American Journal of Gastroenterology

Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2006.00754.x

PRACTICE GUIDELINES

Management and Treatment of Hepatitis C Viral Infection: Recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office

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Chronic hepatitis C virus (HCV) infection affects approximately 1.3% of the general U.S. population and 5–10% of veterans who use Department of Veterans Affairs medical services. Chronic HCV is clearly linked to the development of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease requiring liver transplantation. The consequences of HCV infection constitute a significant disease burden and demonstrate the need for effective medical care. Treatment of chronic HCV is aimed at slowing disease progression, preventing complications of cirrhosis, reducing the risk of HCC, and treating extrahepatic complications of the virus. As part of a comprehensive approach to HCV management, antiviral therapy with peginterferon alfa combined with ribavirin is the current standard of care. Antiviral therapy should be provided to those individuals who meet criteria for treatment and who are at greatest risk for progressive liver disease. Many of these patients may have comorbid medical and psychiatric conditions, which may worsen while on antiviral therapy. Current antiviral regimens are associated with significant adverse effects that can lead to noncompliance, dose reduction, and treatment discontinuation. To overcome these barriers and to address these issues, it has become crucial to facilitate a multidisciplinary team who can respond to and provide HCV-specific care and treatment. Screening for HCV, preventing transmission, delaying disease progression, ensuring appropriate antiviral therapy, and managing treatment-related adverse effects can improve patient quality of life, treatment adherence, and ultimately, improve patient outcomes.

(Am J Gastroenterol 2006;101:2360–2378)

INTRODUCTION

The prevalence of chronic hepatitis C virus (HCV) infection is approximately 1.3% in the general U.S. population and 5–10% in veterans who use Department of Veterans Affairs (VA) medical services (1, 2). Although there is a higher prevalence of HCV in veterans, the following recommendations are intentionally broad enough to apply to the general hepatitis C population.

After initial exposure to hepatitis C, HCV RNA is detectable in blood within 1–3 wk. By 3 months, hepatitis C antibodies are present in 90% of patients. Up to 85% of patients with acute HCV eventually progress to chronic infection. HCV is composed of at least six major genotypes. In the United States, genotype 1 accounts for about 75% of HCV infections with the remainder usually being genotype 2 or 3.

The natural history of HCV is highly variable with some patients advancing to cirrhosis within 15 yr and others never progressing this far (3). Approximately 15–20% of patients with chronic HCV infection will develop cirrhosis. HCV is clearly linked to advanced liver disease, hepatocellular carcinoma (HCC), and has become the leading indication for liver transplantation (4). Treatment of chronic HCV is aimed at slowing disease progression, preventing complications of cirrhosis, reducing the risk of HCC, and treating extrahepatic complications of the virus. Antiviral therapy with interferon-based regimens is an important part of a comprehensive approach to HCV treatment, resulting in sustained elimination of viral replication for a portion of those treated. Sustained virologic response (SVR) is defined as having undetectable virus for at least 6 months after completion of therapy.

All patients with chronic HCV infection are potential candidates for antiviral therapy. Medical care providers should discuss the natural history of HCV infection, the risks and benefits of antiviral therapy and other steps to minimize liver damage with every HCV-infected patient. Currently, standard antiviral treatment for chronic HCV involves once weekly pegylated interferon (peginterferon alfa) injections and daily oral ribavirin. Patients most likely to benefit from antiviral treatment include those at risk for progressive liver disease and those with diminished quality of life secondary to their viral infection. It is crucial that individuals in whom treatment is deferred are reevaluated for treatment candidacy as their comorbid conditions are effectively managed.

The following recommendations summarize the growing literature and current best practices on chronic HCV

Table 1. Grading System Adapted from the AASLD Practice Guidelines on the Diagnosis, Management, and Treatment of Hepatitis C (7)

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

treatment, including treatment in difficult-to-treat populations. These recommendations are based on an extensive review of published data, national consensus recommendations, and input from thought leaders involved in HCV care and treatment (5, 6). Recommendations are graded according to criteria used by the American Association for the Study of Liver Diseases (AASLD) 2004 practice guidelines on the Diagnosis, Management, and Treatment of Hepatitis C (Table 1) (7).

These recommendations should aid health-care providers involved in the management of HCV-infected patients including general internists, medical specialists, mental health clinicians, pharmacists, nurses, and addiction specialists. Additional resources pertaining to the care of the HCV-infected patient have been developed by the VA Hepatitis C Resource Center (HCRC) program and are available at www.hepatitis.va.gov.

Recommendation

1. All patients with chronic HCV infection should be evaluated as potential candidates for HCV antiviral treatment (III).

PRETREATMENT ASSESSMENTS

The 2002 National Institutes of Health Consensus Development Conference recommends antiviral treatment for patients with chronic HCV who are at greatest risk for progression to cirrhosis (6). These are patients with detectable serum HCV RNA and liver histology showing more than portal fibrosis.

Because of limitations in efficacy and the potential for toxicity, each patient needs to be carefully assessed for the relative risks and benefits of beginning therapy immediately, delaying therapy, or deferring treatment indefinitely. Pretreatment assessments and contraindications to antiviral therapy are summarized in Tables 2 and 3.

Laboratory Testing

Treatment should be undertaken only in patients with preserved hepatic function (serum bilirubin <1.5 mg/dL, INR <1.5, albumin >3.4 g/dL, and no evidence of hepatic encephalopathy or ascites) along with sufficient hematological and biochemical parameters to tolerate therapy (Table 4).

HCV genotype should be determined, as genotype can influence treatment duration. Prior to antiviral therapy, a baseline viral load must be measured using a quantitative HCV RNA assay. For patients in whom HCV RNA levels are reported above a cutoff value (*e.g.,* >500,000 IU/mL), the sample should be retested after dilution to provide absolute baseline values. Treatment response may be assessed using both quantitative and qualitative assays. Quantitative assays

Table 2. Pretreatment Assessments in Patients with Chronic HCV Infection

Necessary
- Medical history, including complications of liver disease, presence of significant extrahepatic disease, and symptoms of chronic HCV that may diminish quality of life
- Psychiatric history, including past or ongoing psychiatric and substance use disorders
- Screening for depression and alcohol use
- Biochemical markers of liver injury and assessment of hepatic function, including ALT, albumin, bilirubin (particularly direct bilirubin), and prothrombin time
- White blood cell counts with differential, hemoglobin, hematocrit, and platelets
- Thyroid function tests
- Serum creatinine
- Serum glucose or glycosylated hemoglobin (HbA_{1c}) in diabetics
- Pregnancy test (in women of childbearing age)
- HIV serology
- Serum HBsAg, Anti-HBc, anti-HBs, anti-HAV (total)
- Quantitative HCV RNA measurement
- HCV genotype
- Previous antiviral therapies and response
- Electrocardiogram in preexisting cardiac disease

Highly recommended
- Liver biopsy to stage severity of liver disease (especially in HCV genotype 1 infection)
- Eye exam for retinopathy in patients with diabetes or hypertension
- Serum ferritin, iron saturation, and serum ANA
- Urine toxicology screen for opiates, cocaine, and amphetamines

ALT = alanine aminotransferase; HBsAg = hepatitis B surface antigen; Anti-HBc = antibodies to hepatitis B core antigens; anti-HBs = antibodies to hepatitis B surface antigens; anti-HAV = antibodies to hepatitis A virus; ANA = antinuclear antibodies.

Table 3. Contraindications to HCV Therapy

- Life-determining extrahepatic disease (malignancy, unstable angina, severe chronic obstructive pulmonary disease)
- Clinically decompensated liver disease*
- Uncontrolled autoimmune disorders
- Pregnancy or planned pregnancy in a patient or the patient's sexual partner or unwillingness to use adequate birth control
- Documented nonadherence to prior medical treatment or failure to complete HCV disease evaluation appointments and procedures
- Inability to self-administer 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†

*Select patients with clinically decompensated liver disease may be candidates for treatment.

†NIH Consensus 2002 Statement concluded "Continued alcohol use during therapy adversely affects response to treatment, and alcohol abstinence is strongly recommended before and during antiviral therapy."

Table 4. Monitoring Parameters for Interferon-Based Therapies With or Without Ribavirin

Parameter	Interval	Comments
WBC with differential, Hb, Hct, platelets, serum creatinine	Before treatment, wk 1 or 2, wk 4, then monthly or bimonthly during therapy or more frequently as indicated	Prior to therapy, acceptable hematological and biochemical indices: Hb $\geq$12 g/dL for men and $\geq$11 g/dL for women; ANC $>$1.5 k/mm^3; platelets $>$70 k/mm^3; serum creatinine $<$1.5 mg/dL; creatinine clearance $>$50 mL/min. See Tables 8 and 9 for dose modifications.
Serum ALT	Before treatment, month 1, then every 1–2 months	Monitor when performing other tests.
Pregnancy test	Before treatment, monthly during therapy, and for 6 months after completing therapy	Patients and their partners should use two forms of contraception throughout therapy and for 6 months afterwards; if pregnancy occurs, therapy should be discontinued and the pregnancy monitored closely.
Thyroid-stimulating hormone (TSH)	Before treatment and at least every 12 wk during therapy	If TSH becomes elevated, confirm result and check a free thyroxine (T4) level; consider thyroid replacement therapy if indicated.
Blood glucose	Before treatment and at least every 12 wk during therapy	If blood glucose is elevated, confirm result by checking glycosylated Hb. If elevated, consider starting insulin sensitizer.
HCV RNA by quantitative and/or qualitative assay	Before treatment, 4, 12, and 24 wk during therapy, at end-of-therapy, and 6 months following the completion of therapy	Consider discontinuing treatment at 12 wk if $<$2 $\log_{10}$ reduction in pretreatment HCV RNA. If EVR is not achieved and treatment is continued, discontinue treatment if HCV RNA is detectable at 24 wk if the goal is viral eradication. An assay with a minimum lower detection limit of HCV RNA $<$50 IU/mL should be used at 24 wk, end-of-therapy, and 6 months following completion of therapy.
Assess for adverse effects and adherence	At each routine visit	Nonadherence impairs response.
Depression screen	At baseline and each routine visit	For patients screening positive, consider antidepressant therapy and/or referral to mental health specialist.
Substance use assessment (history of alcohol, cocaine, opiate, heroin, or amphetamine use)	At baseline and each routine visit	If positive, refer to addiction specialist.

ALT = alanine aminotransferase; ANC = absolute neutrophil counts; EVR = early virologic response; Hb = hemoglobin; Hct = hematocrit; WBC = white blood cell count.

are used to measure changes in HCV RNA levels from baseline. For consistency, the same quantitative assay should be used prior to and throughout therapy (7). Sensitive qualitative assays using technology such as transcription-mediated amplification (TMA) or polymerase chain reaction (PCR) have traditionally been used to detect low levels of HCV RNA at intervals during therapy and in follow-up (7). Newer quantitative assays have detection limits similar to those of qualitative PCR, and many laboratories have eliminated qualitative PCR assays.

Liver Biopsy

Liver biopsy is the best method for staging the degree of fibrosis (typically staged from 0–IV with the METAVIR and 0–VI with the Ishak scoring system) and grading inflammation (typically graded from 0–IV) (3, 7). In most cases, patients treated for HCV should have more than portal fibrosis (more than stage I; see section "Patients with Minimal Histologic Evidence of Liver Disease"). Because treatment response in HCV genotype 2 or 3 infection is high, biopsy may not be necessary prior to antiviral therapy (7).

Psychiatric Assessment

All patients should be evaluated for psychiatric disorders, particularly for depression and suicide risk. Uncontrolled psychiatric disorders are an absolute contraindication to interferon-based therapies (Table 3). Patients with psychiatric disorders in remission or stabilized may receive antiviral therapy. Standardized depression instruments such as the Beck's Depression Inventory (BDI) are helpful to use at baseline and during treatment. For example, a patient with a BDI score $>$10 should be evaluated for major depressive disorder and started on antidepressants if criteria are met (8, 9). Patients with a BDI score $>$18 or who meet diagnostic criteria for psychiatric conditions should be referred to a mental health specialist for management prior to initiating antiviral treatment (9).

Assessments for Substance Use Disorders

Patients with substance use disorders who have been stabilized can often be treated safely and effectively with HCV therapy. These patients require close monitoring, and care should be coordinated with addiction specialists. All patients should be evaluated for current substance use. The presence of current heavy alcohol use ($>$14 drinks/wk or $>$4 drinks/day for men, $>$7 drinks/wk or $>$3 drinks/day for women), binge alcohol use ($>$4 drinks per occasion at least once a month), or active current injection drug use requires referral to an addiction specialist prior to treatment initiation (10). Urine toxicology screens for opiates, cocaine, or amphetamines may be used to supplement patient self-report.

Adherence

The importance of treatment adherence should be discussed with patients considering antiviral therapy. Evidence of prior nonadherence to medical, psychiatric, or addiction therapies may predict nonadherence to HCV therapies. When necessary, treatment initiation should be deferred and attempts made to improve adherence.

Autoimmune Disorders

Treatment with interferon may exacerbate underlying autoimmune disorders. Patients with stable autoimmune thyroid disease or diabetes can usually be safely treated with HCV therapy. Patients with severe autoimmune diseases (*e.g.*, psoriasis, Crohn's disease, or rheumatoid arthritis) should not receive HCV therapy unless the autoimmune disorder is controlled and underlying HCV disease is advanced. Decisions to treat patients with these disorders should be undertaken only in close collaboration with a medical specialist in these diseases, and patients should be monitored closely for any worsening of symptoms.

Hepatitis A and B and Other Liver Diseases

Patients should be tested for hepatitis B surface antigen, antibodies to hepatitis B surface and core antigens, and antibodies to the hepatitis A virus to evaluate for active hepatitis B infection and the need for hepatitis A and/or B immunization.

If serum ferritin or transferrin saturation is significantly elevated or there is clinical concern for hemochromatosis, consider evaluating the liver tissue for quantitative iron and/or testing the peripheral blood for hemochromatosis gene mutations. For additional information, refer to the AASLD Practice Guidelines on the Diagnosis and Management of Hemochromatosis.

Pregnancy

A pregnancy test should be obtained from women of childbearing age prior to the initiation of HCV treatment. If a woman is pregnant or attempting to conceive, HCV treatment should not be started because ribavirin is teratogenic. Pregnancy must also be avoided in the partner of an HCV-infected male patient receiving treatment. Contraception for both partners is required and should include at least one barrier method of contraception during and for 6 months after HCV treatment (11, 12). In the event that pregnancy occurs either in the patient or in the partner receiving ribavirin, ribavirin should be immediately discontinued and the pregnancy should be reported to the Ribavirin Pregnancy Registry at 1-800-593-2214 or www.ribavirinpregnancyregistry.com.

Ocular Evaluation

In patients without risk factors for retinal disease, a pretreatment ocular examination is preferable and serves as a baseline evaluation of existing retinal abnormalities. The ocular examination can be repeated while on therapy in the event that retinopathy occurs or worsens while on therapy.

In patients with risk factors for retinal disease (*e.g.*, hypertension, diabetes), an ophthalmic examination should be performed prior to and while on treatment as indicated to identify any worsening disease while on interferon.

Extrahepatic Manifestations of Hepatitis C

HCV infection is associated with a variety of extrahepatic manifestations including leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, and porphyria cutanea tarda. In patients being considered for treatment of these extrahepatic manifestations, baseline serum cryoglobulins, urinalysis, 24-h creatinine clearance, and 24-h urinary protein should be measured.

Evaluation for Human Immunodeficiency Virus Coinfection

Human immunodeficiency virus (HIV) coinfection increases the risk of HCV-related liver damage, may influence the duration of HCV therapy, and appears to lower SVR. All patients with chronic HCV infection considering HCV therapy should be offered a voluntary HIV test if HIV status has not been previously established.

RECOMMENDATIONS IN PATIENTS BEING CONSIDERED FOR HCV THERAPY

2. Patients should undergo pretreatment assessments as summarized in Table 2 (III).
3. Patients with more than portal fibrosis, including those with compensated cirrhosis, who lack contraindications, should be offered antiviral treatment (III).
4. Patients with contraindications summarized in Table 3 should not begin HCV antiviral therapy (III).
5. Patients should be counseled on their likelihood of achieving SVR prior to initiating therapy (III).

DEFINITIONS OF RESPONSE

Treatment response can be measured biochemically (by normalization of serum alanine aminotransferase [ALT]), virologically (by reduction in serum HCV RNA), and histologically (by reduction in liver inflammation or fibrosis on posttreatment liver biopsy). Virologic response is the most common way to evaluate the effectiveness of HCV treatment. Biochemical and virologic responses are usually associated with histologic improvement. Given the invasiveness of liver biopsy, repeat liver biopsy following therapy is not recommended as part of routine care.

Treatment end points are generally defined as:

- Rapid virologic response (RVR): HCV RNA <50 IU/mL at 4 wk into treatment.
- Early virologic response (EVR): ≥ 2 $\log_{10}$ reduction from baseline HCV RNA at 12 wk of treatment.
- End-of-treatment response (ETR): undetectable HCV RNA at the completion of treatment.

Table 5. Antiviral Treatments for Chronic HCV (11, 12, 60, 61)

Treatment	Recommended Dose
Combination Peginterferon Alfa Regimens with Ribavirin	
Peginterferon alfa-2a (Pegasys®)	180 mcg SC once weekly regardless of weight
Peginterferon alfa-2b (PEG-Intron®)	1.5 mcg/kg SC once weekly up to 150 mcg/wk
Ribavirin (Rebetol®, Copegus®)	Genotype 1: 1,000 mg ≤75 kg OR 1,200 mg if >75 kg PO daily (in two divided doses) Genotype 2 and 3: 800 mg PO daily (in two divided doses)
Regimens in certain clinical circumstances	
Peginterferon alfa-2a (Pegasys®) in hemodialysis	135 mcg SC once weekly
Peginterferon alfa-2b (Peg-Intron®) in renal dysfunction	Reduce dose by 25% if Clcr 30–50 mL/min Reduce dose by 50% if Clcr 10–29 mL/min
Peginterferon alfa-2a (Pegasys®) monotherapy	180 mcg SC once weekly regardless of weight
Peginterferon alfa-2b (PEG-Intron®) monotherapy	1.0 mcg/kg SC once weekly up to 150 mcg/wk
IFN alfa-2a (Roferon-A®)	3 million U SC three times weekly
IFN alfa-2b (Intron A®)	3 million U SC three times weekly
IFN alfacon-1 (Infergen®) also known as consensus IFN	9 mcg SC three times weekly 15 mcg SC three times weekly in IFN nonresponders
Ribavirin dose with IFN	1,000 mg PO daily if patient ≤75 kg (in two divided doses) OR 1,200 mg PO daily if patient >75 kg (in two divided doses)

Clcr = creatinine clearance; IFN = interferon; PO = orally; SC = subcutaneous; U = units.

- SVR: undetectable HCV RNA at 24 wk after completion of treatment.
- Relapse: undetectable viremia during and/or at the end-of-treatment but virus is detectable after treatment is stopped.
- Nonresponse: detectable HCV RNA throughout treatment.

THERAPY FOR PREVIOUSLY UNTREATED PATIENTS

With pegylation, the interferon molecule is linked to a polyethylene glycol (PEG) molecule, resulting in reduced interferon clearance. Peginterferon alfa-2a (40 kDa) and peginterferon alfa-2b (12 kDa) are both FDA-approved for use as monotherapy and in combination with ribavirin. Both peginterferon alfa products are administered subcutaneously once weekly. Peginterferon alfa plus ribavirin produces superior responses compared with prior therapies and is the current standard of care for treatment-naïve patients with chronic HCV (Table 5).

Peginterferon Alfa Plus Ribavirin

In two randomized, controlled trials (RCTs), peginterferon alfa combined with ribavirin was more effective than interferon alfa plus ribavirin in HCV genotype 1 infection and at least as effective in genotype non-1 infection (Tables 6 and 7) (13, 14). SVR with peginterferon alfa plus ribavirin was observed in 42–46% with HCV genotype 1 infection and in 76–82% with HCV genotype 2 or 3 infection (Tables 6 and 7) (13, 14). Patients with early-stage disease generally had better results than those with bridging fibrosis or cirrhosis (57–58% *vs* 43–44%, respectively) (13–15).

The optimal ribavirin dose to achieve maximum efficacy with tolerable adverse effects in combination with peginterferon alfa is under investigation. In practice, ribavirin doses of 1,000–1,200 mg/day (or alternatively 10.6 mg/kg/day) for genotype 1 infection are given with either peginterferon alfa product (Table 5) (13, 16). Lower ribavirin doses (800 mg/day) appear sufficient for genotype 2 and 3 infections (16).

The spectrum of adverse effects for peginterferon alfa-2a plus ribavirin is similar to those of peginterferon alfa-2b plus ribavirin in clinical trials. In general, neutropenia and thrombocytopenia appear greater in those receiving peginterferon alfa plus ribavirin than for interferon plus ribavirin (11, 13, 14).

RECOMMENDATIONS FOR TREATMENT IN PREVIOUSLY UNTREATED PATIENTS

1. Peginterferon alfa plus ribavirin is the standard of care for treatment of chronic HCV (I).
2. The peginterferon alfa-2a standard dose is 180 mcg/wk and the peginterferon alfa-2b standard dose is 1.5 mcg/kg/wk administered subcutaneously in combination with ribavirin (I).
3. For patients with genotype 1 infection, the ribavirin dose is 1,000 mg/day if ≤75 kg or 1,200 mg/day if >75 kg in combination with peginterferon alfa (I).
4. For patients with genotype 2 or 3 infection, the ribavirin dose is 800 mg/day in combination with peginterferon alfa (I).

Monotherapy with Peginterferon alfa

For patients with absolute or relative contraindications to ribavirin (Table 3), peginterferon alfa alone or with reduced ribavirin doses, respectively, should be considered. SVR is lower with peginterferon monotherapy compared with peginterferon alfa plus ribavirin (Table 6), and this should be taken into account when counseling patients about the benefits of treatment.

Table 6. Comparison of Sustained Virologic Response (SVR) Rates for Peginterferon Alfa-2a Combination Therapy, Peginterferon Alfa-2a Monotherapy, and Interferon Alfa Combination Therapy Given Over 48 wk (14)

	SVR		
Patient Group	Peginterferon Alfa-2a (40 kDa) Plus Ribavirin*	Peginterferon Alfa-2a (40 kDa) Plus Placebo†	Interferon Alfa Plus Ribavirin‡
Overall	56% ($p < 0.001$)§	29%	44%
HCV genotype 1	46% ($p < 0.01$)§	21%	36%
High viral titer**	41%	13%	33%
Low viral titer‖	56%	39%	43%
HCV genotype 2, 3	76% ($p < 0.05$)	45%	61%
High viral titer**	74%	40%	58%
Low viral titer‖	81%	58%	65%

*peginterferon alfa-2a 180 mcg/wk plus ribavirin 1,000 or 1,200 mg/day.
†Peginterferon alfa-2a 180 mcg/wk plus placebo.
‡IFN 3 million U three times/wk plus ribavirin 1,000 or 1,200 mg/day.
§Compared with interferon alfa plus ribavirin.
**Defined as >2 million copies/mL (COBAS AMPLICOR HCV Test, v. 2.0, sensitivity 100 copies/mL); equivalent to >800,000 IU/mL.
‖Defined as ≤2 million copies/mL (COBAS AMPLICOR HCV Test, v. 2.0, sensitivity 100 copies/mL); equivalent to ≤800,000 IU/mL.

RECOMMENDATION FOR MONOTHERAPY WITH PEGINTERFERON ALFA

1. Peginterferon alfa monotherapy (Table 5) may be used to treat patients with contraindications to ribavirin (Table 3) (III).

Interferon Alfa Plus Ribavirin

Interferon alfa-2b plus ribavirin is more effective than peginterferon alfa monotherapy but less effective than peginterferon alfa plus ribavirin (Table 6) (14). For patients who cannot tolerate peginterferon alfa because of severe cytopenias, interferon alfa-2b plus ribavirin may be an acceptable alternative.

Predictors of Treatment Response to Peginterferon Alfa Plus Ribavirin

BASELINE PREDICTORS. Genotype 1 infection is the strongest negative predictor of response to peginterferon alfa and ribavirin (Tables 6 and 7) (13, 14). Additional independent negative predictors of response with peginterferon alfa-2a or alfa-2b plus ribavirin include high pretreatment HCV RNA level, age ≥40 yr, heavier body weight, and cirrhosis (13, 14, 16). Gender has not been shown to be an independent predictor of response. African Americans consistently have lower responses to peginterferon alfa plus ribavirin than Caucasians (section "African Americans") (17).

Table 7. Comparison of Sustained Virologic Response (SVR) Rates for Peginterferon Alfa-2b and Interferon Alfa Combination Therapies Given Over 48 Wk (13)

	SVR	
Patient Group	Peginterferon Alfa-2b Plus Ribavirin*	Interferon Alfa Plus Ribavirin†
Overall	54% ($p = 0.01$)‡	47%
HCV genotype 1	42% ($p < 0.05$)‡	33%
High viral titer§¶	30%	29%
Low viral titer‖	Not reported	Not reported
HCV genotype 2 or 3	82%	79%
HCV genotypes 4–6	50%	38%

*Peginterferon alfa-2b 1.5 mcg/kg/wk and ribavirin 800 mg/day.
†IFN 3 million U three times weekly plus ribavirin 1,000 or 1,200 mg/day.
‡Compared with interferon alfa plus ribavirin.
§Defined as >2 million copies/mL (NGI, sensitivity 100 copies/mL); equivalent to >800,000 IU/mL.
¶Statistical analysis not performed; data from Peg-Intron package insert.
‖Defined as ≤2 million copies/mL (NGI, sensitivity 100 copies/mL); equivalent to ≤800,000 IU/mL.

ON-TREATMENT PREDICTORS. SVR is more likely to occur in patients who have early viral suppression than a delayed or incomplete viral response on treatment. RVR and EVR can be useful predictors of SVR (section "Duration of Treatment") (14, 18).

Treatment-naïve patients who achieve an EVR with peginterferon alfa plus ribavirin have a 65–76% likelihood of attaining SVR (14, 18). Conversely, those without an EVR have ≤3% chance of achieving SVR and treatment discontinuation should be considered (14, 18). Lack of an EVR was also useful in predicting treatment nonresponse in African Americans and those with HIV coinfection (17, 19). In patients who fail to achieve an EVR, the decision to stop treatment should be made after full consideration of any viral response, treatment tolerability, and underlying liver disease (section "Patients with Compensated Cirrhosis").

RECOMMENDATIONS FOR VIROLOGIC END POINTS ON TREATMENT

1. RVR and EVR should be measured (II-2).
2. Treatment may be discontinued in those failing to achieve an EVR (II-2).
3. In patients with advanced liver disease, treatment may be continued even without an EVR, depending on tolerance of therapy (III).

DURATION OF TREATMENT

Genotype 1

In genotype 1-infected patients, SVR with peginterferon alfa plus ribavirin is greater with 48 wk than with 24 wk of treatment (51% *vs* 41%, respectively) (16). Emerging data suggest

that treatment duration may be shortened or lengthened depending on viral response at 4 wk and/or 12 wk.

Extending Treatment Duration Beyond 48 Wk

Two RCTs suggest that for treatment-naïve genotype 1-infected patients who have a slow decline in virus (detectable HCV RNA at 4 and/or at 12 wk), extending therapy to 72 wk may be beneficial. One study in which >90% had genotype 1 infection, higher SVR occurred with 72 *versus* 48 wk of peginterferon alfa-2a 180 mcg/wk plus ribavirin 800 mg/day in patients who had detectable HCV RNA (≥50 IU/mL) at week 4 (SVR 45% and 32%, respectively, $p = 0.014$) (20). A second study showed a trend toward higher SVR with 72 *versus* 48 wk of the same treatment regimen in patients who were still HCV RNA positive (≥50 IU/mL) at 12 wk and who subsequently had undetectable HCV RNA by 24 wk (SVR 30% and 18%, respectively, $p = 0.08$) (21).

Shortening Treatment Duration to 24 Wk

Some studies suggest that 24 wk of treatment may be sufficient in treatment-naïve genotype 1 patients who demonstrate RVR (22, 23). In a retrospective analysis, high SVR was achieved in patients developing an RVR with peginterferon alfa-2a plus ribavirin for 24 *versus* 48 wk (SVR 88% and 91%, respectively) (22). In an ongoing interim analysis of a prospective RCT, high SVR (67%) was achieved with 24 wk of treatment in patients achieving an RVR on peginterferon alfa-2a and ribavirin (23).

In summary, viral response at 4 wk and/or 12 wk may be useful in tailoring treatment duration. For patients developing RVR but who are poorly tolerant of therapy, discontinuing treatment at 24 wk may not compromise response. However, for those who have slow viral response but demonstrate undetectable virus by 24 wk into treatment and who are tolerating therapy well, extending treatment to 72 wk may be beneficial.

RECOMMENDATIONS FOR TREATMENT DURATION IN GENOTYPE 1 INFECTION

1. For patients who achieve RVR, 24 wk of treatment may be sufficient (III).
2. For patients who fail to achieve RVR but achieve EVR, 48 wk is usually sufficient (I).
3. For patients without an RVR and/or EVR, extending duration to 72 wk may be beneficial if virus is undetectable by 24 wk of therapy (III).
4. For patients who continue to have detectable virus at 24 wk, treatment should be discontinued if the goal of therapy is viral eradication (I).

GENOTYPE 2 OR 3

Patients with genotype 2 or 3 infection are more responsive to antiviral therapy than those with genotype 1 infection. SVR for genotype 2 or 3 infection is similar among patients treated for 24 *versus* 48 wk (SVR range 73–78%); thus, treatment for 24 wk is usually sufficient (16).

Extending Treatment Duration Beyond 24 Wk

Data suggest that SVR is lower in patients with genotype 3 infection than those with genotype 2 infection (SVR 66–79% *vs* 80–93%, respectively) (24, 25). In genotype 3-infected patients with a baseline HCV RNA >600,000 IU/mL and steatosis, a high relapse rate has been demonstrated following 24 wk of therapy with peginterferon alfa-2b and ribavirin. Although data are limited, some have suggested that extending treatment beyond 24 wk may be beneficial in this group (26).

Shortening Treatment Duration

In general, shortening treatment duration appears to compromise SVR. Several studies have evaluated shorter treatment durations of 12–16 wk (24, 25, 27). In a large RCT, overall SVR was lower with peginterferon alfa-2a plus ribavirin for 16 *versus* 24 wk in genotype 2- or 3-infected patients (SVR 65% *vs* 72%, $p < 0.0001$). SVR was lower with 16 *versus* 24 wk of treatment even when HCV RNA <600 IU/mL was achieved by week 4 of therapy (SVR 82% *vs* 90%, respectively). In a subgroup who had a low pretreatment HCV RNA (≤600,000 IU/mL), SVR was similar when treated for 16 *versus* 24 wk (SVR 83% *vs* 87% for genotype 2 and 78% *vs* 81% for genotype 3, respectively) (25). Another smaller RCT demonstrated lower SVR with peginterferon alfa-2b and ribavirin for 12 *versus* 24 wk in genotype 2- and 3-infected patients achieving an RVR, although this difference was not statistically significant (SVR 85% and 91%, respectively). Of potential clinical significance, a higher relapse rate occurred with 12 *versus* 24 wk of treatment (8.9% and 3.6%, respectively, $p = 0.16$), but there were fewer early treatment discontinuations (24).

RECOMMENDATIONS FOR TREATMENT DURATION IN GENOTYPE 2 OR 3 INFECTION

1. Standard treatment duration is 24 wk (I).
2. In patients with a low pretreatment RNA (≤600,000 IU/mL) who are not tolerating therapy, 16 wk of treatment may be sufficient (I).
3. For patients with genotype 3 infection and a baseline HCV RNA >600,000 IU/mL or steatosis, treatment beyond 24 wk may improve response (III).

GROUPS WITH SPECIAL CONSIDERATIONS FOR THERAPY

Given the complexities of current therapies, treatment is more clearly indicated in some patients than in others. The following recommendations have taken into account the natural history of disease, the likelihood of achieving SVR, and the adverse effects and need for dose discontinuations with treatment.

Patients with Compensated Cirrhosis

For patients with advanced fibrosis or cirrhosis, the annual risk of decompensation or HCC is 4–6%. Good response to antiviral treatment is achievable, although patients with bridging fibrosis (stage III) or cirrhosis (stage IV) appear to

respond less well to therapy than those with minimal or no fibrosis (13, 14)

Even in the absence of viral clearance, interferon-based therapy appears to slow fibrosis progression (28, 29). In patients with advanced fibrosis who failed standard treatment, maintenance doses of peginterferon alfa-2a at 90 mcg/wk and peginterferon alfa-2b at 0.5 mcg/kg/wk are under evaluation. Interim data from the ongoing COPILOT study reported a reduced risk of variceal bleeding and no worsening in Child-Pugh score by 2 points with peginterferon alfa-2b maintenance therapy after a median of ≥2 yr (30).

RECOMMENDATIONS IN PATIENTS WITH CIRRHOSIS

1. Patients with compensated cirrhosis and adequate neutrophil (ANC >1.5 k/mm^3) and platelet (>70 k/mm^3) counts to tolerate therapy should be treated with peginterferon alfa plus ribavirin at standard doses (II-2).
2. In patients who do not achieve viral suppression with combination therapy, long-term maintenance therapy with low-dose peginterferon alfa may be considered on an individual basis (III).

Patients Who Have Failed to Respond or Have Relapsed with Prior HCV Therapy

Nonresponders or relapsers to standard interferon with or without ribavirin may be retreated with peginterferon alfa in combination with ribavirin. Currently, no therapy is FDA-approved for patients who do not achieve SVR with peginterferon alfa and ribavirin. The decision to retreat should include consideration of the following factors: (1) prior drug regimen, (2) previous response achieved, (3) stage of fibrosis, (4) previous adherence to treatment, (5) tolerability and side effects with prior therapy, (6) infecting genotype, (7) pretreatment viral load, and (8) patient motivation.

For interferon nonresponders, 28% achieved SVR when retreated with peginterferon alfa and ribavirin for 48 wk. However in nonresponders to both interferon and ribavirin, only 10–15% achieved SVR when retreated with peginterferon alfa and ribavirin (31, 32). Response is better in retreatment of relapsers, with SVR occurring in 39–47% (31, 32). Failure to achieve an EVR was a predictor of nonresponse with continued therapy in patients retreated with peginterferon alfa-2a or alfa-2b and ribavirin, and early treatment discontinuation should be considered (33).

Peginterferon alfa and ribavirin nonresponders rarely benefit from retreatment with the same agents unless treatment doses or adherence can be improved. If retreatment is undertaken in patients previously intolerant of ribavirin or peginterferon alfa, adjunctive therapy with epoetin or granulocyte colony stimulating factor (GCSF) may be considered (section "Growth Factors"). In patients undergoing retreatment who demonstrate viral response, the duration should be at least 48 wk regardless of genotype. Current practice suggests variations in treatment for this group. Studies of consensus interferon and studies of high doses and different durations of peginterferon alfa and ribavirin are currently underway (34). Patients with advanced fibrosis may be considered for maintenance therapy (section "Patients with Compensated Cirrhosis").

RECOMMENDATIONS IN NONRESPONDERS AND RELAPSERS

1. For nonresponders and relapsers to *interferon with or without ribavirin,* retreatment with peginterferon alfa and ribavirin should be considered on an individual basis (II-1).
2. For nonresponders and relapsers to *peginterferon alfa plus ribavirin,* retreatment with peginterferon alfa and ribavirin may be considered *only if* substantial improvements in treatment dose or adherence can be made (III).
3. If retreatment is undertaken, the duration is at least 48 wk in those who demonstrate viral response on therapy (III).

Patients with Minimal Histologic Evidence of Liver Disease

Patients with grade 1 inflammation and minimal fibrosis are at low risk for developing advanced liver disease. After a thorough discussion of prognosis and treatment options, the physician and patient may agree to observation without treatment. Liver biopsy may be repeated in 3–5 yr if results would change management. Treatment should be reconsidered if the liver disease has progressed. Treatment should also be provided to patients, despite minimal fibrosis, who desire treatment and/or who have significant symptoms. Patients with extrahepatic manifestations of HCV infection should be considered for HCV therapy, regardless of the severity of their liver disease. In patients with genotype 2 or 3 infection, the high SVR may shift the risk-benefit ratio in favor of treatment even for those with minimal histologic disease (35).

RECOMMENDATIONS IN PATIENTS WITH MILD DISEASE

1. Treatment should be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy, unless the patient elects to undergo therapy with a goal of viral eradication (III).
2. If treatment is deferred, liver biopsy may be repeated in 3–5 yr if results would change management (III).
3. In patients with histological evidence of disease progression, treatment should be considered (III).

Patients with Persistently Normal Serum ALT

Approximately 30% of patients with chronic HCV have persistently normal serum ALT levels. However, up to 20% of patients with normal ALT levels have bridging fibrosis or cirrhosis (36). Therefore, laboratory evaluation alone without

liver biopsy cannot reliably differentiate between "mild disease" and those with more advanced fibrosis. Patients with proven minimal or no fibrosis on liver biopsy may be reassured about their favorable prognosis, and they may choose to defer therapy; those with more than stage I fibrosis should be advised to consider treatment. SVR with peginterferon alfa and ribavirin in patients with persistently normal ALT levels was similar to those with elevated serum ALT levels (37).

For patients with genotype 2 or 3 infection, SVR with peginterferon alfa plus ribavirin therapy is high; these patients may elect to undergo therapy regardless of stage of disease and thus, obviate the need for liver biopsy.

RECOMMENDATIONS IN PATIENTS WITH NORMAL ALT

1. Liver biopsy to stage fibrosis should be performed prior to starting treatment regardless of ALT level, especially in patients with genotype 1 infection (III).
2. Treatment should be considered in patients with more than portal fibrosis on liver biopsy, regardless of ALT values (I).

Patients with Genotype 4–6 Infections

In patients with genotype 4 infection, higher SVR (79%) was achieved with peginterferon alfa-2a plus ribavirin 1,000 or 1,200 mg/day for 48 wk than with other regimens with shorter treatment durations (67%), lower ribavirin doses (63%), or peginterferon alfa-2a monotherapy (44%) (38, 39). Similarly, high SVR was demonstrated with 36 or 48 wk of treatment with peginterferon alfa-2b and ribavirin in genotype 4-infected patients (SVR 66% and 69%, respectively) (40). Insufficient clinical trial data are available in HCV genotype 5 and 6 infections to make recommendations about optimal regimens at this time.

RECOMMENDATIONS IN PATIENTS WITH HCV GENOTYPE 4 INFECTION

1. Appropriate candidates should be treated with peginterferon alfa-2a 180 mcg/wk or peginterferon alfa-2b 1.5 mcg/kg/wk plus ribavirin 1,000 or 1,200 mg/day for 48 wk (I).

Patients >65 Yr and/or with Significant Comorbidities

Age alone should not preclude antiviral therapy. Before treatment is undertaken in patients >65-yr-old and/or in those with significant concomitant medical conditions (Table 3), careful consideration to initiating therapy should be given in light of reduced life expectancy. If life expectancy is estimated to be shortened by these comorbidities, and particularly if there is the potential for adversely affecting these medical conditions with peginterferon plus ribavirin, treatment should be deferred.

RECOMMENDATIONS IN PATIENTS >65 YR AND/OR WITH COMORBID CONDITIONS

1. In patients with limited life expectancy from significant comorbid conditions, antiviral therapy should be deferred (III).
2. In patients with significant comorbid conditions that will be exacerbated by peginterferon alfa and ribavirin, treatment should be deferred (III).
3. In otherwise healthy patients, treatment should be considered regardless of age (III).

Patients on Methadone Maintenance

Prior or ongoing injection drug users comprise the largest group of individuals with chronic HCV in the United States. Peginterferon alfa and ribavirin treatment has been evaluated in chronic HCV patients on methadone maintenance (41, 42). Although higher treatment discontinuation rates occurred in methadone patients, SVR was similar in methadone patients who completed a full course of therapy compared with those not on methadone. Side effects and antidepressant use were similar in methadone patients compared with control group.

RECOMMENDATIONS FOR PATIENTS ON METHADONE

1. Patients with ongoing injection drug use should be referred to a substance use specialist and reevaluated for HCV treatment at a later date (III).
2. Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy (II-1).
3. HCV treatment should be coordinated with substance abuse specialists (III).

Patients with Ongoing Alcohol Use

Alcohol is an important cofactor in the progression of HCV disease to cirrhosis and HCC (43). Thus, patients with hepatitis C should limit or abstain from alcohol consumption. Limited data suggest that heavy alcohol consumption of >80 g/day (approximately eight drinks or more per day) reduces HCV treatment response. It is unknown whether consuming less alcohol compromises HCV treatment response (44). In patients with recent alcohol consumption, there were higher treatment discontinuation rates; however, in those who completed HCV therapy, SVR was similar in drinkers and nondrinkers (45). Thus, alcohol users should not be excluded from antiviral therapy but treatment adherence should be stressed (9).

RECOMMENDATIONS IN PATIENTS WITH ONGOING ALCOHOL USE

1. Patients should be encouraged to decrease consumption or to abstain (III).

2. Patients should be referred for behavioral intervention to reduce alcohol use (III).
3. Antiviral therapy should be offered to patients regardless of prior alcohol use who otherwise meet criteria for therapy (II-2).
4. Alcohol consumption should be discouraged during antiviral treatment, because alcohol reduces adherence and treatment response (III).

African Americans

African Americans have lower response rates to peginterferon alfa and ribavirin than Caucasians (17, 19). In one study of genotype 1 patients treated with peginterferon alfa-2b plus ribavirin for 48 wk, SVR occurred in 19% of African Americans and 52% of Caucasians (17). In another study of genotype 1 patients treated with peginterferon alfa-2a plus ribavirin for 48 wk, SVR occurred in 26% of African Americans and 39% of Caucasians. Side effects were similar except for a higher incidence of neutropenia in African Americans, but this was not associated with increased risk of infection (19).

RECOMMENDATION IN AFRICAN AMERICANS

1. Antiviral therapy should be offered to patients regardless of race (III).

Patients with Body Mass Index >30 and Hepatic Steatosis

In RCTs of peginterferon alfa plus ribavirin, increased body weight was associated with decreased antiviral response (13, 14). Reasons for reduced response in obese patients are likely multifactorial. Obesity results in steatosis of the liver, which is associated with increased risk of fibrosis and decreased antiviral efficacy (46, 47).

Hepatic steatosis is often associated with metabolic syndromes (*e.g.*, insulin resistance/diabetes mellitus, hypertriglyceridemia) and with HCV genotype 3 infection (26). Metabolic disorders should be managed aggressively prior to interferon therapy, in part because interferon can aggravate these underlying medical conditions. Lifestyle changes (*e.g.*, exercise and weight loss) should be recommended as adjuncts to antiviral therapy. Even modest weight loss (5.9 kg) has been shown to decrease hepatic steatosis (48).

RECOMMENDATIONS IN OBESE PATIENTS AND THOSE WITH HEPATIC STEATOSIS

1. Patients with a BMI >30 should be considered for antiviral treatment (III).
2. Comorbid conditions common in obese patients such as diabetes, hypertension, and hyperlipidemia should be well controlled prior to initiation of antiviral therapy (III).

Patients with HIV/HCV Coinfection

All patients with HIV should be tested for and counseled about HCV. Conversely, those with HCV infection should also be offered HIV testing and counseling. Patients infected with both HIV and HCV may be at greater risk for liver disease progression than those with HCV infection alone, and thus the need for treatment of these individuals is high.

Three RCTs have demonstrated the superiority of peginterferon alfa plus ribavirin compared with interferon plus ribavirin for 48 wk in HIV/HCV coinfected patients (49–51). SVR was lower in this population than those reported in HCV-monoinfected patients, particularly for those with genotype 1 infection.

Peginterferon alfa-2a (180 mcg/wk) plus ribavirin (800 mg/day) is FDA-approved for this indication (52). However, HCV therapy is contraindicated in cirrhotic patients with a Child-Pugh score ≥6 (53). For genotype 1 patients coinfected with HIV, ribavirin dosing of 1,000–1,200 mg/day should be attempted because inadequate ribavirin doses likely contributed to lower observed SVR (49–51). Side effects including cytopenias are more common in HIV/HCV coinfected patients. For more information, see Management and Treatment of Hepatitis C Virus infection in HIV-infected Adults: Recommendations from the Veterans Affairs Hepatitis C Resource Program and National Hepatitis C Program Office (54).

RECOMMENDATIONS IN PATIENTS WITH HIV/HCV COINFECTION

1. Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy (III).
2. Patients should be treated with peginterferon alfa and ribavirin at doses similar to those with HCV monoinfection (III).
3. Patients should be treated with peginterferon alfa and ribavirin for at least 48 wk, regardless of genotype (III).
4. Concomitant use of didanosine (ddI) and ribavirin should be avoided (II-3).
5. Cytopenias related to HCV treatment are more common, and may require erythropoietin and granulocyte colony stimulating growth factors in order to continue therapy (III).
6. HIV/HCV coinfected patients with cirrhosis and a Child-Pugh score ≥6 should not receive HCV antiviral therapy (II-3).

Patients with Renal Disease including Hemodialysis

The prevalence of HCV antibodies in patients on chronic hemodialysis is 8.6% (55) and HCV infection is an independent risk factor for death in this population (56). Although interferon is contraindicated following kidney transplantation because of an increased risk of rejection, HCV therapy should be attempted in patients with end-stage renal disease who are being considered for transplantation.

Case series of interferon monotherapy in dialysis patients had an overall SVR of 33%, with SVR of 26% in genotype 1 patients (57). The role of peginterferon alfa in dialysis patients is being defined. A single dose study of peginterferon

alfa-2a in chronic hemodialysis revealed no added toxicity but clearance was reduced by 30% (58). In hemodialysis patients, peginterferon alfa-2b at 0.5 mcg/kg and 1.0 mcg/kg has been safely used, with the higher dose showing improved EVR but with increased side effects (59).

Both peginterferon alfa-2a and alfa-2b should be used cautiously when the creatinine clearance is <50 mL/min and doses should be renally adjusted (Table 5) (12, 60). Ribavirin is contraindicated when the creatinine clearance is <50 mL/min (11, 61). Virologic relapse and side effects are common with antiviral therapy in hemodialysis patients. Patients should be monitored closely for toxicity.

RECOMMENDATIONS IN PATIENTS WITH RENAL DISEASE

1. Patients should be considered for antiviral therapy with peginterferon alfa at doses modified for renal disease (Table 5) (II-2).
2. Ribavirin should be avoided with a creatinine clearance <50 mL/min (II-3).

Patients with Acute Hepatitis C

Acute HCV infection is rarely identified clinically because infection is asymptomatic in 85% of cases. Yet, treatment in the acutely infected patient is highly effective in preventing persistent infection (62). Studies of treatment for acute HCV infection have been limited.

If spontaneous viral clearance occurs, it is usually within the first few weeks of exposure. Several studies that delayed treatment for 12 wk after diagnosis did not appear to adversely affect SVR. This approach unnecessarily avoids therapy in those who would resolve spontaneously (63, 64). Studies with peginterferon alfa or interferon alfa monotherapy for 24 wk have resulted in SVR of 80–100%, suggesting that treatment duration may be shorter than for those with chronic HCV infection. Two small studies have suggested that ribavirin did not significantly augment treatment response in the acute setting (65, 66).

RECOMMENDATIONS IN PATIENTS WITH ACUTE HCV INFECTION

1. Patients should be observed for a period of 8–12 wk from time of initial exposure in order to monitor for spontaneous resolution of infection (III).
2. For those who fail to resolve infection spontaneously, treatment should be initiated with peginterferon alfa alone for 24 wk, regardless of genotype (II-1).

Patients with Decompensated Cirrhosis

Once clinical complications of cirrhosis develop (*e.g.*, gastroesophageal bleeding, ascites, encephalopathy, jaundice, HCC), liver transplantation is the treatment of choice. In general, HCV therapy is contraindicated in this population because of increased risk for life-threatening bacterial infection and further hepatic decompensation. One large case series from a single center reported using a low, accelerating dose regimen (LADR) of standard interferon and ribavirin in 102 patients (67). SVR was achieved in 11% and 50% of those with genotype 1 and genotype 2/3 infections, respectively (67).

In 2003, an expert panel proposed that patients with HCV cirrhosis and a Child-Pugh score ≤7 and MELD score ≤18 should be considered for antiviral therapy. However, in those with Child-Pugh scores >11 or MELD scores >25, treatment is contraindicated. Those with intermediate scores should be considered on a case-by-case basis (68). Treatment-naïve patients with favorable predictors of response such as genotype 2 or 3 infection should be considered for therapy with low Child-Pugh and MELD scores, despite a history of clinical complications of liver disease. In those with genotype 1 infection, the risk-benefit ratio is lower, since the likelihood of viral clearance with therapy is less. Given the limited safety experience of antiviral therapy in patients with hepatic decompensation, treatment should only be undertaken in centers with specialized expertise. If peginterferon alfa is administered, it should be initiated at a reduced dose, with extremely close follow-up and with early use of growth factors to manage treatment-associated cytopenias. Ribavirin, if administered, should be initiated at reduced doses particularly if there is underlying renal insufficiency but is contraindicated if the clearance creatinine is <50 mL/min.

RECOMMENDATIONS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

1. Liver transplantation is the optimal treatment in patients with decompensated cirrhosis (II-3).
2. Antiviral therapy is contraindicated in most patients with decompensated cirrhosis (II-3).
3. Interferon-based therapy in combination with ribavirin may be considered in patients awaiting liver transplantation with a Child-Pugh score ≤7 and a MELD score ≤18 (II-1).
4. If antiviral therapy is undertaken, reduced interferon doses should be used and growth factors should be given to counteract treatment-associated cytopenias (III).

Patients with a History of Solid Organ Transplantation

In general, interferon therapy is contraindicated in renal, cardiac, or pulmonary transplant recipients because of an increased risk of severe allograft rejection. However, HCV infection is considered an absolute contraindication to transplantation for certain solid organs, such as heart and lung. Thus, eradication of HCV infection in patients who are otherwise good candidates for solid organ transplantation may enhance transplant candidacy.

After liver transplantation for HCV-related disease, graft reinfection is virtually universal. Patients with more than stage I fibrosis on liver histology from recurrent HCV disease

may be considered for antiviral therapy under the guidance of a transplant specialist. Limited data suggest that treatment response in liver allograft recipients is lower than in immunocompetent individuals (69–72). Overall SVR was approximately 20–30% with peginterferon alfa with or without ribavirin for 48 wk; however, SVR may be somewhat higher with genotype 2 or 3 infection (70, 72). Dose reductions for cytopenias are common and early growth factor support is often necessary. If antiviral therapy is initiated, reduced interferon and ribavirin doses should be used with incremental increases until a tolerable dose is reached (72). Based on small case series, the incidence of acute cellular rejection associated with peginterferon alfa appears higher than for standard interferon, and patients must be closely monitored and immunosuppression maintained (73). The optimal treatment regimen remains to be defined.

RECOMMENDATIONS IN PATIENTS FOLLOWING SOLID ORGAN TRANSPLANTATION

1. Interferon-based antiviral therapy is contraindicated following heart, lung, or kidney transplantation (II-3).
2. In patients with biopsy-proven chronic HCV disease following liver transplantation, antiviral therapy with peginterferon alfa and ribavirin for 48 wk may be considered (II-1).
3. If treatment is given following liver transplantation, peginterferon alfa and ribavirin should be initiated at reduced doses (II-3).
4. Toxicities of antiviral therapy in liver transplant recipients should be managed with frequent monitoring, dose reductions, and growth factor support (III).
5. Liver transplant recipients on antiviral therapy should be monitored closely for evidence of rejection and antiviral therapy should be stopped if rejection is documented (II-3).
6. Preemptive antiviral therapy early posttransplantation in patients without histological recurrence should be avoided (II-3).

Monitoring Treatment Safety and Efficacy

Almost all patients receiving hepatitis C antiviral therapy will experience some treatment-related adverse effects. Common adverse effects of therapy include flu-like symptoms, fatigue, bone marrow suppression, mood disorders, gastrointestinal upset, dermatological reactions, and alopecia.

Close clinical and laboratory monitoring is crucial throughout treatment. Poor tolerability can lead to early treatment discontinuation. Clinicians can promote adherence by counseling patients on the recognition and management of treatment-related adverse effects. Patients should be reassured that most treatment-related adverse effects can be treated or minimized.

Periodic laboratory monitoring is necessary in all patients on antiviral therapy (Table 4). Increasing the frequency of testing is advised in patients with significant reductions in white blood cell count, hematocrit, or platelet count or in those who experience significant clinical adverse events. Quantitative and/or qualitative HCV RNA should be performed at 4, 12, and 24 wk on treatment, at the end of treatment, and 24 wk after completion of therapy (section "On-Treatment Predictors"). Patients with a history of depression and substance use should be followed closely. Standardized screening instruments can be used to supplement the clinical exam (section "Psychiatric Assessment").

RECOMMENDATIONS FOR TREATMENT MONITORING

1. Patients should be monitored for HCV treatment-related adverse effects at intervals of 1–2 wk early in the course of therapy, and at intervals of 1–2 months during treatment once adverse effects stabilize (II-1).
2. Patient adherence to therapy should be assessed at every visit (III).
3. Serum markers of biochemical and virological response should be measured, and treatment-related adverse effects should be monitored at intervals as outlined in Table 4 (II-1).
4. Quantitative and/or qualitative virological assays should be performed at 4, 12, and 24 wk on therapy, end of treatment, and at 24 wk after treatment completion (II-1).
5. Patients should be evaluated for depression and suicidal ideations at each visit (II-3).
6. Patients should be counseled about avoiding pregnancy by using two forms of contraception during treatment as well as for 6 months posttreatment, and pregnancy tests should be performed as indicated in Table 4 (III).
7. Patients should be assessed for alcohol intake and illicit drug use at every visit (III).

Dose Modifications

Peginterferon alfa and ribavirin dose reductions are outlined in Tables 8 and 9. In practice, peginterferon alfa dose reductions are done in a step-wise approach (*e.g.*, for peginterferon alfa-2a from 180 mcg to 135 mcg to 90 mcg, and for peginterferon alfa-2b from 1.5 mcg/kg to 1.0 mcg/kg to 0.5 mcg/kg). In practice, ribavirin dose reductions often occur in 200-mg decrements (Table 9). Limiting dose reductions may improve SVR, especially for patients with genotype 1 infection. In a retrospective analysis, genotype 1-infected patients who received at least 80% of interferon and ribavirin doses for at least 80% of the intended duration were more likely to achieve SVR than those who did not fulfill these criteria (74). The timing and degree of both peginterferon alfa and ribavirin dose reduction on SVR are under analysis (31). Supportive therapies such as growth factors to minimize dose reduction may be considered (section "Growth Factors").

Table 8. General Guidelines for Peginterferon Dose Reduction or Discontinuation

Laboratory Value	Manufacturer Package Insert Recommendations
WBC	
$<1.5 \times 10^9$/L	Reduce peginterferon alfa-2b dose by 50% and reevaluate
$<1.0 \times 10^9$/L	Discontinue peginterferon alfa-2b until resolution
ANC*	
$<0.75 \times 10^9$/L	Peginterferon alfa-2a: reduce dose to 135 mcg/wk and reevaluate Peginterferon alfa-2b: reduce dose by 50% and reevaluate
$<0.50 \times 10^9$/L	Discontinue peginterferon alfa until resolution
Platelets†	
<80 k/mm^3	Peginterferon alfa-2b: reduce dose by 50% and reevaluate
<50 k/mm^3	Peginterferon alfa-2a: reduce dose to 90 mcg/wk and reevaluate Peginterferon alfa-2b: discontinue until resolution
<25 k/mm^3	Peginterferon alfa-2a: discontinue until resolution

ANC = absolute neutrophil count; WBC = white blood cell count.
*If dose is maintained outside of manufacturer recommendations, monitor ANC more frequently and counsel patient on neutropenic precautions. In cirrhotic, postliver transplantation or HIV/HCV coinfected patients who remain neutropenic despite dose reduction, consider starting GCSF until resolution.
†If dose is maintained outside of manufacturer recommendations, monitor platelet counts more frequently and for signs and symptoms of unusual bleeding or bruising.

Table 9. General Guidelines for Ribavirin Dose Reduction or Discontinuation

Parameter	Recommendation
Hemoglobin (Hb)	
<11.0 but >10 g/dL	No change in ribavirin dose if patient has minimal symptoms In a symptomatic patient, consider decreasing ribavirin by 200 mg/day and/or starting an erythropoietin growth factor
<10.0 but >8.5 g/dL	Decrease ribavirin by 200 mg/day and/or consider starting an erythropoietic growth factor Recheck Hb levels at least every 2 wk or more frequently if indicated
<8.5 g/dL	Discontinue until resolution

In stable underlying cardiac disease, reduce ribavirin by 200 mg/day for ≥ 2 g/dL drop in Hb over a 4-wk period.
If the Hb level is <12 g/dL after 4 wk of dose reduction, discontinue ribavirin until resolution and reevaluation.

RECOMMENDATION FOR DOSE MODIFICATIONS

1. Peginterferon alfa and/or ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, platelets, or hemoglobin (Hb), as outlined in Tables 8 and 9 (II-1).

Growth Factors

ERYTHROPOIETIN. Recombinant erythropoietin is FDA-approved for treatment of anemia in a variety of clinical situations, but is not approved for anemia associated with HCV therapy. Mean decreases in Hb in patients taking ribavirin are 2–3 g/dL, declines that often lead to symptoms of fatigue and shortness of breath. Options for managing HCV treatment-related anemia include ribavirin dose reduction, ribavirin dose discontinuation, and/or addition of an erythropoietic growth factor.

Ribavirin dose reductions to manage treatment-related anemia may reduce SVR, though the impact on SVR of $\leq 20\%$ dose reduction is unclear. Therefore, maintaining $\geq 80\%$ of the original ribavirin target dose, especially during the first 12 wk of therapy, is reasonable. Clearly, early discontinuation of ribavirin results in a significant reduction in SVR (31).

The role of erythropoietin to limit ribavirin dose reduction or discontinuation has been explored as a strategy to overcome treatment-related anemia. Erythropoietin therapy appears to maintain ribavirin doses and improve quality of life in patients who develop anemia related to HCV therapy (75, 76). However, the impact on SVR still remains to be determined.

Erythropoietin may be more beneficial in patients with bone marrow suppression from HIV infection or from exogenous immunosuppression following liver transplantation. In addition, erythropoietin may be given prior to HCV therapy to patients with mild anemia (Hb <11 g/dL) who might otherwise not tolerate ribavirin, particularly in those with advanced HCV disease. If erythropoietin is administered, the initial dose of epoetin alfa is 40,000 units subcutaneously once weekly (titrated up to 60,000 units subcutaneously once weekly) or darbepoetin alfa 200 mcg subcutaneously every 2 wk (titrated up to 300 mcg subcutaneously every 2 wk). Hemogloblin and hematocrit levels should be monitored at least every 2 to 4 wk. Based on the manufacturers' warning of risks for cardiovascular and thrombotic events, the dose should be reduced if the baseline Hb increases by >1 g/dL in any 2-wk period and if Hb levels exceed 12 g/dL (53, 77, 78).

RECOMMENDATIONS FOR ERYTHROPOIETIN USE

1. Erythropoietin may be administered in patients with symptomatic anemia related to ribavirin therapy and/or to limit anemia-related ribavirin dose reductions or discontinuations, particularly in those who are cirrhotic, postliver transplantation, and HIV/HCV coinfected (I).
2. Erythropoietin may be given preemptively in patients with pretreatment anemia (Hb <11 g/dL) in order to facilitate ribavirin dosing, particularly in those with advanced HCV disease (III).

GRANULOCYTE COLONY STIMULATING FACTOR (GCSF). Moderate neutropenia is a common adverse effect of peginterferon alfa, resulting in ANC <750/mm^3 in

approximately 20% of those treated. Peginterferon alfa doses of <60% of the original dose appear to reduce SVR (31). Limited data suggest that GCSF increases white blood cells and may permit administration of higher interferon doses in managing interferon-induced neutropenia in patients with HCV and/or undergoing liver transplantation (69, 79–81); however, improvements in SVR have not been demonstrated. Furthermore, it is unclear whether the risk of infection is related to the degree of interferon-induced neutropenia (82).

GCSF may be appropriate for patients who are cirrhotic, postliver transplant, or HIV/HCV coinfected with an ANC $<500/mm^3$, particularly if neutropenia persists despite peginterferon alfa dose reduction. Typical dosing of GCSF is 300 mcg subcutaneously once to twice weekly; doses can be titrated to desired ANC $>500/mm^3$ based on ANC nadir levels (69).

RECOMMENDATIONS FOR GCSF USE

1. GCSF should not be given as primary therapy to prevent peginterferon alfa dose reductions (III).
2. GCSF may be administered in patients who are cirrhotic, postliver transplantation, or HIV/HCV coinfected with an ANC $<500/mm^3$, particularly if neutropenia persists despite peginterferon alfa dose reduction (III).

THROMBOPOIETIN. As liver disease worsens, serum thrombopoietin levels decline (83). Limited experience with thrombopoietin in HCV-infected patients on antiviral therapy suggests that platelet counts increased, although fluid retention, an adverse effect of thrombopoietin, was common (84). Until additional safety and efficacy data are available, thrombopoietin cannot be recommended for patients on interferon therapy.

SUMMARY OF CURRENT RECOMMENDATIONS

The management of HCV disease is evolving. We have attempted to provide a guide for the care of patients with hepatitis C. It is crucial to facilitate a multidisciplinary team who can respond to and provide HCV-specific care and treatment. Treatment should be provided to individuals who meet criteria for antiviral therapy and who are at greatest risk for progressive liver disease. The relative risks and benefits of beginning therapy immediately, delaying therapy, or deferring treatment indefinitely need to be carefully considered in each patient.

RECOMMENDATIONS IN PATIENTS BEING CONSIDERED FOR HCV THERAPY

1. All patients with chronic HCV infection should be evaluated as potential candidates for HCV antiviral treatment.
2. Patients should undergo pretreatment assessments as summarized in Table 2.
3. Patients with more than portal fibrosis, including those with compensated cirrhosis, who lack contraindications, should be offered antiviral therapy.
4. Patients with contraindications summarized in Table 3 should not begin HCV antiviral therapy.
5. Patients should be counseled on their likelihood of achieving SVR prior to initiating therapy.

RECOMMENDATIONS FOR TREATMENT IN PREVIOUSLY UNTREATED PATIENTS

1. Peginterferon alfa plus ribavirin is the standard of care for the treatment of chronic HCV.
2. The peginterferon alfa-2a standard dose is 180 mcg/wk and the peginterferon alfa-2b standard dose is 1.5 mcg/kg/wk administered subcutaneously in combination with ribavirin.
3. In patients with genotype 1 infection, the ribavirin dose is 1,000 mg/day if ≤75 kg or 1,200 mg/day if >75 kg in combination with peginterferon alfa.
4. In patients with genotype 2 or 3 infection, the ribavirin dose is 800 mg/day in combination with peginterferon alfa.

RECOMMENDATION FOR MONOTHERAPY WITH PEGINTERFERON ALFA

1. Peginterferon alfa monotherapy (Table 5) may be used to treat patients with contraindications to ribavirin (Table 3).

RECOMMENDATIONS FOR VIROLOGIC END POINTS ON TREATMENT

1. RVR and EVR should be measured.
2. Treatment may be discontinued in those failing to achieve an EVR.
3. In patients with advanced liver disease, treatment may be continued even without an EVR, depending on tolerance of therapy.

RECOMMENDATIONS FOR TREATMENT DURATION IN GENOTYPE 1 INFECTION

1. For patients who achieve RVR, 24 wk of treatment may be sufficient.
2. For patients who fail to achieve RVR but achieve EVR, 48 wk is usually sufficient.
3. For patients without an RVR and/or EVR, extending duration to 72 wk may be beneficial if virus is undetectable by 24 wk of therapy.
4. For patients who continue to have detectable virus at 24 wk, treatment should be discontinued if the goal of therapy is viral eradication.

RECOMMENDATIONS FOR TREATMENT DURATION IN GENOTYPE 2 OR 3 INFECTION

1. Standard treatment duration is typically 24 wk.
2. In patients with a low pretreatment RNA (≤600,000 IU/mL) who are not tolerating therapy, 16 wk of treatment may be sufficient.
3. For patients with genotype 3 infection and a baseline HCV RNA >600,000 IU/mL or steatosis, treatment beyond 24 wk may improve response.

RECOMMENDATIONS IN PATIENTS WITH CIRRHOSIS

1. Patients with compensated cirrhosis and adequate neutrophil (ANC >1.5 k/mm^3) and platelet (>70 k/mm^3) counts should be treated with peginterferon alfa plus ribavirin at standard doses.
2. In patients who do not achieve viral suppression with combination therapy, long-term maintenance therapy with low-dose peginterferon alfa may be considered on an individual basis.

RECOMMENDATIONS IN NONRESPONDERS AND RELAPSERS

1. For nonresponders and relapsers to *interferon with or without ribavirin*, retreatment with peginterferon alfa and ribavirin should be considered on an individual basis.
2. For nonresponders and relapsers to *peginterferon alfa plus ribavirin*, retreatment with peginterferon alfa and ribavirin may be considered *only if* substantial improvements in treatment dose or adherence can be made.
3. If retreatment is undertaken, the duration is at least 48 wk in those who demonstrate viral response on therapy.

RECOMMENDATIONS IN PATIENTS WITH MILD DISEASE

1. Treatment should be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy, unless the patient elects to undergo therapy with a goal of viral eradication.
2. If treatment is deferred, liver biopsy may be repeated in 3–5 yr if results would change management.
3. In patients with histologic evidence of disease progression, treatment should be considered.

RECOMMENDATIONS IN PATIENTS WITH NORMAL ALT

1. Liver biopsy to stage fibrosis should be performed prior to starting treatment regardless of ALT level, especially in patients with genotype 1 infection.
2. Treatment should be considered in patients with more than portal fibrosis on liver biopsy, regardless of ALT values.

RECOMMENDATION IN PATIENTS WITH HCV GENOTYPE 4 INFECTION

1. Appropriate candidates should be treated with peginterferon alfa-2a 180 mcg/wk or peginterferon alfa-2b 1.5 mcg/kg/wk plus ribavirin 1,000 or 1,200 mg/day for 48 wk.

RECOMMENDATIONS IN PATIENTS >65 yr AND/OR WITH COMORBID CONDITIONS

1. In patients with limited life expectancy from significant comorbid conditions, antiviral therapy should be deferred.
2. In patients with significant comorbid conditions that will be exacerbated by peginterferon alfa and ribavirin, treatment should be deferred.
3. In otherwise healthy patients, treatment should be considered regardless of age.

RECOMMENDATIONS FOR PATIENTS ON METHADONE

1. Patients with ongoing injection drug use should be referred to a substance use specialist and reevaluated for HCV treatment at a later date.
2. Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy.
3. HCV treatment should be coordinated with substance abuse specialists.

RECOMMENDATIONS IN PATIENTS WITH ONGOING ALCOHOL USE

1. Patients should be encouraged to decrease consumption or to abstain.
2. Patients should be referred for behavioral intervention to reduce alcohol use.
3. Antiviral therapy should be offered to patients regardless of prior alcohol use who otherwise meet criteria for therapy.
4. Alcohol consumption should be discouraged during antiviral treatment, because alcohol reduces adherence and treatment response.

RECOMMENDATIONS IN AFRICAN AMERICANS, OBESE PATIENTS, AND THOSE WITH HEPATIC STEATOSIS

1. Antiviral therapy should be made available to patients regardless of race.
2. Patients with a BMI >30 should be considered for antiviral treatment.
3. Comorbid conditions common in obese patients such as diabetes, hypertension, and hyperlipidemia should be well controlled prior to initiation of antiviral therapy.

RECOMMENDATIONS IN PATIENTS WITH HIV/HCV COINFECTION

1. Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for antiviral therapy.
2. Patients should be treated with peginterferon alfa and ribavirin at doses similar to those with HCV monoinfection.
3. Patients should be treated with peginterferon alfa and ribavirin for at least 48 wk, regardless of genotype.
4. Concomitant use of ddI and ribavirin should be avoided.
5. Cytopenias related to HCV treatment are more common, and may require erythropoietin and granulocyte colony stimulating growth factors in order to continue therapy.
6. HIV/HCV coinfected patients with cirrhosis and a Child-Pugh score $\geq$6 should not receive HCV antiviral therapy.

RECOMMENDATIONS IN PATIENTS WITH RENAL DISEASE

1. Patients should be considered for antiviral therapy with peginterferon alfa at doses modified for renal disease (Table 5).
2. Ribavirin should be avoided with a creatinine clearance $<$50 mL/min.

RECOMMENDATIONS IN PATIENTS WITH ACUTE HCV INFECTION

1. Patients should be observed for a period of 8–12 wk from the time of initial exposure in order to monitor for spontaneous resolution of infection.
2. For those who fail to resolve infection spontaneously, treatment should be initiated with peginterferon alfa alone for 24 wk regardless of genotype.

RECOMMENDATIONS IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

1. Liver transplantation is the optimal treatment in patients with decompensated cirrhosis.
2. Antiviral therapy is contraindicated in most patients with decompensated cirrhosis.
3. Interferon-based therapy in combination with ribavirin may be considered in patients awaiting liver transplantation with a Child-Pugh score $\leq$7 and a MELD score $\leq$18.
4. If antiviral therapy is undertaken, reduced interferon doses should be used and growth factors should be given to counteract treatment-associated cytopenias.

RECOMMENDATIONS IN PATIENTS FOLLOWING SOLID ORGAN TRANSPLANTATION

1. Interferon-based antiviral therapy is contraindicated following heart, lung, or kidney transplantation.
2. In patients with biopsy-proven chronic HCV disease following liver transplantation, antiviral therapy with peginterferon alfa and ribavirin for 48 wk may be considered.
3. If treatment is given following liver transplantation, peginterferon alfa and ribavirin should be initiated at reduced dose.
4. Toxicities of antiviral therapy in liver transplant recipients should be managed with frequent monitoring, dose reductions, and growth factor support.
5. Liver transplant recipients on antiviral therapy should be monitored closely for evidence of rejection, and antiviral therapy should be stopped if rejection is documented.
6. Preemptive antiviral therapy early posttransplantation in patients without histological recurrence should be avoided.

RECOMMENDATIONS FOR TREATMENT MONITORING

1. Patients should be monitored for HCV treatment-related adverse effects at intervals of 1–2 wk early in the course of therapy, and at intervals of 1–2 months during treatment once adverse effects stabilize.
2. Patient adherence to therapy should be assessed at every visit.
3. Serum markers of biochemical and virological responses should be measured, and treatment-related adverse effects should be monitored at intervals as outlined in Table 4.
4. Quantitative and/or qualitative virological assays should be performed at 4, 12, and 24 wk on therapy, end of treatment, and at 24 wk after treatment completion.
5. Patients should be evaluated for depression and suicidal ideations at each visit.
6. Patients should be counseled about avoiding pregnancy by using two forms of contraception during treatment as well as for 6 months posttreatment, and pregnancy tests should be performed as indicated in Table 4.
7. Patients should be assessed for alcohol intake and illicit drug use at every visit.

RECOMMENDATION FOR DOSE MODIFICATIONS

1. Peginterferon alfa and/or ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, platelets, or Hb, as outlined in Tables 8 and 9.

RECOMMENDATIONS FOR GROWTH FACTOR USE

1. Erythropoietin may be administered in patients with symptomatic anemia related to ribavirin therapy and/or to limit anemia-related ribavirin dose reductions or

discontinuations, particularly in those who are cirrhotic, postliver transplantation, and HIV/HCV coinfected.
2. Erythropoietin may be given preemptively in patients with pretreatment anemia (Hb <11 g/dL) in order to facilitate ribavirin dosing, particularly in those with advanced HCV disease.
3. GCSF should not be given as primary therapy to prevent peginterferon alfa dose reductions.
4. GCSF may be administered in patients who are cirrhotic, postliver transplantation, or HIV/HCV coinfected with an ANC <500/mm^3, particularly if neutropenia persists despite peginterferon alfa dose reduction.

CONCLUDING COMMENTS

Peginterferon alfa plus ribavirin represents the best current treatment available. Yet these therapies have significant toxicities and they are effective in only 50% of those treated. Thus, safe and effective therapies need to be developed for those patients who are currently inadequately served. Through continued HCV research, treatment response should improve, adverse effects should be reduced, and populations for whom treatment are appropriate should expand. As these advances occur, new recommendations will be made.

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Received February 10, 2006; accepted May 03, 2006.

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CONFLICT OF INTEREST

The authors have no relevant financial interests in this manuscript. Helen S. Yee, Pharm.D. is employed by the Department of Veterans Affairs Medical Center, San Francisco and is affiliated with the University of California, San Francisco. Sue L. Currie, M.A., is employed by the University of California, San Francisco and is affiliated with Department of Veterans Affairs Medical Center, San Francisco. Jama M. Darling, M.D., was employed by the Department of Veterans Affairs Medical Center, San Francisco at the time these guidelines were written and is currently employed by the University of North Carolina at Chapel Hill. Teresa L. Wright, M.D., was employed by the Department of Veterans Affairs Medical Center, San Francisco at the time these guidelines were written and is currently employed by Roche Diagnostics.