CLINICAL TRIAL RESULTS FOR HCV THERAPY	
Trials in HCV mono-infected patients ^{87,88}	
	The standard combination of pegylated interferon and had an SVR of approximately 40% to 45% in HCV mono-infected patients with type 1 and up to 80% in those with non-type 1.
Trials in HIV/HCV co-infected patients	
RIBAVIC	Subjects (n = 412) were randomized to receive ribavirin 400 mg orally twice daily plus either pegylated interferon alfa-2b 1.5 µg/kg subcutaneously weekly or standard interferon alfa-2b 3 million units subcutaneously three times weekly for 48 weeks. ⁶⁹ An SVR was obtained in 27% overall in the pegylated interferon group, compared with 20% in the standard interferon group ($p = .047$). The rate of SVR for patients with genotype 1 or 4 was 17% for pegylated interferon and 10% for standard interferon, a significant difference. For patients with HCV genotypes 2, 3, and 5, responses were 44% in the pegylated interferon group versus 43% in the standard interferon group ($p = .88$).
ACTG A5071	In 133 subjects comparing pegylated interferon alfa-2a 180 µg subcutaneously weekly plus ribavirin with standard interferon alfa-2a at 6 million units three times weekly for 12 weeks, followed by the 3 million units three times weekly for an additional 36 weeks, plus ribavirin (600 mg daily with dose escalation to 1000 mg daily), were similar to the RIBAVIC trial, with 27% in the pegylated interferon group experiencing an SVR, compared with 12% in the standard interferon group ($p = .03$). ⁷⁰ Fourteen percent of subjects with genotype 1 in the pegylated interferon with ribavirin group had an SVR, compared with 73% of subjects with non-1 genotypes. Interestingly, histologic responses were still seen in 35% of patients who had a follow-up liver biopsy and experienced virologic failure.
APRICOT	In this international, multicenter trial, HIV/HCV co-infected subjects (n = 860) were randomized to 48 weeks of ribavirin (800 mg daily) plus pegylated interferon alfa-2a 180 µg subcutaneously weekly versus standard 3 million units of interferon three times weekly with ribavirin (800 mg daily) versus pegylated interferon with placebo (no ribavirin). The overall SVR in the pegylated interferon plus ribavirin group was 40%, compared with 12% in the standard interferon group ($p < .001$) and 20% in the pegylated interferon without ribavirin group ($p < .001$). The SVR rate in genotype 1 patients receiving pegylated interferon alfa-2a with ribavirin was 29% compared with a rate of 62% in patients with genotype 2 or 3. ⁷¹
PRESCO	Examined pegylated interferon alfa-2a with weight-based ribavirin. Study subjects (n = 389) received pegylated interferon alfa-2a 180 µg subcutaneously weekly with ribavirin (1000 mg daily if weight was <75 kg and 1200 mg if weight was ≥75 kg). Participants with genotype 1 or 4 were treated for either 48 or 72 weeks, and those with genotype 2 or 3 were treated for 24 or 48 weeks. Overall, 50% of patients achieved an SVR ⁷⁹ : 72% of those with genotype 2 or 3 and 33% to 36% with genotype 4 or 1. Weight-based ribavirin dosing is becoming the standard and is recommended by the 2007 updated guidelines of the HCV-HIV International Panel. ⁵⁰

APPENDIX B

CLINICAL TRIAL RESULTS FOR RETREATMENT OF HCV

TABLE 1 CLINICAL TRIAL RESULTS FOR RETREATMENT OF HCV	
PILOT-NR	A prospective study from Spain evaluated 51 HIV/HCV co-infected patients who had failed prior interferon-based therapy (23% interferon monotherapy, 27% interferon plus ribavirin, and 50% peginterferon with 800 mg/day of ribavirin) and underwent 48 weeks of re-treatment with pegylated interferon alfa-2a and 1000 to 1200 mg of daily ribavirin. Sixty-four percent of these were previous non-responders, and 36% were relapsers. Ninety percent of patients were receiving ART, with the majority having undetectable HIV RNA levels. SVR was obtained in 27.5% of patients, with a 27% response rate with genotype 1 or 4, and 70% with genotype 2 or 3. ⁸²
HALT-C (Hepatitis C Antiviral Long-term Treatment Against Cirrhosis)	Recent results from 1050 patients demonstrated that long-term therapy with pegylated interferon alfa-2a alone at a dose of 90 µg per week did not reduce the rate of disease progression in previous non-responders to pegylated interferon with ribavirin. Despite decreases in serum ALT and HCV RNA levels, no significant difference was found in rates of death, HCC, hepatic decompensation, or increase in fibrosis score between subjects who received maintenance therapy and those who did not. ^{89,90}
SLAM-C (Sustained Long-term Antiviral Maintenance With Pegylated Interferon in HIV/HCV Co-infected Patients)	The trial enrolled 330 HIV/HCV co-infected patients who were treated with pegylated interferon and weight-based ribavirin. Patients who were failing therapy at 12 weeks underwent liver biopsy and were randomized to either maintenance pegylated interferon monotherapy for 72 weeks or observation alone. Rates of fibrosis were compared, and the study did not show any difference in fibrosis progression between the treatment and observation arms, largely because of a lack of progression in the observation arm.
DIRECT trials [Daily-Dose Consensus Interferon (CIFN)* and Ribavirin: Efficacy of Combined Therapy]	These trials treated non-cirrhotic, non-responders with HCV mono-infection who had previously received pegylated interferon plus ribavirin for at least 12 weeks. Among individuals who were able to tolerate the daily 15-µg consensus interferon and ribavirin without dose modification, 17% (16 of 96) were able to achieve SVRs; however, in the intent-to-treat analysis, the rate of SVR dropped to 10%. ⁹¹
REPEAT (REtreatment with PEGasys in PATients Not Responding to Peg-Intron Therapy)	This trial used high-dose interferon to treat non-responders. The trial found that 16% (51 of 318) of HCV mono-infected individuals with HCV genotype 1 who were previously treated with non-pegylated interferon, alone or with ribavirin, achieved an SVR with 360 µg of pegylated interferon alfa-2a weekly and 1200 mg of ribavirin daily for 72 weeks. ⁹²
Consensus IFN-alfa (CIFN) has been noted to be more potent <i>in vitro</i> than other interferon alfas. The amino acid (aa) differences among the interferon alfas are as follows:	
<ul style="list-style-type: none"> • 1-aa difference between IFN-alfa 2a and IFN-alfa 2b • 19-aa difference between IFN alfa 2a and CIFN • 18-aa difference between IFN-alfa 2b and CIFN 	