Management and Treatment of Hepatitis C Virus Infection in HIV-Infected Adults:

Recommendations from the Veterans Affairs Hepatitis C Resource Center Program and National Hepatitis C Program Office

Hepatitis C Resource Centers
Department of Veterans Affairs
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Abstract

Nearly 40% of human immunodeficiency virus-(HIV-) infected veterans on highly active antiretroviral therapy (HAART) in the United States are coinfected with hepatitis C virus (HCV). With the increased survival due to declining opportunistic infections as a result of HAART, HCV-associated liver disease has become a leading cause of death in HIV-infected individuals. HCV infection has been shown to lead to rapid progression of HCV-related liver disease in HIV infection. Results from recent clinical trials in HIV/HCV-coinfected patients show improved response rates using pegylated formulations of interferon plus ribavirin when compared to standard interferon plus ribavirin. However, the treatment of HCV in HIV/HCV-coinfected patients can be complicated by the hepatotoxic and myelosuppressive effects of HIV therapy and HIV infection itself. Prior to initiating HCV therapy, HIV therapy should be optimized by improving immune suppression and avoiding specific antiretroviral drugs that may cause hepatotoxicity and myelosuppression. In the event of treatment-related neutropenia or anemia during HCV therapy, the use of growth factors should be considered to maximize sustained virologic response to HCV therapy. In HIV/HCV-coinfected patients with end-stage liver disease, liver transplantation is being investigated and shows promise as a potential therapeutic option. With the recent advances in the treatment of HCV in HIV/HCV-coinfected individuals, all HIV/HCV-coinfected patients eligible for HCV treatment should be evaluated for HCV combination therapy with careful consideration of their HIV disease.

Introduction

Coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is of concern in U.S. veterans. Nearly 40% of HIV-infected veterans on highly active antiretroviral therapy (HAART) are coinfected with HCV(1) compared to the approximately 25% of HIV-infected patients who are coinfected with HCV in the United States, nationally.(2) The prevalence, however, varies considerably among risk groups. The majority (nearly 100%) of HIV-infected hemophiliacs in the United States are HCV-infected(3), compared to a range of 50-90% of HIV-infected injection drug users(4), and about 2-14% who acquired HIV via sexual contact.(5,6)

Liver disease has become a significant cause of death in men and women with HIV in the era of HAART(7-9), as a result of the decline in mortality due to AIDS and AIDS-related illnesses. In U.S.veterans with HIV, HCV seropositivity is associated with an increased risk of death(1) and among HIV/HCV-coinfected veterans seen at the Houston VA Medical Center, liver disease accounted for 47% of deaths. HIV itself may also accelerate the progression of HCV-related liver disease.(10)

With the recent advances in therapy for HCV, it is becoming increasingly important that all patients infected with HCV be considered for treatment, including those who are also coinfected with HIV. The response rate and safety of HCV therapy in HIV/HCV-coinfected individuals are now well established in several clinical trials, which show improved response rates using pegylated formulations of interferon plus ribavirin when compared to standard interferon plus ribavirin.(11-13) However, the long-term benefits of HCV therapy in the HIV/HCV-coinfected patient including improvements in survival and quality of life have yet to be demonstrated.

In addition, it is important to recognize other considerations when deciding whether or not to initiate HCV treatment in the coinfected population. One study found that only one-third of HIV/HCV-coinfected patients are eligible for HCV treatment.(14) This proportion was not different from patients with HCV infection only. The major barriers to HCV treatment in HIV/HCV-coinfected patients identified in this study included nonadherence to medical visits, active psychiatric disease, ongoing drug or alcohol use in the preceding 6 months, decompensated liver disease, advanced HIV disease, and medical comorbidities.(14) A recent multicenter VA study (Cleveland, Houston, Manhattan)(15) found that of 300 HIV/HCV-coinfected patients, 30% reported current alcohol consumption but only 29% of those who drank reported that they had been advised to stop drinking. Similarly, 16% of the 300 patients reported current illicit drug use; only 12.5% of those who used drugs reported that their doctors were concerned about such drug use. These results suggest that counseling for HIV/HCV-coinfected patients regarding substance abuse can be improved. In addition, the majority of HIV-infected patients identified their HIV provider as their primary care provider, suggesting that recommendations for the management and treatment of HCV in HIV/HCV-coinfected patients should be directed to HIV providers.

The following recommendations (Table 1) emphasize management and treatment issues specific for the HIV/HCV-coinfected patient. Recommendations are graded according to those used by the American Association for the Study of Liver Disease (AASLD) practice guidelines for the diagnosis, management, and treatment of hepatitis C.(16)

Table 1. Grading System Adapted from the AASLD Practice Guidelines for the Diagnosis, Management and Treatment of Hepatitis C

Grade	Definition
I	Randomized, controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytic studies
II-3	Multiple Time-series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology

From (17)

Progression of HCV and HIV in the HIV/HCV-Coinfected Patient

Progression of HCV Disease in HIV/HCV-Coinfected Patients

Establishing the diagnosis of HCV infection in the HIV- infected patient is of primary importance. Studies find that HIV infection is associated with an increased risk of severe liver disease in patients also infected with HCV, and HIV/HCV coinfection may lead to a more rapid progression of liver fibrosis than in those with HCV infection alone.(17-23) A meta-analysis of eight separate studies investigating the role of HIV on liver disease in HCV-infected patients found that HIV/HCV-coinfected patients had approximately two times the risk of cirrhosis diagnosed on liver biopsy and approximately six times the risk of decompensated liver disease (severe liver disease accompanied by clinical conditions including ascites, varices, or encephalopathy) when compared to HCV-monoinfected patients.(24) In one of the eight studies, a median fibrosis progression rate (calculated by the fibrosis score divided by the duration of HCV infection) was found to be greater in HIV/HCV-coinfected patients when compared to HCV-monoinfected patients.(18)

Because the use of HAART is an integral part of the care of the HIV-infected patient, the impact of HAART itself on HCV liver disease is being studied. There are several possible interactions between HAART and the severity of liver disease, both beneficial and detrimental. Potential detrimental interactions between HAART and HCV include hepatotoxic effects of HAART. Several studies show that hepatotoxicity as a result of antiretroviral medications may be worsened in the presence of concomitant HCV infection.(25-27)

Potential beneficial interactions between HAART and HCV include a slowing of HCV-related liver disease in patients on HAART. Data exist suggesting that the long-term use of protease inhibitor containing HAART regimens may have a beneficial impact on HCV-related liver disease independent of CD4 response.(28) In addition, immune reconstitution with HAART might improve: (i) the natural history of HCV-related liver disease in the long term or (ii) the response to HCV treatment. However, the body's improved immune response and thus ability to control HCV-infected hepatocytes may also acutely lead to adverse consequences in the liver. Liver decompensation and acute hepatitis have been reported in HIV/HCV-coinfected patients shortly after initiating antiretroviral therapy.(29, 30)

Progression of HIV Disease in HIV/HCV-Coinfected Patients

While HIV infection and its therapy may affect the progression of HCV-related liver disease, HCV infection conversely may affect the progression of HIV disease. Two large European cohort studies show that after the initiation of potent antiretroviral therapy in HIV-infected patients, CD4 cell recovery was impaired in HIV/HCV-coinfected patients when compared to patients infected with HIV alone. HIV/HCV-coinfected patients also demonstrated more rapid progression to clinical AIDS or death, compared to patients infected with HIV alone.(31, 32) The impaired recovery of CD4 cells in HIV/HCV-coinfected patients was also demonstrated in another study of patients initiating HAART as part of clinical trials.(33) However, in patients enrolled in other large cohort studies in the United States, Europe, and Asia, there was no difference in CD4 cell recovery, progression to clinical AIDS or death between HIV/HCV-coinfected patients and HIV-monoinfected patients.(34-37) Further studies are clearly needed to understand the role of HCV on HIV disease progression.

However, HIV infection does appear to have an adverse effect on the progression of HCV disease. Because of the more rapid progression of HCV-related liver disease in HIV/HCV-coinfected patients, treatment of HCV should be strongly considered in this population, as well as institution of measures that may prevent the progression of liver disease, including hepatitis A and hepatitis B vaccination if not immune, and alcohol counseling.

Diagnosis and Testing of HCV in HIV Patients

Several national guidelines including those from the U.S. Public Health Service and the Infectious Diseases Society of America recommend that all HIV patients be tested for HCV.(38, 39)

Determination of antibodies to HCV is performed using an enzyme immunoassay test (EIA). A third generation EIA is recommended, as it has a sensitivity of greater than 99% in high-risk populations. A positive antibody to HCV (anti-HCV) should be followed up with testing for HCV RNA using a sensitive HCV RNA assay to determine chronic HCV infection.

The qualitative HCV RNA polymerase chain reaction (PCR) assay has a lower limit of detection for HCV of approximately 50 IU/mL, and is reported as "positive" if the test detects more than 50 IU/mL of HCV in the blood; "negative" if less than 50 IU/mL. The qualitative assay is used to determine if any HCV RNA, even low-level viremia, is present. The quantitative HCV RNA assay determines an absolute number of circulating HCV in the serum, also referred as the "HCV viral load." Most FDA-approved quantitative HCV RNA assays have a lower limit of detection that is higher than the qualitative HCV RNA PCR assay.(16) The most cost-effective and pragmatic strategy is to perform the quantitative HCV RNA assay to simultaneously confirm chronic HCV infection and determine the pre-HCV treatment HCV viral load. If the quantitative HCV RNA assay reveals an undetectable HCV viral load, then the qualitative HCV RNA PCR assay can be performed.

It is important to recognize that a patient may have a negative HCV EIA and still have HCV infection. There are two clinical settings in which this may occur: (i) Acute infection: After acute exposure to HCV, there is a "window period" of approximately 30-150 days before anti-HCV is detectable. The window period of HCV seroconversion may be prolonged in the setting of concurrent HIV/HCV seroconversion. However, HCV viremia may be detectable within 7-21 days after acute HCV infection. Therefore, if a patient is assessed during the "window period," the patient may be anti-HCV negative but HCV RNA positive. Serial testing of anti-HCV and HCV RNA is recommended to see if HCV infection spontaneously resolves (loss of HCV RNA without treatment) or persists. HCV therapy in this acute setting should be considered, as some data in HCV-monoinfected patients suggest high rates of HCV RNA clearance after HCV treatment.(40, 41) (ii) Severe immunosuppression due to HIV or chronic dialysis: False negative HCV EIA results have been reported in about 6% of HIV patients using the second generation anti-HCV EIA test.(42, 43) In one study, 6 of 110 HIV-infected patients with a negative anti-HCV were HCV viremic and the median CD4 count was 36 cells/mm^3 compared to 235 cells/mm^3 in the 259 HIV-infected patients that had a positive anti-HCV. Another study found that 20 of 100 HIV-infected patients with a negative anti-HCV were HCV viremic and the mean CD4 count was 225 cells/mm^3 compared to 392 cells/mm^3 in the 30 HIV-infected patients that had a positive anti-HCV. The results from these studies suggest that HIV-induced immunocompromise can lead to a false negative anti-HCV result. Because the range of CD4 counts in the HIV/HCV-coinfected patients with a false negative anti-HCV result in the two studies were so different, it is difficult to suggest a specific CD4 cutoff level whereby all HIV patients with negative anti-HCV should have HCV RNA testing performed. However, in an HIV-infected patient with unexplained liver disease or elevations in liver enzymes and a negative HCV EIA, the HCV RNA qualitative PCR assay should be performed.

Finally, once the diagnosis of chronic HCV infection has been made using these above strategies and techniques, providers should complete the process with the following:

- Patient notification of test results with appropriate posttest counseling. Counseling regarding modes of transmission of HCV including parenteral and sexual transmission.
- Education regarding potential interactions between viral hepatitis and other factors such as alcohol, high doses of acetaminophen, or alternative therapies.
- Evaluation for potential treatment of HCV.
- Vaccination for hepatitis A virus (HAV) and hepatitis B virus (HAB), if seronegative.
- Consideration of hepatocellular carcinoma screening in patients with clinical or histologic evidence of cirrhosis.

Recommendations:

1. All HIV patients should be tested for antibodies to HCV (III).
2. HCV RNA testing should be performed in:

    a. the HIV patient with a positive anti-HCV test to determine chronic HCV infection (III).
    b. the HIV patient with unexplained liver disease and a negative anti-HCV test, particularly in those with HIV-associated immune compromise (III).
    c. the HIV patient with suspected acute HCV infection (III).

Assessment of the HIV/HCV-Coinfected Patient prior to Initiating Anti-HCV Therapy

All HIV patients with confirmed, chronic HCV infection should be evaluated for HCV treatment since: (i) HCV treatment can lead to a sustained virologic response (SVR), defined as an undetectable HCV RNA 6 months after discontinuing therapy; and (ii) HCV treatment may slow the progression of hepatic fibrosis and/or delay the onset of clinical consequences of decompensated cirrhosis.

Each patient needs a careful individualized assessment to determine the relative risks and benefits of beginning therapy immediately versus deferring treatment to a later date versus foregoing treatment. This decision in the HIV/HCV-coinfected patient is even more complex than in those with HCV infection alone, since response rates are lower, the risk of potential toxicities is higher and treatment is potentially complicated by drug interactions between ribavirin and antiretroviral medications.

Key aspects of the evaluation prior to beginning HCV therapy in the HIV/HCV-coinfected patient are summarized in this section. The pre-HCV treatment evaluation for the HIV/HCV-coinfected patient is similar to that for the HCV-monoinfected patient, but additional factors in the medical history relating to HIV must be considered. Table 2 summarizes the pre-HCV treatment assessment and issues specific to the HIV patient are shown in italics. Contraindications for HCV therapy are also similar for HIV/HCV-coinfected and HCV-monoinfected patients and can be found in Table 3.

Table 2. Pretreatment Assessments in a Patient with Chronic Hepatitis C*

Necessary
Medical history, including the determination of complications of liver disease, significant extrahepatic disease, and symptoms associated with chronic HCV, which may reduce quality of life. *HIV-associated opportunistic infections and malignancies must also be assessed.*
Psychiatric history, including the determination of past or ongoing psychiatric and substance use disorders, previous and current treatments and response
Screening for depression and alcohol use**
Biochemical markers of liver injury and assessment of hepatic synthetic function (serum ALT, serum albumin, serum total bilirubin and direct bilirubin, prothrombin time).
Hemoglobin, hematocrit, total white cell count with differential, and platelet count
Creatinine
TSH
Serum glucose or HgbA1C in diabetics
Pregnancy test (necessary for women of child-bearing potential)
Anti-HAV total
Serum HBsAg, anti-HBc (total), anti-HBs
HIV serology; *absolute CD4 count, CD4%, and HIV RNA measurement*
Quantitative HCV RNA measurement by PCR or bDNA
HCV genotype
Electrocardiogram in patients with preexisting cardiac disease
Highly Recommended
Liver biopsy to stage the severity of liver disease
Fundoscopic exams for patients at risk for retinal disease, eg, those with *severe immunosuppression (CD4<100)*, diabetes, and/or hypertension
Serum ferritin
Urine toxicology screen for opiates, cocaine, and amphetamines

*Adapted from the VA Treatment Recommendations for Patients with Chronic Hepatitis C

**Validated screening instruments for depression and alcohol use are available online at: hepatitis.va.gov/vahep?page=tp03-gd-01#S16X and www.niaaa.nih.gov/publications/CliniciansGuide2005/cliniciansguide/clinicians_guide10.htm, respectively.

Table 3. Contraindications to Hepatitis C Therapy*

Life-determining extrahepatic disease (eg, end-stage AIDS, malignancy, unstable angina, severe COPD)
Clinically decompensated liver disease**
Uncontrolled autoimmune disorders
Pregnancy or planned pregnancy in a patient or the patient's sexual partner or unwilling to use adequate birth control
Documented serious nonadherence to prior medical treatment or the failure to complete HCV disease evaluation appointments and procedures
Inability to self-administer parenteral medication or to arrange appropriate administration of parenteral medication
Severe uncontrolled psychiatric disease, particularly depression with current suicidal risk
Ongoing injection drug use
Ongoing alcohol abuse***

*Adapted from the VA Treatment Recommendations for Patients with Chronic Hepatitis C

**Select patients with clinically decompensated disease may be candidates for treatment in research protocols.
***Definitions of alcohol abuse in HCV disease are evolving and await further data. The NIH Consensus Statement concluded, "Continued alcohol use during therapy adversely affects response to treatment."(40)

Assessment of Liver Disease Severity

Candidates for HCV treatment should have evidence of HCV-associated liver disease, yet demonstrate preserved hepatic synthetic function as indicated by a normal or near normal serum albumin, direct serum bilirubin, and prothrombin time. Cirrhotic HIV/HCV-coinfected patients on HAART appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART.(44) The pharmaceutical package insert for pegylated interferon alfa-2a lists hepatic decompensation with Child-Pugh score >=6 in cirrhotic HIV/HCV-coinfected patients as a contraindication for starting or continuing pegylated interferon alfa-2a. While biochemical markers of liver function should be obtained, histologic evidence of liver damage on liver biopsy is the best method to assess liver disease severity, regardless of transaminase levels, especially in the patient coinfected with HIV/HCV. Patients with cirrhosis should also undergo screening for hepatocellular carcinoma.

Liver Function Tests. In the HIV/HCV-coinfected patient, abnormal transaminase levels and hepatic synthetic function studies may also be the result of antiretroviral drug-associated toxicity and/or opportunistic infections, making interpretation of liver enzyme elevations more problematic than for patients with HCV infection alone. In general,causes of abnormal liver function can be broadly classified as hepatic (with elevated serum transaminase levels but normal or near normal serum bilirubin and alkaline phosphatase) and cholestatic (with abnormal alkaline phosphatase and/or serum bilirubin, but only minor changes in serum transaminase levels). In HIV/HCV-coinfected patients, the likelihood of specific pathogens or disease processes causing these patterns of liver injury depends in part on the severity of immune compromise. Table 4 lists possible pathogens or diseases of the liver that are usually but not always seen in the CD4 ranges listed.

Table 4. Hepatic Disease in HIV by Range of CD4 Lymphocyte Count

CD4<500	CD4<200	CD4<100
Predominantly cholestatic		
Drug Toxicity	Fungal Infection	Cytomegalovirus
Tuberculosis	Candidiasis	*Mycobacterium avium* complex (MAC)
Kaposi's sarcoma	Coccidioidomycosis	*Microsporidia*
Lymphoma	Histoplasmosis	
Cholelithiasis	Cryptococcosis	
Acalculous cholecystitis	Blastomycosis	
Bacterial abscess	*Cryptosporidia*	
	AIDS cholangiopathy	
	Bacillary angiomatosis and peliosis due to *bartonella* infection	
Predominantly hepatocellular		
Drug toxicity	*Pneumocystis carinii*	Cytomegalovirus
Steatosis		
Viral hepatitis		
Herpes simplex virus		

Liver Biopsy. Liver biopsy is the best method for quantifying the severity of liver injury. The degree of liver injury is measured by the stage of liver fibrosis and the grade of necroinflammation, which has been shown to determine the rapidity of fibrosis progression. (45) The serum ALT level is not a sensitive marker of HCV-associated liver disease and most HIV/HCV-coinfected patients have some degree of fibrosis, whether or not their serum ALT values are elevated.(46, 47)

The stage of fibrosis is an important factor that should be considered in the decision of whether or not to initiate therapy. In patients without contraindications to HCV therapy who demonstrate histological evidence of fibrosis (more than portal fibrosis to those with cirrhosis, ie, stages 2-4) and/or significant inflammatory activity, HCV antiviral therapy should be initiated. In patients with no fibrosis (stage 0) or who lack evidence of inflammation on liver biopsy (grade 0), HCV antiviral therapy can be deferred. However, recent data show that over 25% of 51 HIV/HCV-coinfected patients seen in an urban clinic with no or minimal fibrosis demonstrated a greater than two-stage fibrosis progression over an approximately 3-yr interval.(48) In patients with genotype 2 or 3 HCV infection, which is generally associated with higher response rates, HCV treatment should be considered even in the presence of no or minimal fibrosis since the chances of eradicating HCV are very good. In HIV/HCV-coinfected patients with genotype 1 HCV infection, some data suggest that those with a low HCV viral load <800,000 IU/mL may have higher response rates than those with HCV viral load >800,000 IU/mL.(44)

A routine liver biopsy should be performed in all HIV/HCV-coinfected patients who are able to undergo biopsy regardless of genotype, because the information obtained on biopsy may: (i) focus screening for hepatocellular carcinoma in patients found to have grade 3 or higher fibrosis and (ii) provide information that guides management of HCV infection prior to the initiation of HCV therapy, but also during HCV therapy. The stage of fibrosis on liver biopsy may influence the decision of whether or not to continue HCV therapy if complications or adverse drug effects should arise during treatment. Patients in whom therapy is deferred, for reasons including minimal histological liver disease, contraindications to treatment, or the patient not being ready to start therapy or waiting for the development of newer HCV therapies, a repeat liver biopsy should be performed at an interval of 3 yr (49) to assess for the rate of disease progression and reassess the need for treatment.

Additional Laboratory Testing

Complete Blood Count (CBC). Patients should have a CBC performed as part of the pretreatment assessment since adverse reactions of combination HCV treatment include anemia, neutropenia, and thrombocytopenia. Prior to initiating HCV treatment, a platelet count >70 k/mm^3, an absolute neutrophil count >1.5 k/mm^3, and a hemoglobin >=12 g/dL for men, and >=11 g/dL for women are desirable. In the HIV/HCV-coinfected patient, there is a higher incidence of anemia and neutropenia than in the HCV-monoinfected patient, as a result of marrow suppression from HIV and other comorbid conditions or medications associated with HIV disease. Therefore, if possible, providers should consider first treating any other conditions and/or changing medications such as zidovudine that may contribute to bone marrow suppression prior to initiating HCV therapy. Patients who continue to have values below these cutoffs may still be considered for therapy, but may require HCV treatment dose reductions and/or the addition of growth factors (eg,erythropoietin, granulocyte-colony stimulating factor [G-CSF]) in order to be able to tolerate doses necessary for achieving treatment benefit. At this time, however, there is an absence of data supporting the preemptive use of growth factors in this patient population.

Renal Function. A creatinine should be performed as part of the pretreatment assessment. A creatinine clearance of less than 50 mL/min is given as a contraindication to the use of ribavirin in the pharmaceutical package insert. Generally, a creatinine <=1.5 mg/dL is desirable.

HCV RNA Quantitative Assay. Table 5 shows the available assays for quantification of HCV RNA in serum and the dynamic range (ie, the lower limit and upper limit of detection) for each assay. Quantification of HCV RNA or the "HCV viral load" is useful in several ways. First, the pretreatment HCV viral load is one of the predictors of response to HCV treatment. The likelihood of achieving an SVR is greater in patients with a pretreatment HCV RNA level of less than 800,000 IU/mL than in those with levels greater than 800,000 IU/mL. Second, quantification of HCV RNA prior to therapy also allows measurement of changes in HCV RNA on treatment.

An early virologic response (EVR) is defined as either a loss of HCV RNA measured by qualitative PCR-based assays and/or a two-log reduction in quantified levels of HCV RNA 12 wk into a course of HCV treatment. Measurement of an EVR is most valuable in predicting who will not achieve an SVR, an observation that appears to be true for HCV-monoinfected as well as HIV/HCV-coinfected patients.(12, 50) Patients who do not have an EVR will rarely clear virus with further therapy. To allow for consistent comparisons in HCV RNA levels, the same HCV RNA quantitative assay should be used throughout the course of therapy in a given patient. However, to better allow for comparisons between the various HCV RNA assays, they have been standardized to international units/mL (IU/mL). Finally, when monitoring HCV treatment response, it is important that an absolute HCV RNA number is reported, because of the prognostic importance of measuring an EVR. In situations where the HCVRNA level is reported as above the range of detection of the assay, specimens may need to be retested in the laboratory using a dilutional technique that will allow the reporting of an absolute HCV RNA number.

Table 5. Assays for Quantitation of HCV RNA in Serum and Their Dynamic Range

Assay	Conversion 1 IU/mL = X copies/mL	Technique	Dynamic Range (IU/mL)
AMPLICOR HCV Monitor V2.0 (Roche molecular systems)	0.9	Manual competitive reverse transcriptase PCR (rtPCR)	600-500,000
COBAS AMPLICOR HCV Monitor V2.0 (Roche molecular systems)	2.7	Semi-automated competitive rtPCR	600-500,000
Versant HCV RNA 3.0 quantitative assay (Bayer diagnostics)	5.2	Semi-automated 'branched DNA' assay	615-7,690,000
LCx HCV RNA quantitative assay (Abbot diagnostics)	3.8	Semi-automated competitive rtPCR	25-2,630,000
SuperQuant (National Genetics Institute)	3.4	Semi-automated competitive rtPCR	30-1,470,000

Adapted from the AASLD Guidelines (17)

Roche Molecular Systems, Branchburg, NJ; Bayer Diagnostics, Tarrytown, NY; Abbot Diagnostics, Chicago, IL; National Genetics Institute, Los Angeles, CA.

HCV Genotype. Patients should have pretreatment testing for HCV genotype. The infecting genotype is an important predictor of SVR rates, with genotypes 1 and 4 associated with lower response rates than genotypes 2 and 3. This test does not need to be repeated after the initial pretreatment test for HCV genotype.

Hepatitis B Testing. Patients should be tested for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBcore (total)), and hepatitis B surface antibody (anti-HBs) to evaluate need for hepatitis B immunization and the possibility of concurrent infection with HBV. It is important to properly interpret the different patterns in HBV testing and understand the implication of these results. First, a negative test to all three HBV markers indicates that the patient has never been exposed to HBV and should now be vaccinated against HBV. Response rates to HBV vaccination are lower in immunocompromised patients with HIV infection than in patients with an intact immune system. Studies performed early in the course of vaccine development revealed that only one-third of HIV-infected patients developed protective immunity to vaccination.(51, 52) Despite these findings, all HIV patients should receive a series of HBV vaccinations (at 0, 1, and 6 months), and follow-up testing for anti-HBs after completion of the series will determine whether seroconversion has occurred. The likelihood of seroconversion in vaccine-nonresponders following repeat immunization is low. Second, a positive HBsAg may indicate acute infection or more likely chronic carrier status and should be further evaluated through HBeAg testing and HBV DNA levels. Third, a positive anti-HBc and anti-HBs indicate natural immunity and no additional follow-up is needed. Fourth, a positive anti-HBc alone (with a negative anti-HBs and negative HBsAg) also likely indicates natural immunity, although this pattern can also indicate low-level HBV replication (detectable HBV DNA by PCR-based methods), particularly in patients with HIV infection.(53, 54) There is no consensus as to whether patients with positive anti-HBc alone will benefit from HBV vaccination. Finally, a positive anti-HBs alone generally indicates vaccine-induced immunity.

Hepatitis A Testing. Antibodies to hepatitis A virus (anti-HAV) should be measured. A positive anti-HAV (ie,anti-HAV, total or HAV IgG) indicates immunity and no additional follow-up is needed. It is not possible to determine whether the immunity is due to prior vaccination or prior infection. A negative anti-HAV, total indicates no prior history of infection and the patient should be vaccinated against HAV. One small study demonstrated a more fulminant course of hepatitis A in patients infected with HCV compared to those with HBV, supporting HAV vaccination in all patients with HCV infection.(55)

Fasting Blood Glucose Level. Because interferon can cause hyperglycemia, patients with impaired glucose tolerance (fasting glucose between 110 and 125 mg/dL) should be monitored closely and those with diabetes (fasting glucose >125 mg/dL on more than one occasion) should be controlled. In addition, certain protease inhibitors such as indinavir may also be associated with hyperglycemia and insulin resistance. HIV patients on these antiretroviral agents should be monitored.

Assessment of Ocular Function

A fundoscopic examination is recommended prior to initiating HCV therapy in HIV patients who are at risk for retinal disease. These include patients with hypertension, diabetes, and/or a CD4 cell count below 100/mm^3. Severe immunosuppression in the HIV-infected patient increases the risk of developing CMV retinitis. Ocular disturbances including cotton wool spots, cataracts, and visual disturbances such as decrease in color vision beginning 9-24 wk after initiating combination therapy with ribavirin and pegylated interferon alfa-2b have been reported in a small study of HIV/HCV-coinfected patients who had baseline ophthalmic examinations and routine follow-up exams every 3 months.(56) The visual abnormalities were thought to be due to the use of pegylated interferon. Abnormalities were often transient and only rarely led to visual impairment. Therefore a baseline assessment to rule out other potential etiologies of ophthalmologic abnormalities is suggested.

Assessment of Mental Health

A careful evaluation of the HIV/HCV-coinfected patient for psychiatric disease is critical when considering initiation of HCV treatment. There is no evidence that the incidence of psychiatric comorbidity is higher in the HIV/HCV-coinfected patient compared to the HCV-monoinfected patient. Similar to the HCV-monoinfected patient, the pretreatment assessment of psychiatric disorders and substance use should be carefully weighed before beginning treatment. Validated screening instruments for depression and alcohol use are available and may be useful in identifying patients who should receive treatment for depression and alcohol use prior to initiation of HCV therapy. They also provide a baseline assessment, should changes occur during treatment for HCV.

In terms of the ability to predict adherence to HCV treatment prior to HCV treatment initiation, a useful marker may be how well the patient adheres to his or her HIV medications.

Recommendations:

1. Consider HCV treatment in all HIV/HCV-coinfected patients (III).
2. Provide education about the pros and cons of HCV treatment in the presence of HIV/HCV coinfection (III).
3. Regardless of ALT level and HCV genotype, perform a liver biopsy (if no contraindications to liver biopsy exist) prior to initiating therapy in order to determine the extent of HCV-related liver disease and the presence of other causes of liver disease (III).
4. Consider the decision to treat the HIV/HCV-coinfected patient on an individual basis including information on the severity of liver disease, genotype, viral quantification, and state of any comorbid conditions (III).

HIV-Specific Assessment Prior to Initiating HCV Therapy

This section highlights HIV-specific issues including optimizing HIV control and minimizing hepatotoxic side effects of HIV drugs to successfully treat HCV in the HIV/HCV-coinfected patient eligible for treatment. However, the risks and benefits of changing HIV drug regimens must be carefully assessed on a case-by-case basis. If options for switching HIV treatment to a less hepatotoxic regimen are limited due to significant HIV resistance, for example, the decision to initiate treatment for HCV should be reassessed. If possible, HIV regimens should be stable and no further changes in the antiretroviral regimen anticipated when initiating HCV therapy.

CD4

Early studies in HIV/HCV-coinfected patients, which were small in sample size demonstrated lower SVR rates among patients with lower CD4 counts. However, recent data from two multicenter randomized clinical trials (12, 13) suggest that baseline CD4 at the time of HCV treatment initiation does not adversely affect response rates. Patients were included into these two trials if they had a baseline CD4 count more than 100 cells/mm^3. Therefore, no safety or efficacy data are available for the use of pegylated interferon in HIV/HCV-coinfected individuals with CD4 below 100 cells/mm^3.

In one trial (13), among those randomized to the pegylated interferon plus ribavirin arm, the rate of SVR was higher in the 17 patients with CD4 cell count below 200 cells/mm^3 when compared to the entire 289 individuals in the pegylated interferon plus ribavirin arm (47% vs 40%).These data should be interpreted with caution, because of the small numbers of individuals with a CD4 cell count below 200 cells/mm^3 in this trial. This trial also did not demonstrate an increased rate of AIDS defining events in patients with a CD4 cell count below 200 cells/mm^3. The second trial (12) did not find any relationship between the baseline CD4 and the SVR to pegylated interferon and ribavirin.

Lactic Acidosis

Drug interactions may compromise the care of HIV/HCV-coinfected patients. Fatal cases of lactic acidosis have been reported in HIV/HCV-coinfected patients treated with the dideoxynucleoside analogs stavudine (d4T) and/or didanosine (ddI) concomitant with ribavirin.(57, 58) Ribavirin treatment is believed to increase exposure to ddI and its triphosphorylated active metabolite and thus increase the toxicity of ddI.(59) Stavudine has most often been associated with lactic acidosis in HIV-monoinfected patients.(60) Because of these reports, ddI and d4T should be avoided in patients receiving HCV treatment. If possible, ddI and d4T should be substituted with other nucleoside or nucleotide analogs such as lamivudine, abacavir, and tenofovir if deemed effective and safe, prior to initiating HCV therapy.

Hepatotoxicity

Drug-induced hepatotoxicity, especially as a result of the use of certain antiretroviral medications is a common problem in HIV. Therefore, all medications, particularly antiretroviral medications must be reviewed, and patients on medications with potential hepatotoxic side-effects should be followed closely. In patients who are ready to start antiretroviral medications, consideration should be used to minimize the initiation of drugs with potential hepatotoxic side-effects. Current FDA approved antiretroviral medications fall into four classes of drugs: the nucleoside reverse transcriptase inhibitors (NRTI), the nonnucleoside reverse transcriptase inhibitors (NNRTI),the protease inhibitors (PI), and the fusion inhibitors (FI). As mentioned above, certain drugs within the NRTI class have been associated with lactic acidosis.

Among the NNRTIs, nevirapine has most often been associated with hepatotoxicity in HIV-infected patients, particularly within the first few weeks after starting therapy.(61-63) The mechanism is believed to be an acute hypersensitivity reaction. Recent data suggest that nevirapine-induced hepatotoxicity may be more common in those with HIV/HCV coinfection and especially those with more advanced histologic liver disease.(64) Women and HIV-infected patients with higher CD4 counts also may be at increased risk for nevirapine-induced hepatotoxicity. The other commonly prescribed NNRTI, efavirenz has also been associated with increased hepatotoxicity, which may also be more common in the HIV/HCV-coinfected patient with more advanced histologic liver disease.(64)

Among the PIs, the incidence of severe hepatotoxicity in patients taking full doses of ritonavir (1,200 mg/day) was greater than that in patients prescribed nucleoside regimens or prescribed other protease inhibitor containing regimens including indinavir, nelfinavir, or saquinavir.(65) Ritonavir given in doses of 400 mg twice a day in conjunction with saquinavir also at 400 mg twice a day resulted in a similar incidence of hepatotoxicity as full doses of ritonavir. This study, however, did not show that severe hepatotoxicity in HIV-infected patients taking ritonavir was increased in the presence of chronic HCV.

Ritonavir used at lower doses in conjunction with other PIs has become the standard of care in HIV. Ritonavir is a potent inhibitor of cytochrome P-450 3A4 metabolism and is used to increase the bioavailability of other PIs including indinavir, lopinavir, saquinavir, amprenavir, and atazanavir, thereby allowing for lower doses of these drugs. Lopinavir/ritonavir is the recommended PI for initial PI-based HAART regimens in recent guidelines for the treatment of HIV infection.(66) Recent studies (67-69) investigating the effect of lopinavir/ritonavir (where ritonavir is administered at a total dose of 200 mg/day) on hepatotoxic events find an increased incidence in HIV/HCV-coinfected patients compared to HIV-infected patients. One study compared liver function tests collected from eight clinical trials of lopinavir/ritonavir through 48 wk.(69) In this study, higher rates of grade 3 or higher elevations (>5 x the upper limit of normal) in AST or ALT were observed in HIV/HCV-coinfected patients compared to HIV-monoinfected patients. However, patients with baseline transaminases more than three times the upper limit of normal were excluded and, therefore, the impact of HCV coinfection may be underestimated.

The incidence of liver enzyme elevations following the initiation of a variety of PI-based regimens with or without low-dose ritonavir was recently studied.(26) In multivariate analyses, HCV infection as well as the use of PI regimens containing indinavir with or without ritonavir and saquinavir/ritonavir (where the ritonavir dose was 800 mg/day) was associated with a twofold greater risk of hepatotoxicity when compared to regimens containing nelfinavir. The addition of low-dose ritonavir to indinavir, however, did not increase the risk of hepatotoxicity. The incidence of severe hepatotoxicity was also compared in those with HIV/HCV coinfection and those with HIV infection only for each PI with and without ritonavir. A higher incidence of severe hepatotoxicity was identified in HIV/HCV-coinfected patients who were taking nelfinavir when compared to HIV-monoinfected patients and in those taking saquinavir/ritonavir. The incidence of severe hepatotoxicity appeared increased in HIV/HCV-coinfected patients taking lopinavir/ritonavir (200 mg/day) but was not statistically significant. There was no difference among HIV/HCV-coinfected and HIV-monoinfected patients taking indinavir/ritonavir (200 or 400 mg/day).

A comparative study between lopinavir/ritonavir and nelfinavir in one trial of antiretroviral naïve HIV/HCV-coinfected patients found a lower incidence of grade 3+ AST and ALT elevations in the patients randomized to lopinavir/ritonavir arm compared to patients randomized to the nelfinavir arm over a 60-wk period.(69) No patients in either arm discontinued therapy due to hepatotoxicity. Isolated hyperbilirubinemia has also been associated with the use of the PIs, indinavir, and atazanavir in HIV-monoinfected patients.

Other medications used in the management of HIV-infected patients may also result in abnormal liver enzymes (Table 6).

Table 6. Common Drugs Associated with Liver Abnormalities Used in the Treatment of HIV and HIV Complications

Predominantly Hepatocellular Disease	Predominantly Cholestatic Disease
Clarithromycin	Atazanavir
Dapsone	Clarithromycin
Delaviridine	Dapsone
Didanosine (ddI)	Indinavir
Dideoxycytidine (ddC)	Ketoconazole
Efavirenz	Rifabutin
Fluconazole	Rifampin
Isoniazid	Trimethoprim-sulfamethoxazole
Itraconazole	
Lopinavir/ritonavir	
Nelfinavir	
Nevirapine	
Pentamidine	
Ritonavir	
Saquinavir	
Stavudine (d4T)	
Trimethoprim-sulfamethoxazole	
Voriconazole	
Zidovudine	

Other HIV and HCV Drug Interactions

Providers should be aware of other effects of HIV therapies in the patient with HIV/HCV coinfection. For example zidovudine causes bone marrow suppression that may aggravate the hemolytic anemia observed with ribavirin. *In vitro* data have shown that ribavirin inhibits the phosphorylation of zidovudine, stavudine, lamivudine, and zalcitabine (ddC), potentially impairing the HIV antiviral activity of these drugs. However, clinical studies have failed to demonstrate an adverse effect of ribavirin at 800 mg/day on intracellular phosphorylation and/or plasma pharmacokinetics of zidovudine, lamivudine, or stavudine in HIV/HCV-coinfected patients.(70)

Trimethoprim/sulfamethoxazole that is commonly used for prophylaxis against *pneumocystis carinii* pneumonia when CD4 counts fall below 200, can also independently cause cytopenias including anemia, thrombocytopenia, and neutropenia.

Recommendations:

1. Prior to initiating HCV therapy, antiretroviral therapy should be optimized in the HIV/HCV-coinfected patient by:

    a. ensuring that the patient is on a stable regimen with maximal CD4 benefit (III).
    b. avoiding ddI (III).
    c. considering a discontinuation of zidovudine because of the risk of synergistic myelosuppression (III).

HCV Treatment Response Rates in the HIV/HCV-Coinfected Patient

Definition of HCV Treatment Endpoints

Treatment endpoints for HCV are the same for HCV-monoinfected patients and HIV/HCV-coinfected patients. An undetectable HCV RNA level or a 2-log reduction in HCV RNA levels at 12 wk is referred to as an EVR. An undetectable HCV RNA at the end of therapy is referred to as an end-of-treatment response (ETR) and an undetectable HCV RNA 6 months after therapy is referred to as SVR. Because failure to achieve an EVR has been shown to predict strongly an inability to achieve an SVR in both HCV-monoinfected and HIV/HCV-coinfected patients, discontinuation of therapy should be considered at 12 wk in the absence of an EVR. (71, 72)

Therefore, in the patient with an undetectable HCV RNA level at 12 wk or an EVR, follow-up HCV RNA levels should be drawn again at the end of treatment. In those with an ETR, a follow-up HCV RNA level should be drawn 6 months after the end of treatment.

HCV Treatment Responses in the HIV/HCV-Coinfected Patient

Three recent studies (11-13) show that in HIV/HCV-coinfected patients, the combination of pegylated interferon plus ribavirin is superior to the combination of standard interferon alfa plus ribavirin. In the AIDS Clinical Trials Group (ACTG) 5071 Study (12), 133 HIV/HCV-coinfected adults were randomized to receive either standard interferon alfa-2a subcutaneously at 3 million international units (MIU) three times a week (tiw) or pegylated interferon alfa-2a (40 kD) subcutaneously at 180 µg/wk, each combined with increasing doses of ribavirin escalated from 600 to 1,000 mg daily. Overall (genotype 1 and genotype non-1 combined) results at both 48 wk (ETR) and 72 wk (SVR) (24 wk after discontinuation of therapy) show that HCV RNA was undetectable in a higher percentage of persons in the pegylated interferon arm when compared to the standard interferon arm (Table 7). Twelve percent of patients in both arms discontinued treatment.

Table 7. Virologic Response Rates in the ACTG 5071 Study

	INF alfa-2a 6 MIU. tiw x 12 wk, then 3 MIU. tiw x 36 wk + RBV 600 mg increasing to 1,000 mg as tolerated over 6 wk	Peg INF alfa-2a (PEGASYS) 180 µg/ wk x 48 wk + RBV 600 mg increasing to 1,000 mg as tolerated over 6 wk
	n = 67	n = 66
ETR (Overall)	12%	41%*
Genotype 1	6%	29%
Non-genotype 1	33%	80%
SVR (Overall)	12%	27%**
Genotype 1	6%	14%
Non-Genotype 1	33%	73%

* $p < 0.001$ versus IFN + RBV; ** $p = 0.03$ versus IFN + RBV.

In the AIDS PEGASYS Ribavirin International Coinfection Trial (APRICOT) (13), 860 HIV/HCV-coinfected adults were randomized to one of three treatment arms: (i) standard interferon alfa-2a at 3 MIU tiw plus ribavirin at 800 mg/day, (ii) pegylated interferon alfa-2a (40 kD) at 180 µg/wk plus ribavirin 800 mg/day, or (iii) pegylated interferon alfa-2a (40 kD) at µg/wk plus placebo. Overall (genotype 1 and genotype non-1 combined) results at both 48 wk (ETR) and 72 wk (SVR) also demonstrate the superiority of pegylated interferon plus ribavirin when compared to standard interferon plus ribavirin (Table 8). Surprisingly, both the ETR rate and the SVR rate in the pegylated interferon plus placebo arm was higher than those on combination therapy with standard interferon plus ribavirin. The treatment discontinuation rate was higher in the standard interferon plus ribavirin group than the pegylated interferon plus placebo arm and the pegylated interferon plus ribavirin arm (39% vs 31% vs 25%, respectively), which may explain the lower than expected response rate in the standard interferon plus ribavirin. Response rates were derived from all patients who initiated therapy regardless of whether or not they later discontinued therapy. Interestingly, pegylated interferon resulted in a 0.9 log decrease in HIV RNA levels.

Finally, in the French RIBAVIC study (11), 412 patients were randomized to either pegylated interferon alfa-2b (12kD) at 1.5 µg/kg per week combined with ribavirin 800 mg/day or standard interferon alfa-2b at 3 MIU tiw combined with ribavirin 800 mg/day, the SVR rates in the pegylated interferon arm was also superior to the standard interferon arm (Table 9). The overall ETR was reported in the pegylated interferon arm.

All three studies showed that combination therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin is superior to combination therapy with standard interferon plus ribavirin. The SVR rates from these studies are lower than those reported in HCV-monoinfected patients, particularly for those with genotype 1 infection. The SVR rates for genotype 2, 3 infection after 48 wk of therapy are comparable to those reported in genotype 2, 3 HCV-monoinfected patients after 24 wk of therapy.

The SVR rates reported in the combination pegylated interferon plus ribavirin arm in the three studies performed in HIV/HCV-coinfected patients also vary. Several factors may account for the lower overall SVR rates in the ACTG 5071 trial and the RIBAVIC Study. In the ACTG 5071 trial, the initial starting dose of ribavirin was lower than the other two studies at a total dose of 600 mg/day. Studies in HCV-monoinfected patients increasingly demonstrate that ribavirin at higher doses initially are important and may prevent relapse.(73) Interestingly, in the ACTG 5071 trial, the overall ETR was 41% for the pegylated interferon plus ribavirin arm and 12% for the standard interferon plus ribavirin arm. However, 24 wk after the discontinuation of therapy, the overall SVR rate in the pegylated plus ribavirin arm had fallen to 27%. In addition, about 33% of the patients in the ACTG 5071 trial were African American, a population that has consistently across many trials been shown to be resistant to HCV therapy.(74)

Table 8. Virologic Response Rates in the APRICOT Study

	INF alfa-2a 3 MIU. tiw + RBV 800 mg/ day x 48 wk	Peg INF alfa-2a (PEGASYS) 180 µg/wk + placebo x 48 wk	Peg INF alfa-2a (PEGASYS) 180 µg/wk + RBV 800 mg/ day x 48 wk
	n = 285	n = 286	n = 289
ETR (Overall)	14%	33%	49%
Genotype 1	8%	21%	38%
Non-Genotype 1	27%	57%	64%
SVR (Overall)	12%	20%*	40%**
Genotype 1	7%	14%	29%
Non-Genotype 1	20%	36%	62%

*p = 0.0078 versus IFN + RBV; ** p < 0.0001 versus IFN + RBV, p < 0.0001 versus PEG only.

In the RIBAVIC trial, treatment discontinuation occurred in 42% of the patients overall, divided equally between both arms. Severe side effects occurred in 31% of patients. The results reported are based on an intent-to-treat analysis. When including those who completed treatment, the overall sustained virologic rates were 36% in the pegylated interferon plus ribavirin arm and 28% in the standard interferon plus ribavirin alone arm. In this study, 80% of the patients had a history of injection drug use (IDU) and 40% had bridging fibrosis or cirrhosis--higher than in the ACTG 5071 trial and the APRICOT Study. Thus differences in response to pegylated interferon plus ribavirin therapy between trials appear to be multifactorial, and a function not only of differences in study design but also in differences in characteristics of the population under investigation.

Dosing of Pegylated Interferon

There are currently two FDA-approved formulations of pegylated interferon: peginterferon alfa-2a (40 kD) which is administered at a dose of 180 µg subcutaneously (SC) regardless of weight once weekly and peginterferon alfa-2b (12 kD), which is administered at a dose of 1.5 µg/kg SC once weekly (Table 9).A randomized controlled trial of the safety and efficacy of the two pegylated formulations, each combined with ribavirin is currently under study in HCV-infected patients. Until these data are available, no definitive conclusions about the potential differences in efficacy and/or safety of these two formulations can be made.

Table 9. Virologic Response Rates in the RIBAVIC Study

	INF alfa-2b 3 MIU. tiw x 48 wk + RBV 800 mg/day x 48 wk	Peg INF alfa-2b (PEG-INTRON) 1.5 µg/kg per week + RBV 800 mg/day x 48 wk
	n = 207	n = 205
ETR (Overall)	NR	37%
Genotype 1	NR	NR
Genotype 2,3	NR	NR
SVR (Overall)	15%	27%*
Genotype 1	5%	15%
Genotype 2,3	40%	46%

*p = 0.031 versus INF + RVB; NR = not reported.

Dosing of Ribavirin

The optimal dose of ribavirin used in combination with pegylated interferon is currently under study, but doses of 1,000-1,200 mg/day (depending on a body weight less than or greater than 75 kg, respectively) have been FDA approved for HCV-monoinfected patients in combination with peginterferon alfa-2a,and doses of 800 mg/day irrespective of weight have been approved for peginterferon alfa-2b (Table 10). Because anemia is so common in HIV-infected patients, especially those with more advanced HIV disease, most published HCV treatment protocols in HIV/HCV-coinfected patients have used the lower dose of ribavirin at 800 mg daily to minimize any ribavirin-induced anemia. However, data in HCV-monoinfected patients have shown that this dose of ribavirin is likely to be subtherapeutic for genotype-1-infected patients.(74) For HCV-monoinfected patients with genotypes 2 or 3, ribavirin at 800 mg daily may be sufficient. In addition, others suggest that combination therapy with ribavirin doses at >10.6 mg/kg per day (which is roughly equivalent to 795 mg for an average 75 kg patient) is the most effective HCV treatment option regardless of genotype.

Table 10. Standard Treatments for Chronic Hepatitis C in the HIV-Infected patient

Generic (Trade Name)	Recommended Dose	Major Adverse Effects*
Peginterferon alfa 2b-12 kD (PEG-Intron^{R})	Weekly dose of 1.5 µg/kg SC	Flu-like symptoms Bone marrow suppression
Peginterferon a-2a-40 kD (Pegasys^{R})	Weekly dose of 180 µg/kg SC	Decrease in absolute CD4 count but not CD4% Aggravation of autoimmune disorders Neuropsychiatric symptoms Seizures Acute cardiac and renal failure Retinopathy Interstitial pulmonary fibrosis More frequent injection site reactions and neutropenia with pegylated formulations of interferon than standard interferon
Ribavirin (Copegus^{R}, Rebetol^{R})	Genotype 1: 1,000 mg daily po, if patient weight <=75 kg; 1,200 mg daily po if patient weight >75 kg	Hemolytic anemia Significant teratogen Headaches
	Genotype 2,3: 800 mg daily po	Shortness of breath GI side-effects

*Adverse effects included are limited to those reported in highest frequency in placebo-controlled studies, or are of sufficient severity to warrant discontinuation of therapy and/or treatment of the adverse effect(s). Consult other references for complete listing of reported adverse effects.

Despite the lack of data on the safety and efficacy of 1,000/1,200 mg daily of ribavirin in coinfected patients, such dosing may be preferable to lower doses, in order to avoid compromising response by inadequate ribavirin dosing. This is particularly important to consider in HIV-infected patients, a population that is inherently difficult to treat successfully. This recommendation has been recently put forth by the AASLD.(17)

Recommendations:

1. In the HIV/HCV-coinfected patient, treat with pegylated interferon and ribavirin (I)

    a. In the genotype 1 patient, ribavirin dose is 1,000 mg/day if weight <=75 kg or 1,200 mg/day if weight >75 kg as tolerated by the patient (III).
    b. In the genotype 2 or 3 patient, ribavirin dose is 800 mg/day (I).

2. Measure HCV RNA by quantitative and/or qualitative assays at specified intervals during and following therapy (III).

HCV Treatment Duration in the HIV/HCV-Coinfected Patient

Similar to the HCV-monoinfected patient, HIV patients infected with HCV genotype 1 should be treated for 48 wk. Currently there are no data regarding the efficacy of 24 wk of HCV therapy for HIV patients with HCV genotype 2 or 3 infection. In the absence of such data, 48 wk of therapy should be offered, as this was the treatment duration studied in clinical trials of HIV-infected patients with concurrent HCV genotype 2 or 3 infection. Benefits of therapy beyond 48 wk are unknown. Treatment can be discontinued in HIV/HCV-coinfected patients who have failed to have at least a 2.0 log fall in HCV RNA levels by 12 wk of therapy, since SVR is unlikely to be achieved. One study found that 100% of the 40 patients without an EVR did not have a SVR.(72) A second study has shown that 93% of those who failed to achieve an EVR also failed to achieve a SVR.(71)

Recommendations:

1. In the HIV/HCV-coinfected patient, treat with pegylated interferon and ribavirin for at least 48 wk regardless of genotype (I).

HCV Treatment Monitoring and Management of Side-Effects

Monitoring for laboratory abnormalities, depression, and substance use while on HCV treatment is an important aspect of the management of the HIV/HCV-coinfected patient. Table 11 outlines the laboratories and screening that should be performed at regular intervals. Frequent laboratory monitoring of hemoglobin, hematocrit, white blood cell count with differential, and platelet counts are of particular importance in the HIV/HCV-coinfected patient. More frequent monitoring may be necessary in the HIV/HCV-coinfected patient who develops significant anemia, neutropenia, or thrombocytopenia.

Table 11. Monitoring While on Pegylated Interferon Plus Ribavirin Combination Therapy*

Parameter	Interval	Recommended Action/Comments
Hgb,Hct,WBC/diff, and Platelet Count	Week 1 or 2, and week 4, then monthly or bimonthly during therapy. Monthly intervals are recommended in patients with values below the lower limit of normal	Permanently discontinue both drugs if Hgb <8.5 g/dl, Neutrophil <0.5 x 10^9/L, or Platelets <25 x 10^9/L**
Serum ALT	Month 1, then every 2-3 months	Monitor when doing other tests
Pregnancy test	Monthly during therapy and for 6 months after completing therapy	Male patients and/or partners receiving combination therapy should use barrier contraceptives plus one other form of effective contraception throughout and for 6 months after therapy If a positive pregnancy test is confirmed, therapy should be discontinued and the outcome of the pregnancy monitored closely
HCV RNA (By a quantitative assay)	12 wk on therapy	Consider discontinuing treatment for patients who remain viremic at 12 wk and who have failed to have at least a two log reduction in viral load from pretreatment level
HCV RNA (By a sensitive assay (minimum lower limit of detection of <50 IU/mL)	End of therapy and 6 months following the completion of therapy	Essential for defining on-treatment and posttreatment response
Depression screen	At each routine visit	For patients screening positive, consider antidepressant and/or Mental Health referral
TSH	Every 6 months before treatment and at 6 and 12 months on treatment	If TSH becomes elevated, confirm result and consider thyroid replacement therapy
Liver biopsy		Repeat after baseline rarely needed

**Adapted from the VA Treatment Recommendations for Patients with Hepatitis C www.hepatitis.va.gov

**The pharmaceutical package insert for pegylated interferon alfa-2a (40 kD) recommends discontinuation when platelets fall below 25 x 10^9/L, but the pharmaceutical package insert for pegylated interferon alfa-2b (12 kD) recommends discontinuation when platelets fall below 50 x 10^9/L.

In patients who develop anemia, the following ribavirin dose reductions are recommended in the pharmaceutical package insert for the two different formulations of pegylated interferon. For pegylated interferon alfa-2b (12 kD), the recommendations are to decrease ribavirin by 200 mg/day if the hemoglobin falls to <10 g/dL or for cardiac patients, if the hemoglobin falls by >=2 g/dL within 4 wk of starting HCV therapy. For pegylated interferon alfa-2a (40 kD), a decrease in the ribavirin dose to 600 mg/day is recommended in the pharmaceutical package insert. However, a reduction in dose by 200 mg/day may be preferable to a larger reduction in ribavirin from 1,000 or 1,200 mg/day to 600 mg/day. Patient quality of life may be significantly impaired by ribavirin-induced anemia,(75) but there are data suggesting that ribavirin dose reductions may compromise virologic response.(73) These observations support the use of growth factors such as erythropoietin in the treatment of anemia resulting from HCV therapy in order to maintain the higher doses of ribavirin, particularly for HCV genotype 1-infected patients.

If the WBC count falls to <1.5 x 10^9/L, the neutrophil count <0.75 x 10^9/L, or the platelet count <80 x 10^9/L, the pharmaceutical package insert for pegylated interferon alfa-2b (12 kD) recommends that the dose of pegylated interferon be reduced by 50%. The pharmaceutical package insert for pegylated interferon alfa-2a (40 kD) recommends that if the absolute neutrophil count falls below 0.75 x 10^9/L, then the dose should be reduced to 135 µg/week and if the platelet count falls below 50 x 10^9/L, then dose should be reduced to 90 µg/week. Recommendations for dose reduction based on total WBC count level are not available in the package insert for pegylated interferon alfa-2a (40 kD). Permanent discontinuation of both pegylated interferon and ribavirin are recommended in the package insert for both pegylated interferon formulations if the hemoglobin falls to <8.5 g/dL or neutrophils <0.5 x 10^9/L. A platelet count <50 x 10^9/L should lead to discontinuation of both pegylated interferon and ribavirin as recommended in the package insert for pegylated interferon alfa-2b (12 kD), but the package insert for pegylated interferon alfa-2a (40 kD) recommends permanent discontinuation when platelets fall below 25 x 10^9/L.

Growth factors such as erythropoietin and G-CSF are not currently FDA approved for HIV/HCV-coinfected patients receiving HCV therapy, but increasing data support the use of erythropoietin to maintain and/or increase hemoglobin during HCV therapy in both HCV-monoinfected and HIV/HCV-coinfected patients.(76,77) In the HIV-infected patient, erythropoietin is FDA approved for the treatment of zidovudine-related anemia and is commonly used. HIV infection itself can cause anemia and the addition of combination HCV therapy may further worsen this anemia.

A recent study randomized 52 anemic HIV/HCV-coinfected patients to either erythropoietin at 40,000 IU subcutaneously once per week or to no erythropoietin. Patients included in the study were on combination interferon plus ribavirin therapy and had either a hemoglobin level of <=12 g/dL or experienced a hemoglobin decrease of at least 2 g/dL from the start of interferon plus ribavirin therapy. The mean change in hemoglobin from baseline to 16 wk was 2.8 + 0.3 g/dL in the erythropoietin group versus 0.4 g/dL in the control group (76). Similar results were found when comparing patients on erythropoietin and a zidovudine-containing HIV regimen versus those on erythropoietin but not on a zidovudine-containing HIV regimen.

Given recent data showing an increased SVR rate in HCV-monoinfected patients who were maintained on optimal ribavirin doses (and not dose reduced) in the first 12-20 wk (78), we recommend starting erythropoietin at 40,000 units per week if the hemoglobin level falls to 12 g/dL or in the cardiac patient, if the Hgb has fallen by <=2 g/dL within 4 wk before dose reduction.

The data on G-CSF for neutropenia remain limited in the HIV/HCV-coinfected patient. G-CSF may be considered to counter the neutropenia resulting from use of pegylated interferon when dose reduction of interferon has failed. G-CSF can be given at a dosage of 300 µg subcutaneously twice a week.

Recommendations:

1. Monitor closely for laboratory abnormalities (III).
2. Reduce doses of ribavirin and/or pegylated interferon for clinically significant adverse events (III).
3. Consider starting erythropoietin for clinically significant anemia (II-3).

Liver Transplantation in the HIV/HCV-Coinfected Patient

In the absence of contraindications, liver transplantation is the treatment of choice in the management of end-stage HCV-related liver disease. Prior to the HAART era, organ transplantation in the HIV-infected patient was associated with high mortality rates due to the development of opportunistic infections as a result of progressive HIV infection and anti-rejection immunosuppression. However, in the post- HAART era, there are emerging data to show that outcomes of liver transplantation in patients with HIV infection are comparable to those in HIV-negative patients with decompensated liver disease.(79) If liver transplantation is undertaken in HIV-infected patients, ideally transplantation should be offered at a center where data are being gathered evaluating the efficacy of liver transplantation and its impact on survival. The largest reported study of liver transplantation in HIV-infected patients reported good short-term outcomes with transplantation in 24 patients, of whom 15 were also infected with HCV, followed for a median of 17 months.(79) Posttransplantation survival has also been shown to be similar between HIV-infected patients and HIV-uninfected patients registered in the United Network of Organ Sharing Data with 12-month cumulative survival rates at 87.1% and 86.6%, respectively. Medium-term outcomes also appear to be good, with survival at 24 months of 72.8% and 81.6% in HIV-infected and HIV-uninfected patients, respectively, and at 36 months, 72.8% and 77.9%, in each group. In HIV-infected patients, those coinfected with HCV infection had a lower survival rate than those without HCV infection. However, the HIV/HCV posttransplant survival rates were not significantly different from the HCV posttransplant survival rates, but an increased sample size and longer-term follow-up are needed.(79) Posttransplant survival is adversely affected by the recurrence of HCV, a nearly universal event, as well as by the toxicities of posttransplantation HCV therapy. Furthermore, in the posttransplant state, the patient may have decreased ability to tolerate necessary HIV therapy and then may suffer additional immune compromise.

The criteria for liver transplantation in HIV-infected patients have generally included those without advanced HIV disease (CD4 >200 and HIV viral load undetectable at <400 copies/mL), or those who have a chance of having an undetectable HIV viral load using available antiretroviral drugs after liver transplantation. Other inclusion criteria include abstinence from alcohol or recreational drugs for at least 6 months. These criteria should be followed when considering the patient for liver transplantation.

Recommendations:

1. Consider orthotopic liver transplantation in HIV/HCV-coinfected patients with complications of liver disease (II-3).

Summary of HCV Treatment Recommendations in the HIV/HCV-Coinfected Patient

1. All HIV patients should be tested for antibodies to HCV (III).
2. HCV RNA testing should be performed in:

    a. the HIV patient with a positive anti-HCV test to determine chronic HCV infection (III);
    b. the HIV patient with unexplained liver disease and a negative anti-HCV test, particularly in those with HIV- associated immune compromise (III);
    c. the HIV patient with suspected acute HCV infection (III).

3. Consider HCV treatment in all HIV/HCV-coinfected patients (III).
4. Provide education about the pros and cons of HCV treatment in the presence of HIV/HCV coinfection (III).
5. Regardless of ALT level and HCV genotype, perform a liver biopsy (if no contraindications to liver biopsy exist) prior to initiating therapy in order to determine the extent of HCV-related liver disease and the presence of other causes of liver disease (III).
6. Consider the decision to treat the HIV/HCV-coinfected patient on an individual basis including information on the severity of liver disease, genotype, viral quantification, and the state of any comorbid conditions (III).
7. Prior to initiating HCV therapy, antiretroviral therapy should be optimized in the HIV/HCV-coinfected patient by:

    a. ensuring that the patient is on a stable regimen with maximal CD4 benefit (III);
    b. avoiding ddI and d4T (III);
    c. considering a discontinuation of zidovudine because of the risk of synergistic myelosuppression (III).

8. In the HIV/HCV-coinfected patient, treat with pegylated interferon and ribavirin (I).

    a. In the genotype 1 patient, ribavirin dose is 1,000 mg/day if weight <=75 kg or 1,200 mg/day if weight >75 kg as tolerated by the patient (III).
    b. In the genotype 2 or 3 patient, ribavirin dose is 800 mg/day (I).

9. Measure HCV RNA by quantitative and/or qualitative assays at specified intervals during and following therapy (III).
10. In the HIV/HCV-coinfected patient, treat with pegylated interferon and ribavirin for at least 48 wk regardless of genotype (I).
11. Monitor closely for laboratory abnormalities (III).
12. Reduce doses of ribavirin and/or pegylated interferon for clinically significant adverse events (III).
13. Consider starting erythropoietin for clinically significant anemia (II-3).
14. Consider orthotopic liver transplantation in HIV/HCV-coinfected patients with complications of liver disease (II-3).

Contributors

VA National Hepatitis C Program of the Public Health Strategic Health Care Group: Michael Rigsby, MD (director), Jane Burgess, ACRN, MS, Victoria Davey, RN, MPH, Connie Raab, Lawrence R. Deyton, MSPH, MD (chief consultant); VA Hepatitis C Resource Centers: Teresa L. Wright, MD, Samuel B. Ho, MD, Guadalupe Garcia-Tsao, MD, and Jason Dominitz, MD, MHS; Core Working Group for the VA HIV/HCV Coinfection Recommendations: Phyllis C. Tien, MD, Harry Lampiris, MD, Peter Jensen, MD, and Sue Currie, MS; and members of technical advisory groups, organizations, and providers who reviewed these recommendations.

Dr. Tien and Dr. Wright are the lead authors of these recommendations.

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