

# UPDATE ON PHARMACOTHERAPY OF CHRONIC HEPATITIS B AND C

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## Learning Objectives

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1. Demonstrate an understanding of laboratory testing and serologic or virologic markers used to diagnose and monitor hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.
2. Evaluate patients with chronic HBV or HCV infection and determine whether initiation of treatment is appropriate.
3. Analyze factors that contribute to disease progression and factors that may affect treatment responses.
4. Distinguish between advantages and disadvantages of current treatment options for chronic HBV and HCV infection.
5. Design individualized treatment regimens for patients with chronic HBV and HCV infection based on clinical characteristics and prognostic factors.
6. Develop strategies to modify or change treatment regimens based on individual patient response.
7. Devise a plan to manage adverse effects of treatment and optimize treatment responses during chronic HBV and HCV treatment.

## Introduction

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Viral hepatitis is a global health problem and an important cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. At least 350 million people worldwide have chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg]) for more than 6 months), including up to 1.4 million people in the United States. Vaccination and public health measures during the past 15–20 years have reduced the incidence of HBV infection in the United States, but the infection remains an important health problem primarily because of individuals immigrating to the United States from areas of high prevalence.

Globally, more than 170 million people are infected with hepatitis C virus (HCV). In the United States, HCV is the most common chronic bloodborne infection, a leading cause of end-stage liver disease, and the most common indication

for liver transplantation. According to the Centers for Disease Control and Prevention (CDC), at least 4.1 million Americans have been infected with HCV and, of these, 3.2 million are chronically infected. Since its identification in 1989 and the availability of sensitive blood screening tests in 1992, the incidence of HCV infection has declined considerably. The CDC estimates that a mean of 232,000 new HCV infections occurred per year in the 1980s compared with 19,000 estimated new infections in 2006. However, the prevalence of chronic HCV infection has increased and is likely much higher than current estimates. In addition, because it may take several decades for complications from HCV infection to develop, the true magnitude of burden from HCV-related chronic liver disease has yet to be realized. Complications from HCV-induced cirrhosis (including liver-related deaths, hepatic decompensation, and hepatocellular carcinoma) are expected to rise dramatically in the next 5–10 years.

Infections with HBV and HCV are important causes of chronic liver disease and hepatocellular carcinoma. Thus, there is a clear and urgent need both to prevent transmission and identify chronically infected individuals, as well as to implement measures that slow or prevent progression to cirrhosis, hepatocellular carcinoma, and end-stage liver disease. This chapter provides an update on the treatment of adults with chronic HBV and HCV infection. Because of this limited scope, interested readers are encouraged to consult additional resources for more comprehensive information on these topics.

## Hepatitis B Virus

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Hepatitis B virus is a hepatotropic DNA virus. Eight genotypes (A–H) have been identified with various geographic distributions. Currently, HBV genotype testing is not routinely performed in clinical practice, but preliminary data suggest that genotypes A and B are associated with higher virologic response rates to treatment with interferons (IFNs), whereas genotype C is associated with more severe liver disease and increased risk of hepatocellular carcinoma. Transmission of HBV can occur after percutaneous, perinatal, or sexual exposure, as well

## Abbreviations in This Chapter

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IFN	Interferon
pegIFN	Pegylated (polyethylene glycol-attached) interferon

as by prolonged close personal contact (e.g., open cuts or wounds, sharing toothbrushes or razors).

In September 2008, the CDC published updated and expanded guidelines for HBV testing. All pregnant women and individuals at high risk of HBV infection should be screened (Table 1-1). Age and immune status play an important role in determining the likelihood of chronic infection. After an acute exposure, chronic HBV infection occurs in less than 5% of immunocompetent adults, compared with 90% to 95% of newborn infants (who are exposed to HBV through perinatal transmission) and 25% to 30% of young children. Immunosuppressed individuals, regardless of age, are more likely to develop chronic HBV infection after acute exposure. The natural course of chronic HBV infection is complex, and the wide variability in clinical characteristics has led to its classification into several categories or phases (Table 1-2).

### Evaluation of Patients with Chronic HBV Infection

After a patient receives an initial diagnosis of chronic HBV infection, laboratory tests are used to monitor the disease course and assess the need for antiviral treatment.

Current treatment options suppress but do not eradicate HBV, and their long-term efficacy is limited by the development of resistance to antiviral drugs. It is essential to carefully consider patient age, liver disease severity, likelihood of treatment response, potential adverse effects of treatment, and risk of drug resistance. Treatment is not recommended for patients with minimal disease or for those who are unlikely to achieve a sustained response, such as inactive carriers and hepatitis B e antigen (HBeAg)-positive patients in the immune-tolerant phase (particularly young patients). The presence of HBeAg indicates active viral replication; patients who are HBeAg-positive often have high serum HBV DNA concentrations and are considered highly infectious. The immune-tolerant phase of chronic HBV infection is characterized by HBeAg-positivity and high HBV DNA concentrations but absence of liver disease (Table 1-2). Because of the fluctuating nature of chronic HBV infection, patients initially not considered for treatment still require continued clinical and laboratory monitoring every 3–6 months and hepatocellular carcinoma screening every 6–12 months. Practice guidelines (Table 1-3) and algorithms for the management of chronic HBV infection are periodically updated and published by expert panels of hepatologists as well as national and international organizations.

Several laboratory tests are used to evaluate patients with chronic HBV infection, but recent data focus on the clinical use of serum HBV DNA and an awareness of the limitations of serum alanine aminotransferase (ALT) concentration. Serum HBV DNA concentration identifies candidates for treatment, is essential to measure antiviral treatment response, and provides a marker for early detection of antiviral resistance during therapy. Several reports suggest HBV DNA concentration may be more predictive of cirrhosis and hepatocellular carcinoma than serum ALT concentration. In a recent landmark trial, HBV DNA concentrations greater than  $1 \times 10^4$  copies/mL were shown to be a strong predictor of risk for hepatocellular carcinoma independent of HBeAg,

**Table 1-1. People Who Should Be Screened for HBV and/or HCV Infection**

Hepatitis B*	Hepatitis C
People born in geographic areas with intermediate or high endemicity (HBsAg prevalence $\geq$ 2%)	Illicit injection drug users (current or past)
People born in the United States and not vaccinated as infants whose parents were born in a geographic area with high HBsAg prevalence ( $\geq$ 8%)	People with hemophilia who received clotting factor concentrates before 1987
Household and sexual contacts of HBsAg-positive people	People who received an organ transplant before 1992
People receiving cytotoxic or immunosuppressive therapy	People who received a blood transfusion before 1992
Illicit injection drug users (current or past)	People with HBV or HIV infection
People with elevated AST or ALT of unknown etiology	People with elevated AST or ALT of unknown etiology
Hemodialysis patients (current and past)	Hemodialysis patients (current and past)
Health care workers with occupational exposure	Health care workers with occupational exposure
Men who have sex with men	Children born to women with HCV infection
People with HCV or HIV infection	
Infants born to HBsAg-positive mothers	
All pregnant women	

\*Seronegative people should be vaccinated.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

**Table 1-2. Phases in Natural History of Chronic Hepatitis B**

Phase	ALT	Liver Histology	HBV DNA	HBeAg	HBsAg
Immune tolerance	Normal or minimal elevation	Minimal activity, scant fibrosis	High ( $10^8$ – $10^{11}$ copies/mL)	Present	Present
HBeAg-positive chronic hepatitis B	Elevated, usually persistent	Active with variable amounts of fibrosis	High ( $10^6$ – $10^{10}$ copies/mL)	Present	Present
HBeAg-negative chronic hepatitis B	Elevated, usually fluctuating	Active with variable amounts of fibrosis	Moderate; often fluctuating ( $10^3$ – $10^8$ copies/mL)	Absent	Present
Inactive carrier state	Normal	Inactive with variable, usually minimal fibrosis	Low or undetectable ( $< 10^4$ copies/mL)	Absent	Present
Recovery	Normal	Inactive with scant amounts of fibrosis	Undetectable in serum (possible low concentrations in liver)	Absent	Absent

ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid.

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serum ALT concentration, and liver cirrhosis. Quantitative HBV DNA values are now standardized and reported in international units per milliliter (IU/mL). Most commercial assays also provide a conversion factor to determine the equivalent number of copies (1 IU/mL = about 5 or 6 copies/mL for most assays). Ideally, the most sensitive assay with the broadest dynamic range should be used for longitudinal HBV DNA monitoring, and all patients with chronic HBV infection should be consistently monitored using the same assay.

Serum ALT concentration is an indicator of neuroinflammatory activity but, unlike serum HBV DNA, the serum ALT concentration is not always a reliable predictor of liver disease progression. Several recent reports have demonstrated that despite persistently normal ALT concentrations, 12% to 43% of patients with chronic HBV infection had stage 2 or greater fibrosis on liver biopsy (particularly patients older than 40 years). In addition, although elevated ALT concentrations typically suggest a more rapid rate of disease progression and hepatocellular carcinoma, one study showed more than 80% of patients with hepatocellular carcinoma had ALT concentrations less than 45 IU/L. Increased awareness of the limitations of serum ALT concentration has led many clinicians to perform liver biopsy earlier in selected patients. Moreover, based on results of recent studies, including a large prospective cohort of more than 140,000 patients between 35 years and 59 years of age, many experts now recommend lowering the upper limit of normal for serum ALT concentration and aspartate aminotransferase (AST) concentration from the current 40–50 IU/L to 30 IU/L and 19 IU/L for men and women, respectively.

#### HBeAg-Positive Chronic HBV Infection

The presence of serum HBeAg indicates active viral replication and is often associated with high serum HBV DNA concentrations and increased risk of hepatocellular carcinoma. Patients with HBeAg-positive chronic HBV infection should be considered for treatment if the HBV DNA concentration is greater than 20,000 IU/mL and either

serum ALT concentration is greater than 2 times the upper limit of normal or liver biopsy indicates moderate to severe hepatitis. If HBeAg-positive patients have compensated liver disease, treatment initiation may be delayed 3–6 months to determine if spontaneous HBeAg seroconversion to hepatitis B e antibody occurs; however, if patients become jaundiced or if the serum ALT concentration increases significantly, treatment should be promptly initiated.

In patients with high viral loads and evidence of continuing active replication, drugs with rapid onset of action and low resistance rates are preferred. Patients with HBeAg-positive chronic HBV infection and HBV DNA concentrations greater than 20,000 IU/mL but minimally elevated serum ALT concentration are typically not treated; these patients are believed to be in the immune-tolerant phase of infection and therefore have low risk of complications. Similarly, HBeAg-positive patients with chronic HBV infection, HBV DNA concentrations less than 20,000 IU/mL, and normal serum ALT concentrations are also not typically treated. Liver biopsy should be considered in HBeAg-positive patients older than 40 years with either fluctuating or normal ALT concentrations. If the liver biopsy reveals severe inflammation or significant fibrosis, treatment should be considered.

#### HBeAg-Negative Chronic HBV Infection

In patients with chronic HBV infection, loss of HBeAg or HBeAg seroconversion to hepatitis B e antibody may occur spontaneously or during antiviral therapy. However, absence of HBeAg may also be seen in patients who have active viral replication but, because of mutations in the precore or core promoter regions of the HBV genome, HBeAg either is not produced or is only poorly produced. Assessing treatment outcomes of patients with HBeAg-negative chronic HBV infection is considerably more challenging than patients with HBeAg-positive chronic HBV infection because there are fewer defined end points. In patients who are HBeAg-negative, HBeAg loss or seroconversion cannot be used to assess treatment response; therefore, ALT and HBV DNA

**Table 1-3. Recommendations for Treatment of Chronic Hepatitis B<sup>a</sup>**

HBeAg	HBV DNA(PCR)	ALT	Treatment Strategy
Positive	> 20,000 IU/mL	≤ 2 × ULN	Low efficacy with currently available treatment; observe Consider treatment if ALT becomes elevated Consider biopsy in people older than 40 years, if ALT persistently high normal to 2 × ULN, or with family history of hepatocellular carcinoma Consider treatment if HBV DNA > 20,000 IU/mL and biopsy shows moderate or severe inflammation or significant fibrosis
Positive	> 20,000 IU/mL	> 2 × ULN	Observe for 3–6 months and treat if no spontaneous HBeAg loss; consider liver biopsy before treatment if compensated Immediate treatment if icteric or clinical decompensation IFN-α, pegIFN-α, LAM, ADV, ETV, or LdT may be used as initial therapy LAM and LdT not preferred because of high rate of drug resistance IFN-α nonresponders or contraindications to IFN-α: use ADV, ETV End point of treatment: seroconversion from HBeAg to anti-HBe Duration of therapy: IFN-α: 16 weeks pegIFN-α: 48 weeks LAM, ADV, ETV, LdT: minimum 1 year; continue for at least 6 months after HBeAg seroconversion
Negative	> 20,000 IU/mL	> 2 × ULN	IFN-α, pegIFN-α, LAM, ADV, ETV, LdT may be used as initial therapy; LAM and LdT not preferred because of high rate of drug resistance IFN-α nonresponder or contraindications to IFN-α: use ADV, ETV End point of treatment: not defined Duration of therapy: IFN-α, pegIFN-α: 1 year LAM, ADV, ETV, LdT: > 1 year
Negative	> 2000 IU/mL	1 to > 2 × ULN	Consider liver biopsy and treat if liver biopsy shows moderate to severe necroinflammation or significant fibrosis
Negative	≤ 2000 IU/mL	≤ ULN	Observe; treat if HBV DNA or ALT concentrations increase
Positive or negative	Detectable	Cirrhosis	Compensated: HBV DNA > 2000 IU/mL: treat; LAM, ADV, ETV, LdT may be used as initial therapy; LAM and LdT not preferred because of high rate of drug resistance HBV DNA < 2000 IU/mL: consider treatment if ALT concentration is elevated Decompensated: coordinate treatment with transplant center; LAM (or LdT) plus ADV or ETV alone preferred; refer for liver transplant
Positive or negative	Undetectable	Cirrhosis	Compensated: observe Decompensated: refer for liver transplant

<sup>a</sup>Tenofovir disoproxil fumarate does not appear because it received FDA approval after the guidelines were developed; however, use of tenofovir disoproxil fumarate would be appropriate wherever ADV appears in the table.

ADV = adefovir; ALT = alanine aminotransferase; anti-HBe = hepatitis B e antibody; ETV = entecavir; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; IFN-α = interferon alpha; LAM = lamivudine; LdT = telbivudine; PCR = polymerase chain reaction; pegIFN-α = pegylated IFN-alpha; ULN = upper limit of normal.

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are the primary biochemical and virologic measures of treatment response.

Relapse after discontinuation of antiviral treatment is also more common in HBeAg-negative patients; therefore, longer treatment durations are required. Current guidelines recommend treatment for patients with HBeAg-negative chronic HBV infection if HBV DNA concentration is greater than 20,000 IU/mL and ALT concentration is greater than 2 times the upper limit of normal. In patients with HBeAg-negative chronic HBV infection, HBV DNA concentrations of 2000–20,000 IU/mL, and minimally elevated ALT, the

decision to treat is less clear, and biopsy should be considered. Because of high relapse rates and need for longer treatment duration, drugs with lower resistance rates are preferred for the treatment of HBeAg-negative chronic HBV infection.

### Pharmacologic Treatment Options for Chronic HBV Infection

In patients identified as appropriate candidates for antiviral therapy, the primary treatment goals are to achieve sustained suppression of HBV replication and prevent progression of liver disease. Antiviral treatment responses

can be classified as biochemical (normalization of ALT), virologic (clearance of detectable HBV DNA), serologic (loss of HBeAg, HBeAg seroconversion, loss of HBsAg), or histologic (improvement in liver histology). It is important to assess virologic responses not only during antiviral treatment but also after treatment is stopped, as well as to assess the emergence of resistance in patients who continue on long-term therapy.

As of August 2008, seven drugs were approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic HBV infection. Two are forms of interferon (IFN- $\alpha$ 2b) and pegylated interferon (pegIFN- $\alpha$ 2a), and five are oral nucleos(t)ide analogues (lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate). Table 1-4 lists current treatment options. Each has its own advantages and disadvantages, and the choice of antiviral agent may be influenced by efficacy, safety, risk of drug resistance, method of administration, cost, and various pretreatment factors (e.g., serologic and virologic markers, serum ALT concentration, stage and severity of liver disease).

### Interferons for Chronic HBV Infection

Standard IFN, the first drug used clinically to treat chronic HBV infection, has been supplanted for treatment of adult patients by the more recently marketed pegIFN- $\alpha$ 2a. Currently, pegIFN- $\alpha$ 2b is not labeled for treatment of chronic HBV infection, but Phase III trials are in progress. The primary advantages of pegIFN compared with standard IFN include a longer half-life (therefore less-frequent administration), improved efficacy, and improved tolerability because of more sustained absorption and smaller fluctuations in plasma concentrations. In patients with chronic HBV infection, high pretreatment serum ALT concentrations, lower baseline serum HBV DNA, and significant inflammation on histologic examination are important predictors of response to IFN or pegIFN therapy. In addition, because higher virologic response rates to IFN or pegIFN have been observed in patients infected with HBV genotypes A and B, genotype testing may be beneficial for patients in whom IFN or pegIFN therapy is being considered.

The use of pegIFN has not been directly compared in clinical trials with standard IFN for treatment of patients with chronic HBV infection. The current recommended

**Table 1-4. Drugs Approved for the Treatment of Chronic Hepatitis B Infection**

Drug	NA Type	Indications	Original Approval Date (for HBV infection)	Route	Adult Dosage	Duration	Tolerability
Lamivudine	L-nucleoside analogue (cytidine)	HBV, HIV	1998 (adult) 2001 (ped)	Oral	100 mg daily <sup>a,b</sup>	Unclear	Well tolerated
Adefovir dipivoxil	Nucleotide analogue (adenosine)	HBV	2002 (adult) 2007 ( $\geq 12$ years)	Oral	10 mg daily <sup>a</sup>	Unclear	Well tolerated (nephrotoxicity)
Entecavir	Nucleoside analogue (guanosine)	HBV	2005 (16 years and older)	Oral	NA-naïve: 0.5 mg daily <sup>a,c</sup> LAM-R: 1 mg daily	Unclear	Well tolerated
Telbivudine	L-nucleoside analogue (thymidine)	HBV	2006 (adult)	Oral	600 mg daily <sup>a</sup>	Unclear	Well tolerated (myopathy)
Tenofovir disoproxil fumarate	Nucleotide analogue (adenosine)	HBV, HIV	2008 (adult)	Oral	300 mg daily <sup>a</sup>	Unclear	Well tolerated (nephrotoxicity)
IFN- $\alpha$ 2b	–	HBV, HCV	1986 (adult) 1998 (ped)	Subcutaneous injection	10 MIU three times/week or 5 MIU daily <sup>d</sup>	16–24 weeks	Poorly tolerated
pegIFN- $\alpha$ 2a	–	HBV, HCV	2005 (adult)	Subcutaneous injection	180 mcg weekly <sup>e</sup>	48 weeks	Poorly tolerated

<sup>a</sup>Adjust dosage or frequency if creatinine clearance (CrCl) less than 50 mL/min. For patients taking ADV, ETV, LdT, or TDF, adjust frequency as follows: CrCl 30–49 mL/min, administer every 48 hours; CrCl 10–29 mL/min, administer every 72 hours; hemodialysis, administer ADV, ETV, and TDF every 7 days (after dialysis) and LdT every 96 hours (after dialysis). For patients taking LAM adjust dosage as follows: CrCl 30–49 mL/min, 100 mg first dose, then 50 mg daily; CrCl 15–29 mL/min, 100 mg first dose, then 25 mg daily; CrCl 5–14 mL/min, 35 mg first dose, then 15 mg daily; CrCl <5 mL/min, 35 mg first dose, then 5 mg daily.

<sup>b</sup>Use higher dosage for HIV coinfection (e.g. 300 mg/day with normal renal function) as part of multidrug regimen.

<sup>c</sup>Adjust dose (135 mcg/week) in patients with end-stage renal disease undergoing hemodialysis.

<sup>d</sup>No specific recommendation; use cautiously in patients with renal impairment.

<sup>e</sup>Administer on empty stomach.

ADV = adefovir dipivoxil; CrCl = creatinine clearance; ETV = entecavir; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; LAM = lamivudine; LdT = telbivudine; LAM-R = lamivudine resistant; MIU = million international units; NA = nucleos(t)ide analogue; ped = pediatric; pegIFN = pegylated interferon; TDF = tenofovir disoproxil fumarate.

pegIFN- $\alpha$ 2a dosage regimen for treatment of patients with HBeAg-positive or HBeAg-negative chronic HBV infection is 180 mcg injected subcutaneously once per week for 48 weeks. However, observations during Phase II and III clinical trials suggest that patients with HBeAg-positive chronic HBV infection may be treated with a lower dosage or shorter duration of pegIFN- $\alpha$ 2a. In contrast, patients with HBeAg-negative chronic HBV infection possibly may benefit from longer durations (beyond 48 weeks) of pegIFN- $\alpha$ 2a. Additional data are needed to further define the optimal dosage and duration of pegIFN for treatment of patients with chronic HBV infection. Overall, compared with oral nucleoside or nucleotide analogues, IFN or pegIFN therapy has the advantages of a finite treatment course, more durable response, and a lack of resistance. The most notable disadvantage of IFN or pegIFN treatment is poor patient tolerability; adverse effects of IFN or pegIFN therapy are described in the HCV section of this chapter.

### Oral Nucleoside and Nucleotide Analogues for Chronic HBV Infection

Nucleoside or nucleotide analogues are synthetic drugs that mimic naturally occurring purine (adenosine, guanine) and pyrimidine (thymidine, cytidine) nucleotides. Current nucleos(t)ide analogues are indicated for treatment of patients with chronic HBV infection who have evidence of active viral replication and either persistently elevated ALT concentrations or histologically active disease.

During the past decade, nucleos(t)ide analogues made a substantial contribution to the advancement of chronic HBV infection treatment with increased convenience and improved safety profiles compared with IFN or pegIFN. However, durability of response is lower, necessitating longer treatment durations and an associated increased risk of resistance compared with IFN or pegIFN. Laboratory tests to assess response and emergence of resistance should be performed every 3–6 months during nucleos(t)ide analogue treatment.

All nucleos(t)ide analogues used for treatment of chronic HBV infection are cleared from the body predominantly by renal elimination, and dosage or dosing interval adjustments are recommended in patients with an estimated creatinine clearance less than 50 mL/minute (Table 1-4). None of the nucleos(t)ide analogues indicated for treatment of chronic HBV infection are substrates of or affect cytochrome P450 drug-metabolizing enzymes. Nucleoside and nucleotide analogues are generally well tolerated, but warnings exist for the entire drug class, including the risk of lactic acidosis and severe hepatomegaly with steatosis (although this toxicity appears to be much less common with nucleos(t)ide analogues used for chronic HBV treatment than with some nucleos(t)ide analogues used for treatment of HIV infection). Discontinuation of a nucleos(t)ide analogue may lead to severe acute hepatitis exacerbation; therefore, patient adherence to therapy is essential, and close monitoring is necessary if nucleos(t)ide analogue treatment is stopped. Finally, because nucleos(t)ide analogue monotherapy in patients with unrecognized or untreated HIV infection may lead to development of HIV mutations and resistance, it is important to screen for HIV in patients at risk before beginning nucleos(t)ide analogue treatment for chronic HBV infection.

### Lamivudine

Lamivudine, the first oral antiviral drug labeled for use in the United States for treatment of chronic HBV infection in adults, is also indicated for the treatment of children infected with HBV as well as for HIV infection. Lamivudine is effective in suppressing HBV DNA in HBeAg-positive and HBeAg-negative patients, and it can stabilize or improve liver function in patients with advanced liver disease, including decompensated cirrhosis.

The advantages of lamivudine include convenient oral administration, lower cost compared with other agents, and excellent tolerability and safety. However, the usefulness of lamivudine monotherapy for chronic HBV infection treatment is significantly limited by high rates of resistance. Resistance to lamivudine increases with duration of therapy and has been reported in 16% to 32%, 42%, and 60% to 70% of patients after 1 year, 2 years, and 5 years of treatment, respectively. Lamivudine may still have a role in selected patients, but because of high resistance rates, lamivudine monotherapy is no longer preferred in patients with chronic HBV infection who require long-term therapy.

### Adefovir Dipivoxil

Adefovir dipivoxil, a prodrug of adefovir, is indicated for treatment of chronic HBV infection in adults and adolescents at least 12 years of age. Adefovir is effective at suppressing HBV DNA in both wild-type and lamivudine-resistant HBV. In comparison with lamivudine, resistance occurs more slowly during adefovir dipivoxil treatment, and resistance rates of 0%, 3%, and 30% have been reported after 48 weeks, 96 weeks, and 240 weeks of treatment, respectively. Adefovir dipivoxil is generally well tolerated, but nephrotoxicity is observed at higher dosages (e.g., 30 mg daily) and can occur when underlying renal impairment is present or during concomitant therapy with nephrotoxic drugs. In addition, primary nonresponse (attributed to the low dosage used for chronic HBV treatment) occurs in 20% to 50% of patients. Alternative treatment options should be considered for patients with primary nonresponse to avoid resistance. Higher adefovir dipivoxil dosages have greater potency against HBV but at the unacceptable cost of increased nephrotoxicity.

### Entecavir

Entecavir is indicated for treatment of chronic HBV infection in adults and adolescents at least 16 years of age, including patients with evidence of lamivudine-resistant HBV infection. The most notable advantages of entecavir are its excellent potency and low rates of resistance in nucleos(t)ide analogue-naïve patients. Entecavir resistance in nucleos(t)ide analogue-naïve patients has been reported in 0.2%, 0.5%, and 1.2% of patients after 48 weeks, 96 weeks, and 192 weeks of therapy, respectively. In contrast, when entecavir is administered to patients with lamivudine-refractory chronic HBV infection, resistance is much higher and has been reported in 6%, 15%, and 46% of treated patients after 48 weeks, 96 weeks, and 192 weeks, respectively. Overall, entecavir is potent and well tolerated and has extremely low resistance rates in nucleos(t)ide analogue-naïve patients. Because entecavir resistance is greater in patients with preexisting lamivudine resistance, it is not preferred in these patients.

### **Telbivudine**

Telbivudine, labeled for use in the treatment of chronic HBV infection in adults, is effective at rapidly lowering serum HBV DNA concentrations in both HBeAg-positive and HBeAg-negative patients. Genotypic resistance has been reported in about 3% to 4% and 9% to 22% of telbivudine-treated patients after 1 year and 2 years of treatment, respectively. Although telbivudine has enhanced potency and lower resistance rates compared with lamivudine, it is not effective against lamivudine-resistant HBV. Overall, telbivudine is generally well tolerated, but cases of myopathy and elevated creatine phosphokinase have been reported several weeks to months after beginning therapy. Predisposing factors for myopathy during telbivudine therapy are unknown, but caution should be exercised if patients are taking other drugs that may also cause myopathy. In addition, although neuropathy rarely occurs during telbivudine monotherapy, a warning was issued in 2008 because of reports of increased peripheral neuropathy (some severe) when it was used in combination with pegIFN.

### **Tenofovir Disoproxil Fumarate**

Tenofovir disoproxil fumarate is the most recent antiviral agent to receive FDA approval for labeled use in the treatment of adults with chronic HBV infection. Tenofovir disoproxil fumarate is also indicated for treatment of HIV infection. Although structurally similar to adefovir dipivoxil, tenofovir disoproxil fumarate can be used in higher dosages and appears to have more potent antiviral activity with comparable adverse effects. Tenofovir disoproxil fumarate is effective against lamivudine-resistant HBV and is effective in the treatment of some patients who have an inadequate response to adefovir dipivoxil. In two Phase III clinical trials, tenofovir disoproxil fumarate 300 mg daily demonstrated superior virologic efficacy and a significantly higher overall response rate than adefovir dipivoxil 10 mg daily in both HBeAg-positive and HBeAg-negative patients. Decreases in bone mineral density were reported in patients with HIV infection treated with tenofovir disoproxil fumarate. Although this has not been observed in patients with chronic HBV infection, bone mineral density monitoring should be considered in patients with a history of bone fracture or at risk of osteopenia. In addition, although nephrotoxicity has infrequently been reported during tenofovir disoproxil fumarate therapy, renal function should be monitored closely and concomitant nephrotoxic drugs avoided, if possible. Overall, tenofovir disoproxil fumarate is well tolerated and appears to be a promising addition to the antiviral armamentarium for treatment of chronic HBV infection; in the future, it will likely replace the role of adefovir dipivoxil.

### **Combination Antiviral Therapy for Chronic HBV Infection**

Although combination therapy is the mainstay of treatment for HIV and HCV infection, this approach has not yet achieved the same degree of success for treating chronic HBV infection. Several combinations of antiviral agents have been evaluated in clinical trials and in clinical practice with varying results.

The addition of pegIFN- $\alpha$ 2a to lamivudine therapy reduces the development of lamivudine resistance (1% to 4% for combination therapy vs. 27% to 32% for lamivudine monotherapy after 48 weeks); but overall, sustained response rates are not significantly different from pegIFN- $\alpha$ 2a monotherapy. Similarly, when the combination of lamivudine and adefovir dipivoxil was compared with lamivudine monotherapy in nucleos(t)ide analogue-naïve patients, lower rates of lamivudine resistance (15% vs. 43% in the monotherapy group), lower serum HBV DNA concentrations, and higher rates of ALT normalization were seen in the combination therapy group; however, serologic outcomes were similar for both groups after 2 years. More importantly, in patients who already have lamivudine-resistant HBV, the addition of adefovir dipivoxil and continued treatment with the combined regimen is preferred because it reduces the risk of developing adefovir resistance.

To avoid additive nephrotoxicity, adefovir dipivoxil should not be combined with tenofovir disoproxil fumarate. In addition, the combination of telbivudine and lamivudine is inferior to telbivudine monotherapy and therefore is not recommended. Finally, because lamivudine and telbivudine resistance predisposes a person to entecavir resistance, the combination of either drug with entecavir should be avoided.

At present, no combination of antiviral agents has proved superior to monotherapy in nucleos(t)ide analogue-naïve patients. Combination therapy (e.g., nucleoside plus nucleotide or nucleos(t)ide analogue plus pegIFN) appears to reduce the incidence of antiviral resistance, but the optimal combination has yet to be determined.

### **Antiviral Resistance**

Antiviral resistance is an important cause of treatment failure in patients with chronic HBV infection. Resistance has not been reported with IFN or pegIFN, but treatment with IFNs is inconvenient and poorly tolerated. In contrast, nucleos(t)ide analogues are more convenient and better tolerated but result in low rates of sustained viral suppression if therapy is stopped after 48–52 weeks. Although prolonged treatment durations are often necessary, they are associated with increased risk of resistance with virologic or biochemical breakthrough and potential cross-resistance to other nucleos(t)ide analogues.

The nomenclature for nucleos(t)ide analogue resistance previously lacked standardization but is now better defined (Table 1-5). Primary nonresponse during nucleos(t)ide analogue treatment may be a reflection of nonadherence, inadequate drug potency, poor absorption, polymorphisms in the enzymes responsible for converting the drug into its active form, or preexisting genotypic resistance. Virologic or biochemical breakthrough may occur as a result of antiviral resistance, but it is important for clinicians to confirm patient adherence before ordering additional expensive tests for genotypic resistance mutations.

Primary genotypic drug resistance mutations result in reduced susceptibility to an antiviral drug, but initially, the mutated virus does not replicate as efficiently as the wild-type virus. Replicative activity of the mutated virus is restored after subsequent, secondary, or compensatory mutations cause additional amino acid substitutions.

**Table 1-5. Terms Used to Describe Antiviral Response or Resistance to Nucleos(t)ide Analogue Treatment**

Term	Description
Primary treatment failure or nonresponse	Inability of NA to reduce serum HBV DNA at least 1 log <sub>10</sub> IU/mL (NIH criteria) or 2 log <sub>10</sub> IU/mL (AASLD criteria) after 24 weeks of treatment
Secondary treatment failure or virologic breakthrough	Serum HBV DNA increases by at least 1 log <sub>10</sub> IU/mL on two occasions (1 month apart) during NA therapy after initial virologic response had been achieved
Biochemical breakthrough	Serum ALT becomes elevated during therapy after achieving initial normalization
Genotypic resistance	Detection of virus particles with amino acid substitutions (primary or compensatory) in the reverse transcriptase region of the HBV genome that causes phenotypic resistance
Phenotypic resistance	Decreased susceptibility of an HBV polymerase to an antiviral agent in vitro

AASLD = American Association for the Study of Liver Diseases; ALT = alanine aminotransferase; HBV = hepatitis B virus; NA = nucleoside or nucleotide analogue; NIH = National Institutes of Health.

As more nucleos(t)ide analogues become available and additional drug resistance mutations are identified, determining the optimal management of patients with chronic HBV becomes increasingly difficult. Entecavir appears to have the lowest resistance rates in nucleos(t)ide analogue-naïve patients, possibly because resistance to entecavir occurs through a two-step mechanism. Tenofovir disoproxil fumarate also appears to have extremely low rates of resistance. Management of antiviral resistance can be challenging; treatment approaches must vary based on virologic response to previous treatments, the specific pattern of mutations detected at the time of virologic breakthrough, and the antiviral activity of other nucleos(t)ide analogues against HBV with the specific mutation(s) (Table 1-6). Clearly, judicious use of nucleos(t)ide analogue therapy is vital to prevent resistance. If antiviral therapy is indicated, maximal early viral suppression using the most potent nucleos(t)ide analogue with the lowest rate of resistance is essential. Alternative treatment regimens should be used in patients with primary nonresponse, and the importance of drug adherence must be stressed.

### Management of Chronic HBV in Special Populations

#### HIV/HBV Coinfection

The natural course of chronic HBV infection is accelerated in patients with HIV coinfection, with more rapid progression of liver disease and increased risk of hepatocellular carcinoma compared with patients infected with HBV alone. Lamivudine, emtricitabine, and tenofovir disoproxil fumarate exhibit activity against both viruses. Emtricitabine is not labeled for use in patients with chronic HBV but has demonstrated activity against HBV with resistance rates similar to lamivudine. The combination of tenofovir disoproxil fumarate and either lamivudine or emtricitabine is often included as part of the treatment regimen of patients coinfecting with HIV and HBV.

Many experts recommend using two drugs with anti-HBV activity as part of the HIV treatment regimen in patients coinfecting with HBV, particularly patients with cirrhosis. Immune restoration associated with initiation of highly active antiretroviral therapy for HIV infection can potentially improve control of HBV replication but it can also lead to increased immune-mediated liver injury. In patients with cirrhosis, immune reconstitution after initiation of highly active antiretroviral therapy can cause

hepatitis flares and precipitate hepatic decompensation. To avoid hepatitis flares when altering HIV treatment regimens of coinfecting patients, it is important to ensure that an anti-HBV drug is not discontinued without adding another drug that has anti-HBV activity.

To avoid the risk of HIV resistance, nucleos(t)ide analogues with dual activity should never be used as monotherapy in patients coinfecting with HIV and HBV. In addition, although entecavir was originally thought to have only anti-HBV activity, HIV resistance mutations have been reported during entecavir monotherapy in patients with untreated HIV infection. If chronic HBV treatment is necessary in coinfecting patients who are not receiving HIV treatment, agents that lack clinical HIV activity are preferred (e.g., pegIFN- $\alpha$ 2a, adefovir dipivoxil 10 mg daily, possibly telbivudine once more data are available).

#### Pregnancy

Pregnancy presents a dilemma for treatment of chronic HBV infection. Lamivudine, entecavir, and adefovir dipivoxil are classified as FDA pregnancy category C, but more safety experience derived from pregnant women infected with HIV is available for lamivudine. Telbivudine and tenofovir disoproxil fumarate are both pregnancy category B. Interferons are classified as pregnancy category C. Decisions about initiating or continuing nucleos(t)ide analogue therapy during pregnancy depend on the mother's stage of liver disease and the potential benefit from therapy compared with the risk to the fetus. Although nucleos(t)ide analogue therapy has not been shown consistently to prevent HBV transmission to the fetus, a recent study showed a lower HBV infection rate in children born to mothers who received lamivudine compared with those who did not. Regardless of whether antiviral therapy is used during pregnancy, an initial dose of hepatitis B immune globulin and HBV vaccination should be administered to the newborn within 12 hours of delivery.

#### Decompensated Cirrhosis

Interferons are contraindicated in patients with decompensated cirrhosis, but nucleos(t)ide analogues have been safely administered to patients with advanced liver disease. Most of the experience using nucleos(t)ide analogues in advanced liver disease has been with lamivudine. In one landmark study, long-term lamivudine therapy in patients with chronic HBV and advanced fibrosis or cirrhosis was



**Table 1-6. Hepatitis B Viral Resistance Mutations and Management Options**

Drug	Resistance Rate	Alternative Treatment Options
Lamivudine	1 yr: 16% to 32% 2 yr: 42% 5 yr: 60% to 70%	Add ADV or TDF Switch to TDF plus FTC Switch to ETV (least preferred)
Adefovir dipivoxil	Nucleoside and nucleotide naïve: 48 weeks: 0% 240 weeks: 30% LAM resistant: 2 years: 20% (ADV alone) 2 years: 0% (LAM+ADV)	Add LAM, LdT, or ETV (unless already resistant) Switch to TDF plus FTC Switch to ETV
Entecavir	Nucleoside and nucleotide naïve: 48 weeks: < 1% 192 weeks: 1.2% LAM resistant: 1 year: 6% 4 years: 46%	Add ADV or TDF Switch to ADV or TDF
Telbivudine	1 year: 3% to 4% 2 years: 9% to 22%	Add ADV or TDF Switch to TDF plus FTC Switch to ETV (least preferred)
Tenofovir disoproxil fumarate	1 year: 0%	Not yet determined

ADV = adefovir; ETV = entecavir; FTC = emtricitabine; LdT = telbivudine; LAM = lamivudine; TDF = tenofovir disoproxil fumarate.

associated with delayed progression of liver disease and lower rates of hepatic decompensation and hepatocellular carcinoma. As expected, benefits were greatest in patients who maintained a virologic response and did not develop lamivudine resistance.

In addition to referral for liver transplantation evaluation, patients with decompensated cirrhosis should be promptly treated with a nucleos(t)ide analogue that can produce rapid viral suppression with a low risk of drug resistance. In decompensated cirrhosis, the combination of lamivudine and adefovir dipivoxil or tenofovir disoproxil fumarate (with close monitoring of renal function) may be beneficial to reduce the risk of resistance. Entecavir and telbivudine are also expected to be beneficial in treatment of decompensated cirrhosis, but more data are needed. Regardless of the antiviral treatment selected, coordination with a liver transplant center is essential.

#### Liver Transplantation

Patients with HBV-associated fulminant hepatic failure or patients with chronic HBV who progress to cirrhosis and/or hepatocellular carcinoma should be referred for liver transplant evaluation. A key factor to ensuring long-term survival after liver transplantation in patients infected with HBV is preventing reinfection of the allograft. Historically, in the absence of prophylaxis, HBV infection recurred after liver transplantation in up to 80% of patients, resulting in rapid allograft failure and increased mortality. Before the use of prophylactic measures, early results after liver transplantation of patients with HBV infection were disappointing, and at one time, HBV infection was a contraindication for liver transplantation. However, substantial progress has been made in the past 15–20 years,

and currently, HBV-related liver disease is a universally accepted indication for liver transplantation.

The combination of high-dose intravenous hepatitis B immune globulin and nucleos(t)ide analogue(s) therapy prevents HBV infection recurrence in most patients after liver transplantation. Factors that increase the risk of HBV infection recurrence include active viral replication at the time of transplantation; high pretransplant viral load (i.e., HBV DNA greater than 100,000 copies/mL); genotypic resistance to nucleos(t)ide analogues; mutations in the “a” determinant of the surface antigen protein (which result in reduced immune globulin binding); short-term or inadequate quantitative hepatitis B surface antibody levels; and, finally, nonadherence. Currently, there is no universal consensus regarding the optimal prophylactic regimen, and protocols vary among transplant centers.

#### Hepatitis B Reactivation

Reactivation of HBV replication with increasing HBV DNA has been reported in 20% to 50% of HBV carriers undergoing intensive immunosuppressive therapy or cancer chemotherapy, particularly when regimens include corticosteroids. Although many hepatitis flares are asymptomatic, some patients may develop jaundice. In severe cases, hepatic decompensation and (rarely) deaths have been reported.

Patients should be screened for HBV before undergoing cancer chemotherapy or intensive immunosuppressive therapy. Prophylactic antiviral therapy is recommended for HBV carriers when chemotherapy is initiated, during chemotherapy, and then for at least 6 months afterward with close monitoring after nucleos(t)ide analogue withdrawal. Lamivudine is well tolerated, cost-effective and considered

an acceptable agent for prophylaxis. The efficacy of lamivudine has been documented in several studies and case reports; however, further studies are needed to determine the most appropriate nucleoside or nucleotide analogue for antiviral prophylaxis in patients undergoing chemotherapy, as well as the optimal duration after completion of chemotherapy. Patients with detectable HBV DNA who meet criteria should be treated according to current practice guidelines.

## Hepatitis C Virus

Hepatitis C virus is a small, hepatotropic RNA virus. Six HCV genotypes and more than 50 subtypes have been identified. Unlike HBV, in which the role of genotype is still being elucidated, knowledge of HCV genotype is well established and extremely important because it is predictive of response to antiviral therapy and helps guide treatment selection. Genotype 1 is not only the most common HCV genotype in the United States, representing 75% of infected patients, but it is also the least responsive to antiviral treatment.

Hepatitis C virus is transmitted primarily through percutaneous and, to a lesser extent, permucosal (i.e., sexual and perinatal) exposure. Transfusion of infected blood or blood products was the primary source of HCV infection before its discovery in 1989 and before sensitive blood screening tests became available in 1992. Currently, illicit injection drug use is the most common source of HCV infection in the United States. People at risk should be screened for HCV (Table 1-1).

After acute exposure, some individuals will spontaneously clear the virus within 6 months, but most (75% or more) progress to chronic infection. Cirrhosis occurs in about 15% to 20% of patients with chronic HCV. Although progression is generally slow, requiring 15–20 years or longer, it may also be accelerated. Factors that increase the rate of liver disease progression include alcohol consumption, male sex, age (older than 40 years) at the time of infection, HBV or HIV coinfection, immunosuppression, and obesity or hepatic steatosis. Persistent inflammation associated with chronic HCV leads to hepatic fibrosis, and as the stage of fibrosis progresses to cirrhosis, the risk of hepatocellular carcinoma increases. Patients with chronic HCV infection rarely develop hepatocellular carcinoma in the absence of cirrhosis; after progression to cirrhosis, the risk of hepatocellular carcinoma is about 2% to 8% per year.

### Evaluation of Patients with Chronic HCV

Hepatitis C infection is rarely diagnosed during the acute phase because most patients are asymptomatic. Diagnosis is based on serologic antibody assays and molecular tests that detect HCV RNA. Initial screening is typically performed using an enzyme immunoassay to detect antibodies to HCV. In patients who are seropositive, additional testing is done to detect the presence of HCV RNA. Chronic HCV infection is defined as detectable HCV RNA for more than 6 months. Qualitative assays for measurement of HCV RNA have a lower limit of detection than quantitative assays and are useful for initial diagnosis and documentation of viral eradication after antiviral treatment is completed. In

acutely infected patients, it may take several months before HCV antibody is detectable, but HCV RNA can often be detected within 1–3 weeks after acute exposure. Therefore, qualitative HCV RNA testing may be a more useful initial test than HCV antibody in people with a known recent exposure (e.g., needle stick injury). In addition, qualitative HCV RNA testing may be useful for diagnosis in immunocompromised patients with diminished antibody production (e.g., hemodialysis, patients infected with HIV). Quantitative HCV RNA testing is an important factor in predicting the likelihood of response before initiating antiviral therapy and is also used to monitor response during treatment. Several assays for quantitative measurement of HCV RNA are available with varying sensitivity and dynamic ranges. Results are now reported in standardized international units, and conversion factors are available to determine the equivalent number of copies. These vary among assays, however, so longitudinal HCV RNA monitoring in patients with chronic HCV should be performed using the same assay. Important points at which to monitor HCV RNA during treatment are at baseline; weeks 4, 12, and 24 and end of treatment (24 or 48 weeks); and 24 weeks after treatment ends.

Serum ALT concentration is a relatively insensitive measure of assessing the severity of liver disease in patients with chronic HCV; in many studies, degree of ALT elevation was only weakly associated with liver histology. Elevated ALT is not required for initiation of treatment, but in patients with baseline elevated serum ALT concentrations, normalization during or after antiviral therapy is an indicator of disease (biochemical) response. Liver biopsy is not necessary for the diagnosis of chronic HCV, but histologic liver examination may be useful to assess the degree of inflammation and stage of fibrosis as well as to exclude other causes of chronic liver disease.

Various guidelines exist for the management of patients with chronic HCV. Treatment is recommended for patients with detectable HCV RNA and a liver biopsy showing portal or bridging fibrosis and at least moderate inflammation and necrosis. Once the severity of liver disease progresses to advanced fibrosis or compensated cirrhosis, HCV treatment becomes much more difficult, and response rates are lower. Selection of patients for antiviral therapy is a complex clinical decision, and careful consideration of potential benefits and possible risks is necessary. Because of the significant toxicities associated with HCV therapeutic regimens, patients must be not only medically appropriate but also motivated and willing to adhere to treatment requirements. Interferon-based therapy should not be used in patients with autoimmune hepatitis, decompensated liver disease, major uncontrolled depression or neuropsychiatric illness, pregnancy, or severe comorbid diseases (e.g., uncontrolled hypertension, seizures, diabetes, thyroid disorders, unstable coronary artery disease). Ribavirin should not be used during pregnancy or in patients with severe anemia, unstable coronary artery disease, renal failure, or hemoglobinopathies (e.g., thalassemia, sickle cell disease) or in those who are unable or unwilling to use adequate contraception.

### Pharmacologic Treatment Options for HCV

The primary goal of HCV treatment is to eradicate the virus from infected individuals and thereby slow liver disease progression, prevent complications of cirrhosis,

and reduce the risk of hepatocellular carcinoma. Response rates to antiviral therapy for chronic HCV can be classified as biochemical, virologic, and histologic, but the most important treatment end point for chronic HCV is sustained virologic response, defined as undetectable serum HCV RNA 6 months after completion of antiviral treatment. Several factors before and during treatment can influence response to antiviral therapy in patients with chronic HCV. Factors associated with sustained virologic response include age younger than 40 years, body weight less than 75 kg, mild liver disease (i.e., fibrosis grade 0 or 1), genotype 2 or 3, lower HCV RNA (less than 800,000 IU/mL), rapid (measured at 4 weeks) or early (measured at 12 weeks) virologic response, and treatment adherence. Rapid virologic response (an undetectable HCV RNA 4 weeks after treatment initiation) and early virologic response (defined as either negative HCV RNA or at least a 2 log<sub>10</sub> reduction in HCV RNA after 12 weeks of therapy), are important predictors of sustained virologic response.

During combination pegIFN and ribavirin treatment, 65% to 72% of patients with an early virologic response subsequently achieved a sustained virologic response, but of the patients who did not experience an early virologic response, 97% did not achieve a sustained virologic response. Treatment discontinuation should be considered after 12–24 weeks in patients who do not demonstrate an early virologic response because of the low likelihood of achieving a sustained virologic response with further treatment. The current standard for treatment-naïve patients with chronic HCV is the combination of subcutaneous pegIFN plus oral ribavirin. Pegylated IFN can be used as monotherapy if ribavirin is contraindicated, but response rates are lower. In addition, although ribavirin is an important component of treatment, ribavirin alone does not clear HCV and is not recommended as monotherapy. Characteristics of antiviral drugs labeled for use in the treatment of chronic HCV in the United States are listed in Table 1-7.

**Table 1-7. Antiviral Agents Indicated for the Treatment of Chronic Hepatitis C**

	IFN- $\alpha$ 2b	PegIFN- $\alpha$ 2a	PegIFN- $\alpha$ 2b	IFN alfacon-1	Ribavirin
Relevant indication(s)	HBV and HCV	HBV and HCV (including HIV/HCV)	HCV	HCV	HCV (in combination with IFN or pegIFN)
Peg chain	–	40 kDa, branched	12 kDa, linear	–	–
Mean elimination half-life	2–3 hours	160 hours	40 hours	–	12 days
Usual adult dosage <sup>a,b</sup>	3 MIU	Monotherapy: 180 mcg  Combination therapy: 180 mcg	Monotherapy: 1 mcg/kg  Combination therapy: 1.5 mcg/kg	Treatment naïve: 9 mcg  IFN nonresponder: 15 mcg	If used with pegIFN- $\alpha$ 2b: ≤ 65 kg: 800 mg/day 66–85 kg: 1000 mg/day 86–105 kg: 1200 mg/day > 105 kg: 1400 mg/day  If used with pegIFN- $\alpha$ 2a: G2 or 3: 800 mg/day G1 and < 75 kg: 1000 mg/day G1 and ≥ 75 kg: 1200 mg/day HIV: 800 mg/day  If used with IFN- $\alpha$ 2b: < 75 kg: 1000 mg/day ≥ 75 kg: 1200 mg/day <sup>c</sup>
Route	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Oral
Frequency	Three times per week	Once weekly	Once weekly	Three times per week	Total daily dosage administered in two divided doses (every 12 hours)
Duration <sup>d</sup>	G1 or 4: 48 weeks G2 or 3: 24 weeks	G1 or 4: 48 weeks G2 or 3: 24 weeks HIV: 48 weeks (all genotypes)	G1 or 4: 48 weeks G2 or 3: 24 weeks	Treatment naïve: 24 weeks IFN nonresponder: 48 weeks	24–48 weeks

<sup>a</sup>Avoid RBV use if estimated creatinine clearance is less than 50 mL/minute.

<sup>b</sup>PegIFN- $\alpha$ 2a dose should be reduced to 135 mcg for patients undergoing hemodialysis; pegIFN- $\alpha$ 2b dose should be reduced by 25% for patients with creatinine clearance 30–50 mL/minute and by 50% for patients with creatinine clearance 10–29 mL/minute or patients undergoing hemodialysis. No specific recommendations for IFN- $\alpha$ 2b or IFN alfacon-1: use with caution in patients with renal impairment.

<sup>c</sup>RBV dose obtained from current prescribing information recommendations, but some experts now advocate weight-based RBV dosing in HIV-coinfected patients

<sup>d</sup>Treatment discontinuation should be considered in patients who have not achieved an adequate virologic response after 12–24 weeks of treatment.

Abbreviations: G = genotype; HBV = hepatitis B virus; HCV = hepatitis C virus; IFN = interferon; kDa = kilodalton; MIU = million international units; peg = polyethylene glycol; pegIFN = pegylated interferon; RBV = ribavirin.

### Standard IFN-Based Therapy

Standard or conventional IFN was the first antiviral agent used for the treatment of chronic HCV, but sustained virologic response rates after 48 weeks of IFN- $\alpha$  monotherapy (3 million units three times/week) were disappointingly low (less than 20% overall response). The addition of ribavirin improved overall sustained virologic response rates to about 40% but with added toxicity (e.g., anemia). As in the treatment of chronic HBV, the role of standard IFN for the treatment of chronic HCV in adults has been replaced by more effective, more convenient, and better tolerated pegIFNs.

### Interferon alfacon-1 (Consensus IFN)-Based Therapy

Consensus IFN is a recombinant, nonnaturally occurring type 1 IFN. Like standard IFN, IFN alfacon-1 must be administered three times per week and is less convenient than pegIFNs. However, recent attention has focused on the role of high-dose (9 mcg, 15 mcg, or 24 mcg) daily IFN alfacon-1 combined with ribavirin (800–1400 mg daily) for treatment of pegIFN nonresponders. The results of two clinical trials of consensus IFN with ribavirin in patients with nonresponse or partial response to pegIFN therapy are yet to be published.

### Pegylated IFN-Based Therapy

Currently, two pegylated IFNs, pegIFN- $\alpha$ 2a and pegIFN- $\alpha$ 2b, are labeled for use in the treatment of chronic HCV as monotherapy or in combination with ribavirin. PegIFN- $\alpha$ 2a in combination with ribavirin is also labeled for use in treating chronic HCV for patients coinfecting with HIV. PegIFN- $\alpha$ 2b has a larger volume of distribution and is dosed based on body weight (1–1.5 mcg/kg once weekly), whereas pegIFN- $\alpha$ 2a is administered in a fixed dosing regimen (180 mcg once weekly). Compared with standard IFN therapy, pegIFN-based regimens result in significantly higher sustained virologic response rates. Overall sustained virologic responses of 25% to 40% can be achieved with pegIFN monotherapy compared with a sustained virologic response of less than 20% with standard IFN monotherapy. In addition, patients who successfully complete 48 weeks of pegIFN and ribavirin combined therapy can be expected to achieve an overall sustained virologic response of 50% to 60%; and sustained virologic response rates of 40% to 50% and 70% to 80% for infections with HCV genotype 1 and genotype 2 or 3, respectively.

Evidence from clinical trials clearly identifies the importance of individualizing chronic HCV treatment based on several factors, particularly HCV genotype. In a pivotal clinical study evaluating different ribavirin doses and pegIFN- $\alpha$ 2a plus ribavirin treatment durations, the highest sustained virologic response rates in HCV genotype 1-infected patients were achieved with standard ribavirin dosages (1000–1200 mg/day based on weight) and longer treatment duration (48 weeks). In contrast, patients infected with HCV genotype 2 or 3 appeared to be adequately treated with pegIFN- $\alpha$ 2a and a lower ribavirin dose (800 mg/day) for 24 weeks.

In a second study, patients receiving pegIFN- $\alpha$ 2b combined with weight-based (800–1400 mg/day) or fixed (800 mg/day) ribavirin dosing were evaluated. Sustained virologic response rates were significantly higher in patients

who received weight-based ribavirin dosing compared with patients treated with fixed ribavirin dosages, particularly in patients infected with HCV genotype 1. As a result, in April 2008, the prescribing information for pegIFN- $\alpha$ 2b combined with ribavirin was updated to reflect the new weight-based ribavirin dosages. This study also confirmed earlier observations that extending treatment durations to 48 weeks in patients with HCV genotype 2 or 3 provides no additional benefit.

Shorter treatment durations (16 weeks) in patients infected with HCV genotype 2 or 3 are not recommended because of higher relapses and an overall lower sustained virologic response. In addition, the recommended duration of combination pegIFN- $\alpha$ 2a/ribavirin for all patients coinfecting with HIV is 48 weeks regardless of HCV genotype.

Until recently, no data were available directly comparing the two pegIFNs. The first clinical study to compare the two pegIFNs in combination with ribavirin involved more than 3000 treatment-naïve patients with chronic HCV. Overall, sustained virologic response rates were similar among treatment groups; however, fewer patients in the pegIFN- $\alpha$ 2b groups experienced relapses after achieving an end-of-treatment response. A common critique of this study is that it was not a true head-to-head comparison of regimens because the ribavirin dosage was not comparable between groups and relapse rate differences may have been caused by variations in ribavirin dosing. Subsequent smaller studies comparing the pegIFNs reported higher sustained virologic response rates after combination pegIFN- $\alpha$ 2a and ribavirin treatment compared with pegIFN- $\alpha$ 2b plus ribavirin. However, these studies were designed as “real-life” studies, and many confounding factors may have affected the results. Because of conflicting data, additional studies comparing the pegIFNs in combination with ribavirin are needed before any conclusions can be drawn.

### Managing Adverse Effects of Chronic HCV Treatment

The most significant limitation to any IFN-based therapy is poor patient tolerability. Adverse effects are common during chronic HCV treatment, and treatment-related toxicity can reduce overall effectiveness because of a need for dosage reductions or treatment discontinuation. The most common adverse effects observed during IFN or pegIFN therapy include influenza-like symptoms (e.g., fever, headache, myalgia, fatigue), hematologic abnormalities (e.g., neutropenia, thrombocytopenia), neuropsychiatric disorders (e.g., depression and anxiety), injection site reactions, diarrhea, nausea, insomnia, alopecia, pruritis, and anorexia. Other less common but serious adverse effects include severe psychiatric (i.e., suicidal ideation), cardiovascular (i.e., myocardial infarction), endocrine (e.g., thyroid dysfunction, diabetes mellitus), immune (e.g., psoriasis, lupus), pulmonary, and ophthalmologic disorders, as well as pancreatitis, colitis, and other serious infections. Adverse effects typically associated with ribavirin therapy include hemolytic anemia (which can be particularly problematic in patients with heart disease), fatigue, pruritis, rash, and gout. In addition, ribavirin is a well-known teratogen and is FDA pregnancy category X. Because of a long elimination half-life and persistence in nonplasma

compartments for up to 6 months, it is imperative that female patients of childbearing age and male patients with female partners of childbearing age use at least two reliable forms of contraception during ribavirin therapy and for at least 6 months after treatment is discontinued.

Treatment adherence is an essential component for successful antiviral therapy, and more attention is being focused on proper adverse effect management to avoid dosage reductions and treatment discontinuation. It has been suggested that the greatest likelihood of achieving a sustained virologic response in patients infected with HCV genotype 1 requires maintaining at least 80% of the initial pegIFN dosage and at least 80% of the initial ribavirin dosage for at least 80% of the total treatment period. Additional studies have confirmed that dosage reductions within the first 12 weeks of therapy are more detrimental to treatment success than later reductions.

### Management of Hematologic Adverse Effects

Hematologic abnormalities such as anemia, thrombocytopenia, and neutropenia are common during combination therapy with IFN or pegIFN and ribavirin. Bone marrow suppression during IFN or pegIFN therapy not only causes neutropenia and thrombocytopenia but also contributes to worsening ribavirin-induced anemia. In most clinical trials, dosage reductions for anemia were necessary in up to 23% of patients, but treatment discontinuation was uncommon. Outside of clinical trials, however, treatment discontinuation caused by toxicity is probably much higher. Altogether, hematologic abnormalities are a common reason for dosage reduction and treatment discontinuation; therefore, appropriate management of these adverse effects is essential to optimize treatment response. Anemia, which can occur as early as 1–2 weeks after initiating therapy, reduces patients' health-related quality of life, contributes to fatigue, and can be particularly problematic in patients with heart disease. Furthermore, because ribavirin has a long elimination half-life and is excreted by the kidneys, accumulation occurs in patients with renal impairment, resulting in more severe and often prolonged anemia. Ribavirin is not recommended in patients with an estimated creatinine clearance less than 50 mL/minute.

Several studies evaluating the erythropoietic growth factors such as epoetin alfa (40,000–60,000 units weekly) and darbepoetin alfa (3 mcg/kg every 2 weeks) have demonstrated efficacy in maintaining hemoglobin and ribavirin dosing and in producing improved health-related quality of life scores. In March 2007, the FDA issued a black box warning regarding increased mortality risk when patients with chronic kidney disease receiving erythropoiesis-stimulating agents maintained hemoglobin concentrations above 12 g/dL. Clearly erythropoietic growth factors have an important role for anemia management in patients undergoing treatment with pegIFN plus ribavirin, but additional studies are needed to determine the optimal dosage, frequency, and duration, as well as the target and threshold hemoglobin concentrations at which to initiate therapy.

Interferon-induced neutropenia appears to occur more often during pegIFN therapy compared with standard IFN. Treatment of neutropenia is not only important to avoid dosage reductions but also to prevent infection. In pivotal

trials for pegIFN- $\alpha$ 2a and pegIFN- $\alpha$ 2b, dosage reductions because of neutropenia were necessary in 24% and 18% of patients, respectively. Results of several studies indicate that use of recombinant granulocyte colony stimulating factor (filgrastim) is safe and effective for increasing neutrophil counts during chronic HCV treatment. Additional studies are needed to determine optimal management of neutropenia during chronic HCV treatment.

Although IFNs reduce platelet counts, the etiology of thrombocytopenia in patients with liver disease is often multifactorial, and many patients with chronic HCV have preexisting thrombocytopenia because of splenic sequestration or decreased thrombopoietin production. Oprelvekin (recombinant interleukin-11) is not often used in patients with HCV-related cirrhosis and thrombocytopenia, primarily because of its limited efficacy and several adverse effects (e.g., fluid retention). Eltrombopag, an orally active thrombopoietin receptor agonist that received FDA approval for the treatment of chronic idiopathic thrombocytopenia purpura in November 2008, may be a potential solution for management of thrombocytopenia during chronic HCV treatment. However, eltrombopag is available only through a restricted distribution program and prescribing information contains warnings regarding hepatotoxicity. In one phase II trial, eltrombopag was well-tolerated and increased platelet counts in a dose-dependent manner, thereby permitting the initiation and continuation of antiviral therapy in patients with chronic HCV. Results of continuing Phase III studies evaluating longer eltrombopag treatment duration in patients with chronic HCV treated with pegIFN and ribavirin are yet to be published.

### Management of Neuropsychiatric Adverse Effects

Neuropsychiatric effects of IFN or pegIFN therapy such as depression, anxiety, mania, and fatigue can result in substantial morbidity and mortality. Prompt recognition and early treatment is essential to optimize patient safety and improve patient tolerability. The precise mechanism by which IFNs induce depression remains unclear.

Depression has been reported in up to 44% of IFN- or pegIFN-treated patients, with most symptoms occurring within the first 3 months of therapy. Because serious neuropsychiatric effects have occurred in IFN- or pegIFN-treated patients without prior history of mental illness, it is not surprising that additional concerns arise regarding initiation of chronic HCV treatment in patients with previous substance abuse and mental illness. In all patients undergoing IFN or pegIFN therapy, particularly those patients with preexisting conditions, close monitoring and follow-up with a hepatologist, mental health provider, and addiction specialist, if appropriate, is crucial. Prophylactic antidepressant therapy is debated; at a minimum, patients undergoing IFN/pegIFN treatment should be followed closely using clinical interviews and screening tests such as the Beck Depression Inventory and the Center for Epidemiologic Studies Depression Scale. Uncontrolled severe psychiatric disorders are a contraindication for chronic HCV treatment, but patients with stable or remitting illness may still be eligible for treatment.

## Treatment Challenges

In addition to HCV genotype 1 infection, other factors can reduce treatment effectiveness and contribute to treatment failure. These factors include high viral load (HCV RNA greater than 800,000 IU/mL), advanced fibrosis and cirrhosis, continued drug and/or alcohol use, psychiatric conditions, coinfection with HBV or HIV, advanced age, immunosuppression (e.g., liver transplantation recipients), African American race, obesity, insulin resistance, and previous treatment with suboptimal therapy. Data are available regarding each of these factors, but only a few will be discussed here.

### African American Patients

In most clinical trials evaluating chronic HCV treatment, African Americans were underrepresented and, as a result, an accurate assessment of response rates in this patient population was difficult. More recent studies evaluating chronic HCV treatment specifically in African American patients have demonstrated strikingly different response rates compared with white patients. In two prospective, multicenter clinical trials designed to evaluate pegIFN and ribavirin therapy in African American patients, sustained virologic response occurred in only 19% to 28% of HCV genotype 1 infected African American patients treated with pegIFN and ribavirin therapy, in contrast to the 40% to 50% seen in other studies. Differences in response rates among African American patients have not been explained by factors such as disease characteristics, baseline viral load, or drug dosages. Many questions still remain regarding mechanisms of reduced response, and new strategies clearly are needed to optimize treatment responses in this patient group.

### HIV and HCV Coinfection

Because of shared risk factors, a significant proportion of individuals infected with HIV (about 30%) are also infected with HCV. The introduction of potent antiretroviral therapy dramatically improved survival of patients infected with HIV, but complications of HCV coinfection have emerged as a common and important cause of morbidity and mortality in this population. The effect of HCV infection on HIV progression is not entirely clear, but infection with HIV clearly contributes to more rapid progression of HCV-related liver disease. Treatment of chronic HCV in patients coinfecting with HIV is considerably more challenging, and the response rates are lower compared with patients infected with HCV alone.

The efficacy and safety of pegIFN and ribavirin combined therapy in patients coinfecting with HIV and HCV was evaluated in several clinical trials. Overall sustained virologic response rates for pegIFN and ribavirin treatment in patients coinfecting with HIV and HCV ranged from 27% to 40%. In addition, sustained virologic response rates of 43% to 73% and 11% to 38% were achieved in patients with genotype 2 or 3 and genotype 1 patients, respectively. In general, chronic HCV treatment should be considered in patients coinfecting with HIV who are monitored closely, and in whom the likelihood of treatment response and risk of serious liver disease complications outweigh the risks associated with chronic HCV treatment. A threshold CD4 count of at least 350 cells/ $\mu$ L has been suggested for

initiation of antiviral therapy; treatment is not recommended in patients with CD4 counts lower than 200 cells/mL.

Currently, the only chronic HCV treatment indicated for patients coinfecting with HIV is a combination of pegIFN- $\alpha$ 2a plus ribavirin, and the recommended treatment duration is 48 weeks regardless of genotype. The ribavirin dosage indicated for patients coinfecting with HIV is 800 mg/day, but because a recent study demonstrated improved sustained virologic response rates with weight-based ribavirin dosing (1000–1200 mg/day), some experts now advocate higher ribavirin dosages in this group. Additional studies to evaluate safety and efficacy of higher ribavirin dosages in this patient population are warranted.

Factors that influence sustained virologic response rates in HIV-negative patients also influence sustained virologic response rates in patients coinfecting with HIV; thus, treatment discontinuation should be considered in patients who do not achieve an early virologic response. Two important considerations in patients coinfecting with HIV are drug interactions and treatment tolerability. Adverse effects are more common among patients coinfecting with HIV/HCV, and treatment discontinuation rates are higher. Concomitant use of zidovudine with ribavirin can contribute to worsening anemia and a need for ribavirin dosage reductions. In addition, the combination of didanosine and ribavirin has been associated with severe mitochondrial toxicity, pancreatitis, liver failure, and death. Thus, neither didanosine nor zidovudine should be used in patients treated with ribavirin. Patients coinfecting with HIV and HCV who have decompensated cirrhosis should be evaluated for liver transplantation at experienced centers.

### Treatment Nonresponse or Relapse

Currently, no specific treatment regimen is indicated for chronic HCV infections that do not respond to, or that relapse after, pegIFN-based therapy. High-dose IFN alfacon-1 in combination with ribavirin is currently being evaluated in clinical trials for partial or no response to pegIFN-based therapy. In one study among patients with chronic HCV genotype 1 that is slow to respond to treatment (i.e., HCV RNA reduced by at least 2  $\log_{10}$  but still detectable at 12 weeks and undetectable at 24 weeks), extension of combination treatment with pegIFN plus weight-based ribavirin to 72 weeks improved sustained virologic response rates. Finally, the hypothesis that patients infected with HCV genotype 1 who relapse or do not respond to treatment with pegIFN and RBV may possibly benefit from longer treatment duration (beyond 48 weeks) has prompted the initiation of several long-term trials to evaluate whether low-dose maintenance pegIFN monotherapy can slow the progression of liver disease in these patients.

### Liver Transplantation

Hepatitis C virus–related end-stage liver disease is the most common indication for liver transplantation in the United States. There are currently no effective regimens for preventing HCV infection recurrence after liver transplantation; hence, HCV recurrence is essentially universal, progression of liver disease is accelerated, and optimizing treatment regimens in these patients can be extremely complex. Within 5 years after transplantation, 20% to 40% of liver allografts progress to cirrhosis;

once cirrhosis develops, 60% to 70% experience hepatic decompensation within 3 years. Patient response rates to pegIFN and ribavirin treatment for recurrent HCV infection after liver transplantation are lower than for patients in the pretransplant setting, and toxicity remains a limiting factor. Full-dose therapy is used in less than 50% of liver transplant recipients with recurrent HCV infection, and about one-third of these patients require treatment discontinuation.

### **Future Therapies for Chronic HCV Infection**

Although substantial progress has been made in the treatment of chronic HCV infection, many challenges still exist and more data are needed to overcome obstacles that limit treatment efficacy. The introduction of pegIFNs in 2001 and 2002 revolutionized chronic HCV treatment, but up to 50% of patients still do not achieve a sustained virologic response. Improved understanding of HCV molecular virology has led to development of novel agents that target specific viral proteins or nucleic acids. Improved formulations of currently available drugs and adjuvant treatment are also being evaluated.

Albinterferon, a long-acting IFN created from the fusion of albumin and IFN, has a longer half-life than pegIFNs and can be administered less often (e.g., every 2 weeks). Preliminary data suggest that albinterferon plus ribavirin appears comparable with a combination pegIFN and ribavirin regimen but with less frequent injections. Alternative agents with less hematologic toxicity such as taribavirin, a prodrug of ribavirin, are also being investigated. Initial clinical trials evaluating pegIFN and fixed-dose taribavirin (about 13–18 mg/kg/day) were disappointing, but preliminary results of a continuing trial using higher taribavirin dosages (20–30 mg/kg/day) have demonstrated efficacy similar to ribavirin with reduced anemia.

Hepatitis C virus NS3-NS4A serine protease inhibitors are a new class of oral agents designed specifically to target HCV. Clinical development of ciluprevir, the first serine protease inhibitor to be tested, was stopped because of cardiotoxicity concerns, but several other new drugs, including telaprevir (VX-950) and boceprevir, appear to be promising additions to pegIFN-based therapies. Serine protease inhibitors appear to be beneficial new agents for treatment of chronic HCV, but several resistance mutations have been identified, and additional data is needed to better understand how best to prevent and manage this issue. Other potential new drug classes effective for treatment of HCV include helicase inhibitors, nucleoside and non-nucleoside polymerase inhibitors, and adjuvant immune-modulating agents such as thymosin alfa.

## **Role of the Pharmacist**

During the past decade, substantial progress has been made in the management of both chronic HBV and chronic HCV. However, despite excellent efficacy in clinical trials, the true effectiveness of newer treatment options outside of a controlled setting can be variable and dependent on several factors, particularly patient adherence to therapy. An essential component to ensure adherence and the greatest likelihood of treatment success is patient education, an area in which pharmacists can make an important contribution.

In addition, measures to prevent transmission of HCV or HBV also need to be addressed.

Other counseling points to emphasize regarding transmission is that HBV and HCV infection are not spread by kissing, hugging, coughing, ingesting food or water, sharing utensils or drinking glasses, or casual contact. Furthermore, patients initiated on pegIFN and ribavirin treatment for chronic HCV must not only be counseled regarding the potential for teratogenicity and the need for strict contraceptive measures, but also the potential for adverse effects and ways to manage toxicities. In order to minimize further liver damage in patients with chronic HBV and/or chronic HCV infection, avoidance or minimization of alcohol ingestion should be encouraged, and vaccination against hepatitis A should be obtained (because risk of fulminant hepatic failure caused by hepatitis A virus is higher in patients with underlying liver disease). Patients should be instructed not to use over-the-counter drugs or herbal products without consulting a health care provider. Hepatitis B vaccination is recommended for HBV-seronegative patients with chronic HCV, as well as household and sexual contacts of patients with chronic HBV infection. Patients with chronic HBV who are treated with a nucleos(t)ide analogue must understand the risk of acute hepatitis exacerbation if treatment is discontinued abruptly.

Management of chronic HBV and chronic HCV clearly requires a multidisciplinary approach, and pharmacists are a key component of the health care team. In recent years, several reports have described the benefits of collaboration between clinical pharmacists and physicians or other health care professionals in the management of drug therapy in patients with chronic disease(s). Clinical pharmacist participation in drug therapy management facilitates patient adherence to therapy and contributes to improved therapy outcomes and increased cost-effectiveness of treatment. Pharmacist involvement is particularly important for patients who are undergoing treatment of chronic HCV with pegIFN and ribavirin because treatment duration is prolonged and is associated with many adverse effects. Adverse effects of pegIFN and ribavirin therapy are important causes of dosage reduction and treatment discontinuation in patients with chronic HCV; however, informing patients in advance and taking proactive measures to minimize these adverse effects helps patients endure treatment and promotes therapy adherence.

Failure to quickly recognize and manage hematologic or neuropsychiatric effects of pegIFN/ribavirin therapy can directly lead to increased patient morbidity and treatment nonadherence or dosage reductions. The manufacturers of IFN alfacon-1, pegIFN- $\alpha$ 2a, and pegIFN- $\alpha$ 2b have each established patient support programs specifically designed to help patients undergoing treatment for HCV infection with educational materials and 24-hour telephone assistance. However, continued personalized counseling and management in a clinic environment is still vital to ensure optimal treatment outcomes.

Several published reports specifically describe patient education and treatment strategies implemented by clinical pharmacists who are actively involved in managing patients with chronic HCV infection. After initial evaluation is completed, patient education provided by the pharmacist in hepatitis C clinics often includes topics such as precautions

to reduce risk of transmission to other people, lifestyle changes (e.g., alcohol avoidance) to limit disease progression, basic information regarding HCV infection (e.g., HCV genotype and likelihood of achieving a sustained virologic response), drug administration techniques, potential adverse effects, and methods for monitoring and managing these adverse effects. Regularly scheduled visits with a clinical pharmacist as well as supplemental telephone contact enable the pharmacist to continually provide education while simultaneously evaluating the patient's ability to perform subcutaneous self-injections and addressing treatment-related issues.

A recently published retrospective analysis supports the effectiveness of pharmacist-managed hepatitis C care clinics within the U.S. Department of Veterans Affairs. In this report, patients managed by a clinical pharmacist for HCV treatment demonstrated results comparable with patients managed with traditional care. Further studies are warranted, but clearly pharmacist involvement in management of patients undergoing pegIFN and ribavirin treatment is valuable. Altogether, pharmacy collaboration with other members of a multidisciplinary team and active involvement of patients in their own care optimize antiviral treatment for both HBV and HCV infection.

## Conclusion

Despite tremendous progress during the past two decades, chronic viral hepatitis continues to be an important global health care problem. Prevention of chronic viral hepatitis through vaccination and education is clearly the most desirable solution, but for patients who already have chronic HBV infection or chronic HCV, optimizing treatment options is essential. Antiviral therapy for chronic HBV and HCV infection has advanced significantly in recent years, but many treatment challenges still remain. It is hoped that continued research and development will provide novel therapies as well as new strategies to optimize treatment of patients with chronic viral hepatitis, particularly those patient populations that are more challenging to manage.

## Annotated Bibliography

1. Lok AS, McMahon BJ. AASLD practice guidelines: chronic hepatitis B. *Hepatology* 2007;45:507–39. Erratum in *Hepatology* 2007; 45: 1347. Available at [www.aasld.org/practiceguidelines/Documents/Practice%20Guidelines/chronichepBcorrection.pdf](http://www.aasld.org/practiceguidelines/Documents/Practice%20Guidelines/chronichepBcorrection.pdf). Accessed December 2, 2008.

This latest version of the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines for chronic HBV infection has several key updates. When the 2004 guidelines were published, standard IFN, lamivudine, and adefovir dipivoxil were the only drugs labeled for use in the treatment of chronic HBV infection. However, four additional drugs have since received approval for use in treating chronic HBV (i.e., pegIFN- $\alpha$ 2a, entecavir, telbivudine, and tenofovir disoproxil fumarate). Clearly, new guidelines to delineate the role of newer antiviral agents were needed. These 2007 Practice Guidelines are endorsed by the Infectious Diseases Society of America and provide

a comprehensive, evidence-based approach combined with expert opinion for the management of patients with chronic HBV. Although these guidelines are an extremely valuable tool for clinicians in the management of patients with chronic HBV, it is still important to consider that new information is released regularly; therefore, there are limitations to the provided recommendations. For example, tenofovir disoproxil fumarate is mentioned in the guidelines but it was not yet labeled for use in the treatment of chronic HBV at the time the guidelines were released. As a result, tenofovir disoproxil fumarate is not included in some of the key treatment algorithms or tables within the guidelines. In addition, one criticism of the current guidelines is that many experts now question the treatment threshold values for ALT and HBV DNA. Data reported during the past several years indicate that patients with chronic HBV infection who have elevated ALT activity and HBV DNA concentrations below current thresholds can still progress to serious liver disease including cirrhosis or hepatocellular carcinoma. As more data become available, these threshold values may need to be reevaluated. In the meantime, an individualized approach is necessary to protect certain patients from cirrhotic complications and hepatocellular carcinoma. Overall, the current AASLD guidelines for chronic hepatitis B infection are an essential tool to guide clinicians in the appropriate management of patients with chronic HBV.

2. Strader DB, Wright T, Thomas DL, Seeff LB. AASLD Practice Guidelines. Diagnosis, management and treatment of hepatitis C. *Hepatology* 2004;39:1147–71. Available at [www.aasld.org/practiceguidelines/Documents/Practice%20Guidelines/hepatitisc.pdf](http://www.aasld.org/practiceguidelines/Documents/Practice%20Guidelines/hepatitisc.pdf). Accessed December 2, 2008.

Although developed and published several years ago, the AASLD Practice Guidelines represent the most recent published by this organization for the management of chronic HCV infection. These recommendations combine an evidence-based approach with expert opinions to guide clinicians in the diagnosis, management, and treatment of patients with HCV infection. The guidelines are fully endorsed by the Infectious Diseases Society of America and the American College of Gastroenterology. Although pegIFNs, which became available in 2001 and 2002, represent the most recent drugs to receive approval for use in treating chronic HCV, several new antiviral agents and many new strategies for management of challenging patients are being evaluated in clinical trials. As more information becomes available and new drugs are marketed, these guidelines will likely require an extensive update in the near future. In the interim, the current AASLD Practice Guidelines provide a valuable foundation to build on and use for providing optimal treatment of patients with chronic HCV.

3. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, et al, for the PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346–55.

This pivotal trial was designed to assess the efficacy and safety of 24 or 48 weeks of treatment with pegIFN- $\alpha$ 2a plus a low dose (800 mg/day) or standard dose (1000–1200 mg/day) of ribavirin. This randomized, double-blind trial included 1311 patients from 99 international centers. Overall, in patients infected with HCV genotype 1, it was found that 48 weeks of treatment were statistically superior to 24 weeks, and a standard dose of ribavirin was statistically superior to low-dose ribavirin. The highest sustained virologic response rate achieved in patients infected with genotype 1 (52%) was



achieved in the group treated for 48 weeks with standard ribavirin (1000–1200 mg/day) dosing. However, sustained virologic response rates were much higher (79% to 84%) in patients infected with HCV genotypes 2 or 3 regardless of the treatment these patients received (not statistically significantly different among the four treatment groups). This important clinical trial data will help patients infected with HCV genotype 2 or 3 avoid unnecessary exposure to the toxicities of antiviral treatment. In addition, this trial increased awareness of the need for more aggressive antiviral treatment in patients chronically infected with HCV genotype 1.

4. Cehn CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al, for the REVEAL-HBV study group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65–73.

This landmark study is the largest and most thorough longitudinal study to evaluate hepatocellular carcinoma. A cohort of 3653 Taiwanese participants with untreated chronic HBV infection was followed for a mean of 11.4 years to evaluate the association between serum HBV DNA concentration and hepatocellular carcinoma. Elevated serum HBV DNA concentrations (i.e., greater than 10,000 copies/mL) were shown to be a strong risk predictor of hepatocellular carcinoma independent of HBeAg, serum ALT concentration, and liver cirrhosis. This study provided important information regarding the clinical use of serum ALT concentrations. Although elevated serum ALT is an indicator of necroinflammatory activity, patients with persistently normal concentrations may still be at risk of liver disease progression and hepatocellular carcinoma. In this study, 80% of hepatocellular carcinoma cases occurred in patients with serum ALT concentrations of less than 45 IU/L. In summary, the results of this study, as well as others, confirm the importance of serum HBV DNA monitoring and raise concerns regarding patients with normal ALT concentrations but who may have significant liver disease.

5. Alsatie M, Chalasani N, Kwo PY. Management of hepatitis C infection after liver transplantation. *Drugs* 2007;67:871–85.

Hepatitis C recurrence after liver transplantation is universal, and many treatment challenges exist. Unlike HBV, no effective prophylactic strategies are available for prevention of recurrent HCV infection after liver transplantation. Furthermore, because the natural progression of HCV infection is accelerated in liver transplant recipients, and treatment is poorly tolerated and less effective after transplantation, the need for more effective and better-tolerated therapies is obvious. Factors associated with severe recurrence and reduced patient and allograft survival are identified, the efficacy of different antiviral treatment strategies is analyzed, and treatment challenges pertaining specifically to transplant recipients are discussed. This review provides a concise but complete summary to familiarize clinicians with some of the problems that are encountered in patients who require liver transplantation for HCV-related liver disease and the strategies used to manage them.

6. Terrault N, Roche B, Samuel D. Management of hepatitis B virus in the liver transplantation setting: a European and an American perspective. *Liver Transplantation* 2005;11:716–32.

This article is a comprehensive review of the history and progress of liver transplantation for HBV-related liver disease. Advancements in prophylactic measures are described from

the early days (when outcomes were poor and HBV was considered a contraindication) to the present day (when HBV is a universally accepted indication for liver transplantation with outcomes similar to other indications). One significant limitation of this otherwise excellent review is that knowledge is continuously changing, and therefore readers must refer to newer sources, particularly regarding antiviral agents that became available after this review was published. Currently there is no universal consensus regarding prevention of HBV recurrence after liver transplantation, and protocols differ among transplant centers. An individualized approach is ideal, but clearly some type of guidelines would assist in management of this specific population of liver transplant recipients.

7. McHutchison JG, Dusheiko G, Shiffman ML, Rodriguez-Torres M, Sigal S, Bourliere M, et al, for the TPL102357 Study Group. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med* 2007;357:2227–36.

This study represents a significant breakthrough for the management of thrombocytopenia in patients with chronic HCV. Thrombocytopenia is a common complication of chronic liver disease and often limits the use of antiviral treatment. The etiology of thrombocytopenia in patients with chronic liver disease is multifactorial and is a common reason for pegIFN dose reductions and/or discontinuation in patients undergoing treatment for chronic HCV. Eltrombopag, an orally active thrombopoietin-receptor agonist, represents the first drug in a new class of agents. In this international, multicenter, double-blind, randomized, placebo-controlled, Phase II clinical trial, 74 patients with HCV-related cirrhosis and baseline platelet counts between 20,000 and 70,000/mm<sup>3</sup> were randomly assigned to receive eltrombopag (30, 50, or 75 mg daily) or placebo for 4 weeks. Patients who reached the primary end point (platelet count greater than 100,000/mm<sup>3</sup>) by week 4 were eligible to begin pegIFN and ribavirin therapy with continuation of eltrombopag or placebo for an additional 12 weeks. At week 4, 75%, 79%, and 95% of patients receiving 30, 50, or 75 mg of eltrombopag, respectively, achieved platelet counts greater than 100,000/mm<sup>3</sup> compared with none in the placebo group. Furthermore, 12 weeks of antiviral therapy were completed by 36%, 53%, and 65% of patients receiving eltrombopag doses of 30, 50, and 75 mg, respectively, compared with only 6% in the placebo group. Eltrombopag was well tolerated, with headache reported as the most common adverse effect. Overall, eltrombopag increased platelet counts in a dose-dependent manner in patients with chronic liver disease, permitting initiation and continuation of pegIFN and ribavirin therapy for up to 12 weeks. Eltrombopag appears to be a potentially useful agent for the management of thrombocytopenia in patients with chronic liver disease, particularly patients with chronic HCV who require antiviral therapy. Phase III trials evaluating longer durations of eltrombopag therapy in patients undergoing pegIFN-based treatment for chronic HCV are under way.

8. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Solá R, et al, for the ACCELERATE Investigators. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007;357:124–34.

Although this trial produced negative results, it is an important example of a strategy that, although appealing, does not appear successful for chronic HCV treatment. Several reports have suggested that patients infected with HCV genotypes 2 or 3 can be treated adequately with durations of antiviral therapy shorter than used for patients with HCV

genotype 1 infection (24 weeks vs. 48 weeks). In this clinical trial, investigators randomly assigned 1469 patients with chronic HCV genotype 2 or 3 infection to receive 180 mcg of pegIFN- $\alpha$ 2a plus 800 mg/day of ribavirin for either 16 or 24 weeks. Although high sustained virologic response rates have been observed in patients treated for 24 weeks and were also observed in this trial, the same success was not achieved with a shorter duration (16 weeks). In patients treated for 16 weeks, sustained virologic response rates were significantly lower than patients treated for 24 weeks (62% vs. 70% for 24 weeks,  $p \leq 0.001$ ). However, an interesting observation in this trial was that the sustained virologic response rates were much higher among patients with a rapid virologic response, defined as undetectable HCV RNA after 4 weeks of treatment (79% in the 16-week group vs. 85% in the 24-week group). This study has important implications for clinical practice because it further confirms the strong predictive value of the rapid virologic response at 4 weeks; it also demonstrates that although genotype 2 or 3 patients can be effectively treated for shorter durations than genotype 1, the duration should not be less than 24 weeks.

9. Conjeevaram HS, Fried MW, Jeffers LJ, Terrault NA, Wiley-Lucas TE, Afdhal N, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 2006;131:470–77.

This study is one of several clinical trials designed specifically to evaluate the efficacy of antiviral treatment for African American patients with chronic HCV. African American patients were underrepresented in many of the large clinical trials initially evaluating pegIFNs; therefore, the efficacy of combination pegIFN/ribavirin therapy in this population was difficult to assess. In this multicenter study, 196 African American and 206 white, American, treatment-naïve patients with genotype 1 chronic HCV were treated with pegIFN- $\alpha$ 2a (180 mcg/week) and ribavirin (1000–1200 mg/day) for 48 weeks. Sustained virologic response rates were significantly lower among African American patients (28% vs. 52% for white patients,  $p < 0.0001$ ). These differences were not explained by disease characteristics, baseline viral loads, or the amount of drug taken. The findings of this important study, as well as several other similar studies, clearly highlight the need to discover more effective strategies for this patient population.

10. Lok AS, Zoulim F, Locarnini S, Bartholomeusz A, Ghany MG, Pawlotsky JM, et al. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology* 2007;46:254–65.

This article is a useful reference to help clarify uncertainties and confusion surrounding antiviral drug-resistant HBV. Although drug resistance is a major factor contributing to chronic HBV infection treatment failure with nucleos(t)ides, it is not well understood by many clinicians. This updated review explains the various nomenclature and terminology used when referring to antiviral drug resistance and offers alternative solutions to help manage this treatment challenge. In addition, this review describes methods used to detect and quantify drug resistance, to interpret drug resistance data, and to apply this information to clinical practice.

11. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med* 2007;356:1445–54.

Chronic HBV and HCV infections are important causes of morbidity and mortality in patients coinfecting with HIV. This review eloquently describes the epidemiology, disease course, and treatment options in this complex patient population. Peer-reviewed literature and expert opinion published during the past decade are described, as well as results from presentations and recommendations of the first European Consensus Conference on the Treatment of Chronic Hepatitis B and C in HIV-Coinfected Patients. The information summarized in this review is useful to enhance knowledge and assist clinicians in optimizing antiviral treatment for both chronic HBV infection and chronic HCV in patients coinfecting with HIV.

12. Smith JP, Dong MH, Kaunitz JD. Evaluation of a pharmacist-managed hepatitis C care clinic. *Am J Health Syst Pharm* 2007;64:632–6.

Chronic HCV infection is a growing public health problem. Current treatment options have many adverse effects and require close monitoring for toxicity. Patient education and effective drug therapy management are critical to ensure adherence to the treatment regimen and to facilitate optimal treatment outcomes. This article is an excellent illustration of the important contributions that pharmacists can make in managing patients with chronic HCV. Strategies used by a clinical pharmacist at a hepatitis C care clinic are described, and treatment outcomes for patients managed in this pharmacist's clinic are evaluated and presented. This report demonstrates how strategies used by clinical pharmacists in a clinic setting can facilitate successful treatment outcomes for patients with chronic HCV while allowing the patient to maintain a reasonable health-related quality of life. The only significant limitation of this excellent article is that it is derived from experience at clinics within the U.S. Department of Veterans Affairs and thus may not be entirely applicable to clinical pharmacists outside the Veterans Affairs health system.

13. Jacobson IM, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, et al, and the WIN-R study group. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007;46:971–81.

This prospective, multicenter, open-label study was conducted at 236 academic- or community-based sites in the United States to evaluate whether weight-based ribavirin dosing would be more effective than fixed dosing when combined with pegIFN- $\alpha$ 2b for chronic HCV treatment. In this clinical trial, 5027 treatment-naïve adult patients with chronic HCV were randomly assigned to receive pegIFN- $\alpha$ 2b 1.5 mcg/kg/week plus either fixed (800 mg/day) or weight-based ribavirin dosing for 48 weeks. In the weight-based ribavirin group, patients weighing less than 65 kg received 800 mg/day, patients weighing 65–85 kg received 1000 mg/day, patients weighing 86–105 kg received 1200 mg/day, and patients weighing 106–125 kg received 1400 mg/day. Overall sustained virologic response rate was significantly higher in patients who received pegIFN- $\alpha$ 2b with weight-based ribavirin dosing compared with those who received fixed-dose ribavirin (44.2% vs. 40.5%,  $p = 0.008$ ). A significantly higher sustained virologic response rate was also observed with weight-based ribavirin dosing in patients infected with HCV genotype 1 (34% vs. 28.9%;  $p = 0.005$ ). A subanalysis of African American patients infected with HCV genotype 1 also demonstrated a significantly higher sustained virologic response rate with weight-based ribavirin dosing when compared with fixed dosing (20.7% vs. 10.1%;

p=0.006); however, response rates were still lower than reported in other ethnic groups. In patients infected with HCV genotype 2 or 3, sustained virologic response rates were not significantly different between weight-based and fixed doses (61.8% vs. 59.5%; p=0.252), and extending the treatment duration to 48 weeks did not provide any additional benefit with either dosing strategy. Safety profiles were similar among the dosage groups, and although anemia (hemoglobin less than 10 g/dL) occurred more often in the weight-based ribavirin group (19.3% vs. 12.5%), only 1% of patients discontinued treatment because of anemia. Overall treatment discontinuation because of adverse effects was similar in both groups (14.9% for the weight-based and 14.5% for the fixed-dose groups, respectively) and was primarily because of depression and fatigue.

14. Jacobson IM, Brown RS Jr, McCone J, Black M, Albert C, Dragutsky MS, et al, and the WIN-R study group. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. *Hepatology* 2007;46:982–90.

This clinical trial was unique because it only involved patients within the United States and represented a “real world” approach to HCV infection treatment by involving several community and academic sites. However, significant limitations of the study design included missing data and the absence of the kind of rigorous adherence monitoring performed in trials conducted for marketing registration. The study has important clinical implications because it demonstrated the importance of adjusting ribavirin dosing in obese patients and confirmed that pegIFN- $\alpha$ 2b plus weight-based ribavirin is more effective than fixed-dosed ribavirin, particularly in patients (including African American patients) with genotype 1 HCV. In addition, the trial results established the efficacy and safety of a new ribavirin dosage (1400 mg/day for patients weighing 106–125 kg), and the new information subsequently led to a labeling change for ribavirin dosing when combined with pegIFN- $\alpha$ 2b. Finally, this clinical study confirmed that 24 weeks of fixed-dose ribavirin is adequate treatment for patients with genotype 2 or 3 HCV, and extending the treatment duration to 48 weeks provides no additional benefit.

15. Keeffe EB, Dieterich DT, Pawlotsky J-M, Benhamou Y. Chronic hepatitis B: preventing, detecting, and managing viral resistance. *Clin Gastroenterol Hepatol* 2008;6:268–74.

This review is an excellent updated reference regarding the prevention, detection, and management of viral resistance in patients with chronic HBV. Written by several viral hepatitis experts, this concise review includes essential information for clinicians caring for patients with chronic HBV. Consequences of resistance are defined, current approaches to resistance testing are described, and limitations of assays that are used for detection of resistance mutations are identified. In addition, treatment strategies to minimize emergence of resistance, and regimens that may be effective after resistance has occurred are discussed. As more antiviral agents become available for chronic HBV infection treatment, and as new resistance mutations are identified, providing optimal management of patients with chronic HBV infection is becoming more difficult and complex. References such as this are essential resources because clinicians need to be aware of current approaches to prevention, detection, and, most important, appropriate management of viral resistance in patients with chronic HBV infection.

16. Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, et al. Care of patients coinfecting with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS* 2007;21:1073–89.

General guidelines for diagnosis and management of patients with HCV infection have been developed and released within the past several years, but information specifically pertaining to patients coinfecting with HIV is only included in one section of most guidelines. This updated version of the international guidelines for treatment of patients coinfecting with HCV and HIV identifies 11 key areas in which new recommendations were needed since the release of the previous guidelines in 2004. Developed by an international panel of experts in the fields of infectious diseases and hepatology, these guidelines identify the importance of appropriate management in this complex patient population and offer updated recommendations in the 11 key areas: (1) patients with persistently normal ALT and AST; (2) proper assessment of liver fibrosis; (3) predictors of sustained virologic response; (4) optimal pegIFN/ribavirin dosing; (5) optimal duration of chronic HCV treatment; (6) treatment strategies for nonresponders and relapsers; (7) management of patients with end-stage liver disease; (8) treatment of acute HCV infection; (9) management of patients infected with several hepatitis viruses; (10) interactions between HCV treatment and antiretroviral drugs; and (11) hepatotoxicity of antiretroviral drugs. As with other resources, these guidelines highlight the limitations of serum ALT as a marker of liver disease progression, and the authors propose that antiviral treatment should be recommended based on the individual patient’s motivation, disease duration, fibrosis stage, and virologic profile regardless of ALT concentration. In addition, although previous guidelines recommend a lower, fixed ribavirin dose (800 mg/day) in patients coinfecting with HIV, the updated 2008 guidelines provide data to support improved efficacy using higher weight-based ribavirin doses (1000–1200 mg/day). Furthermore, the authors propose that HIV patients coinfecting with HCV genotype 2 or 3 who experience a rapid virologic response (e.g., 4 weeks) may benefit from shorter treatment durations (e.g., 24 weeks). In contrast, HIV patients coinfecting with HCV genotypes 1 and 4 who experience an early virologic response (at 12 weeks) but not a rapid virologic response (at 4 weeks), may benefit from longer treatment durations (e.g., 60–72 weeks). These updated recommendations are extremely useful for providing optimal management of patients coinfecting with HCV and HIV.

17. Soriano V, Puoti M, Peters M, Benhamou Y, Sulkowski M, Zoulim F, et al. Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B Virus International Panel. *AIDS* 2008;22:1399–410.

Similar to HCV infection, several guidelines are available for management of chronic HBV, but most only devote a section to the care of patients coinfecting with HBV and HIV. This updated version of the international guidelines focuses specifically on issues related to patients coinfecting with HBV and HIV, and it identifies nine key areas in which new recommendations were needed since the release of previous guidelines in 2005. Developed by an international panel of experts in the fields of hepatology and infectious diseases, these recommendations provide new information to assist clinicians in the management of this complex patient population. Important topics discussed include the following: (1) changes in epidemiology/natural history of HBV and HIV coinfection; (2) new diagnostic tools; (3) chronic HBV infection treatment in patients with HIV coinfection;

(4) antiviral drug resistance; (5) significance of hepatitis delta virus coinfection; (6) infection with several hepatitis viruses; (7) hepatotoxicity of antiretroviral drugs; (8) HBV vaccination in patients coinfecting with HIV; and (9) liver transplantation in patients coinfecting with HBV and HIV. An important point emphasized in the new guidelines is that, given the accelerated course of chronic HBV infection in HIV-coinfecting patients, initiation of antiviral treatment should be considered earlier than in HIV-negative patients. Overall, these updated recommendations are extremely useful in the optimal management of patients coinfecting with HBV and HIV.

18. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al; Department of Health and Human Services Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR* 2008;57(RR-8):1–20.

This recent report updates and expands previous guidelines for HBsAg testing and includes new recommendations for public health evaluation and management for individuals with chronic HBV infection and their contacts. Hepatitis B testing is now recommended for: people with HIV infection; pregnant women; infants born to HBsAg-positive mothers; household contacts and sexual partners of HBsAg-positive people; health care workers after known occupational exposure; people born in geographic areas in which HBsAg prevalence is at least 2%; people born in the United States but not vaccinated as infants and whose parents were born in geographic areas with HBsAg prevalence of at least 8%; men who have sex with men; people with liver enzyme elevations of unknown etiology; and injection drug users. This latest version of the CDC guidelines summarizes current HBsAg testing recommendations, expands previous recommendations to increase the identification of chronically infected individuals, and defines the components of programs needed to successfully identify HBV-infected people. This report serves as an excellent comprehensive resource for health care professionals involved in the development of HBV prevention programs, as well as those involved in the clinical care of HBV-infected individuals.

# SELF-ASSESSMENT QUESTIONS

## Questions 1–3 pertain to the following case.

A.B., a 46-year-old African American man (weight 80 kg), has been referred to the hepatology clinic for management of his chronic hepatitis C virus (HCV) infection. His medical history is significant for hypothyroidism and hypertension. His social history is significant for a remote history of illicit injection drug use (last used 25 years ago). A.B.'s current drugs are: levothyroxine 100 mcg daily, nifedipine XL 60 mg daily, and hydrochlorothiazide 25 mg daily. His blood pressure today is 118/73 mm Hg. Laboratory test results are as follows: hepatitis C antibody, positive; thyroid-stimulating hormone, 3.5 mIU/L; alanine aminotransferase (ALT) 23 U/L; total bilirubin 2.3 mg/dL; serum creatinine 1.2 mg/dL; HCV RNA 1,200,000 IU/mL; HCV genotype 1b; white blood cell count  $6.3 \times 10^3/\text{mm}^3$ ; platelet count 120,000/ $\text{mm}^3$ ; hemoglobin 13.6 g/dL; and hematocrit 41%.

- In addition to A.B.'s HCV genotype 1b, which one of the following sets of factors is most likely to reduce the chances of a sustained virologic response to antiviral treatment?
  - African American race and HCV RNA concentration.
  - HCV RNA concentration and illicit injection drug use.
  - Hypertension, hypothyroidism, and HCV RNA concentration.
  - African American race and ALT concentration.
- A.B. undergoes additional testing, including a liver biopsy. Histologic examination reveals changes consistent with chronic hepatitis with moderate to severe necroinflammatory activity and early bridging fibrosis. The hepatologist would like to start A.B. on antiviral treatment. Which one of the following initial treatment regimens is most likely to result in a sustained virologic response in A.B.?
  - Pegylated (polyethylene glycol–attached) interferon (PegIFN)- $\alpha$ 2a 180 mcg subcutaneously once weekly plus ribavirin 400 mg orally twice daily.
  - PegIFN- $\alpha$ 2b 80 mcg subcutaneously once weekly plus ribavirin 400 mg orally in the morning and 600mg in the evening.
  - IFN- $\alpha$ 2b 3 MIU three times weekly plus ribavirin 600 mg orally twice daily.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly plus ribavirin 600 mg orally twice daily.
- A.B. returns to the hepatology clinic 3 months after starting antiviral treatment. Which laboratory test or procedure would be most useful to determine if A.B. is responding to antiviral treatment and to predict whether he will or will not achieve a sustained virologic response?
  - HCV antibody.
  - HCV RNA concentration.

- Serum ALT concentration.
- Liver biopsy.

- J.S. is a 54-year-old white man with chronic HCV and HIV coinfection. His social history is significant for active heroin and cocaine use and drinking four or five alcoholic beverages daily. His laboratory test are reported as: ALT 54 IU/L; HCV RNA 2,400,000 IU/mL; HCV genotype 1a; HIV RNA 36,000 copies/mL; and a CD4<sup>+</sup> count of 282 cells/ $\mu\text{L}$ . What factors present in J.S.'s case may accelerate progression of chronic liver disease?
  - White race, HIV coinfection, and HCV genotype 1a.
  - HIV coinfection, alcohol use, and male sex.
  - HCV RNA concentration, HCV genotype 1a, and HIV coinfection.
  - HIV coinfection, HCV genotype 1a, and alcohol use.

## Questions 5 and 6 pertain to the following case.

J.C., a 38-year-old married woman (weight 56 kg) with two children, was recently diagnosed with chronic HCV infection. Her medical history is significant for mild depression with generalized anxiety disorder, gastroesophageal reflux disease, and a motor vehicle collision in 1986 after which she received several blood transfusions. Her current drugs include omeprazole 20 mg daily and escitalopram 10 mg daily. Laboratory tests are reported as: HCV antibody, positive; HCV genotype 2a; HCV RNA 490,000 IU/mL; serum creatinine 0.8 mg/dL; ALT 19 IU/L; total bilirubin 1.2 mg/dL; white blood cell count  $6.2 \times 10^3/\text{mm}^3$ ; platelet count 160,000/ $\text{mm}^3$ ; hemoglobin 13.5 g/dL; and hematocrit 40%.

- If J.C. is initiated on antiviral therapy for chronic HCV, which one of the following treatment regimens is the most appropriate initial therapy?
  - PegIFN- $\alpha$ 2b 80 mcg subcutaneously once weekly plus ribavirin 400 mg orally twice daily for 24 weeks.
  - PegIFN- $\alpha$ 2b 180 mcg subcutaneously once weekly plus ribavirin 400 mg orally twice daily for 24 weeks.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly plus ribavirin 400 mg orally twice daily for 48 weeks.
  - PegIFN- $\alpha$ 2b 50 mcg subcutaneously once weekly plus ribavirin 400 mg orally twice daily for 48 weeks.
- J.C. should be counseled before starting treatment with a combination of pegIFN and ribavirin. Which one of the following statements is the most important information to include in your counseling session?

- A. Because pegIFN can worsened depression, J.C.'s escitalopram dosage should be increased to 20 mg daily before she starts treatment.
- B. She should use two forms of contraception during pegIFN and ribavirin treatment and for at least 6 months after completion of therapy.
- C. The likelihood of achieving a sustained virologic response with pegIFN and ribavirin treatment is about 50%.
- D. If her HCV RNA is negative at 12 weeks after starting treatment she may require only 16 weeks of antiviral treatment.
7. S.T. is a 53-year-old man (weight 85 kg) with HCV genotype 1 chronic HCV infection. He started antiviral treatment 24 weeks ago with pegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly and ribavirin 600 mg orally twice daily. S.T. experienced a rapid virologic response (HCV RNA undetectable at 4 weeks) and has been able to maintain full pegIFN and ribavirin treatment dosages. His laboratory tests are reported as: serum creatinine 1.1 mg/dL; ALT 39 IU/L; total bilirubin 1.4 mg/dL; white blood cell count  $8.4 \times 10^3/\text{mm}^3$ ; platelet count  $35,000/\text{mm}^3$ ; hemoglobin 14.5 g/dL; and hematocrit 45%. S.T. is concerned that his platelet count continues to decline. What investigational agent could potentially help manage this adverse effect of pegIFN?
- A. Taribavirin.
- B. Albinterferon.
- C. Eltrombopag.
- D. Telaprevir.
8. J.K. is a 30-year-old woman with nucleos(t)ide analogue-naïve chronic hepatitis B virus (HBV) infection. Laboratory tests were reported as: hepatitis B surface antigen (HBsAg) positive; HBV core antibody positive; hepatitis B e antigen (HBeAg) negative; ALT 32 IU/L; and HBV DNA undetectable. Her family history is significant for chronic HBV infection and hepatocellular carcinoma in her father. Which one of the following statements provides the best classification of J.K.'s chronic HBV infection as well as the best treatment plan?
- A. J.K. is a chronic inactive HBV carrier. Antiviral treatment is not indicated at this time, but she should continue periodic laboratory testing and screening for hepatocellular carcinoma.
- B. J.K. is a chronic inactive HBV carrier. Antiviral treatment with pegIFN should be started after HBV genotype testing is performed.
- C. J.K.'s chronic HBV is in the immune-tolerant phase. Antiviral treatment is not indicated at this time, but she should continue periodic laboratory testing and screening for hepatocellular carcinoma.
- D. J.K. has active HBeAg-negative chronic HBV infection. A potent antiviral drug with low resistance rates should be started.
9. A.T., a 46-year-old woman (weight 65 kg) with chronic HBV infection, comes to the hepatology clinic for a follow-up appointment. She appears anxious because, although her liver function tests have been normal for years, laboratory tests drawn 2 weeks ago revealed elevated liver enzymes. Three months ago her reported laboratory results were: HBsAg positive; HBeAg negative; ALT 35 IU/L; serum creatinine 0.7 mg/dL; HBV DNA undetectable. The concerning laboratory tests drawn 2 weeks ago were: HBsAg positive; HBeAg negative; HBV DNA 3000 IU/mL; ALT 198 IU/L; and serum creatinine 0.8 mg/dL. A.T. denies alcohol use and adamantly insists she has never missed a dose of her antiviral drugs, a fact supported by pharmacy refill records. Her current drugs include: lamivudine 100 mg daily, calcium citrate 500 mg three times daily, and paroxetine 20 mg daily. What is the most likely explanation for the recent change in A.T.'s laboratory values?
- A. Genotypic resistance to lamivudine.
- B. Primary nonresponse to lamivudine.
- C. Biochemical and virologic breakthrough because of nonadherence.
- D. Inhibition of lamivudine absorption by calcium citrate resulting in decreased efficacy.
10. S.K. is a 53-year-old man with chronic HBV infection. S.K. has been taking lamivudine mg daily for the past 4 years to treat his chronic HBV. Laboratory tests 6 months ago are reported as: AST: 40 IU/L; ALT 22 IU/L; serum creatinine 0.9 mg/dL; HBV DNA undetectable; HBsAg positive; HBeAg positive. Laboratory tests 2 weeks ago are reported as: AST 125 IU/L; ALT 230 IU/L; serum creatinine 0.8 mg/dL; HBV DNA 32,000 IU/mL; HBsAg positive; HBeAg positive. Based upon his most recent laboratory test results, which of the following treatment options is most appropriate for S.K.?
- A. Discontinue lamivudine; begin entecavir 1 mg daily.
- B. Continue lamivudine but increase the dosage to 150 mg twice daily.
- C. Continue lamivudine and add adefovir dipivoxil 10 mg daily.
- D. Discontinue lamivudine; begin adefovir dipivoxil 10 mg daily.
11. M.J. is a 46-year-old man with chronic HBV infection. His laboratory tests results were reported as: HBsAg positive; HBeAg negative; hepatitis B e antibody negative; hepatitis B core antibody total positive; HBV DNA 70,000 IU/mL; and ALT 132 IU/L. The hepatologist would like to initiate antiviral treatment for M.J. Which of the following statements regarding antiviral treatment options for M.J. is correct?
- A. PegIFN therapy has greater efficacy and less resistance than standard IFN therapy for treatment of M.J.'s HBeAg-negative chronic HBV infection.
- B. Nucleos(t)ide analogue-based therapy would be better tolerated and has a more durable response than IFN-based therapy to treat M.J.'s chronic HBV infection.
- C. The duration of nucleos(t)ide analogue therapy for M.J. is unclear.

- D. Telbivudine is the preferred antiviral agent for M.J. because of its high potency.
12. R.S. is a 45-year-old man (weight 80 kg) with chronic nucleos(t)ide-naïve HBV infection, chronic renal insufficiency, hyperlipidemia, and hypertension. His current drugs include atorvastatin 20 mg daily and lisinopril 10 mg daily. Laboratory test results were reported as: HBV DNA 37,000 IU/mL; HBeAg positive; ALT 134 U/L; and serum creatinine 2.7 mg/dL. Which one of the following is the best long-term treatment option for R.S.?
- Adefovir dipivoxil 10 mg daily.
  - Entecavir 0.5 mg every 48 hours.
  - Lamivudine; first dose 100 mg, then 50 mg daily.
  - Telbivudine 600 mg every 48 hours.
13. C.D. is a 53-year-old man (weight 72 kg) with chronic HCV infection. His recent laboratory test results were: HCV genotype 1b; HCV RNA 300,000 IU/mL; ALT 83 IU/L; serum creatinine 2.6 mg/dL; hemoglobin 14.7 g/dL; hematocrit 43%; white blood cell count  $7.6 \times 10^3/\text{mm}^3$ ; and platelets  $144,000/\text{mm}^3$ . Which one of the following is the most appropriate treatment option for C.D.?
- PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly plus ribavirin 1000 mg once daily for 48 weeks.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly for 48 weeks.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly and ribavirin 600 mg twice daily for 28 weeks.
  - PegIFN- $\alpha$ 2b 80 mcg subcutaneously once weekly for 48 weeks.
- Questions 14–16 pertain to the following case.**
- J.K. is a 42-year-old man (weight 80 kg) with chronic HCV and HIV coinfection. His laboratory test results were: HCV RNA 1,400,000 IU/mL; ALT 43 IU/L; HCV genotype 2b; serum creatinine 0.9 mg/dL; CD4<sup>+</sup> count  $374/\text{mm}^3$ ; and HIV viral load, negative. J.K.'s current antiretroviral regimen consists of didanosine, lamivudine, and lopinavir plus ritonavir.
14. Which one of the following treatment regimens is most likely to produce a sustained virologic response in J.K.?
- PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly and ribavirin 400 mg twice daily for 48 weeks.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly and ribavirin 400 mg twice daily for 24 weeks.
  - PegIFN- $\alpha$ 2b 120 mcg subcutaneously once weekly and ribavirin 400 mg twice daily for 24 weeks.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly for 48 weeks.
15. Which one of J.K.'s antiretroviral drugs should be changed or discontinued to avoid increased toxicity before he begins treatment for HCV?
- Lamivudine.
  - Didanosine.
  - Lopinavir.
  - Ritonavir.
16. Six months after initiating pegIFN/ribavirin treatment, J.K.'s HCV RNA is unchanged. How should his HCV treatment regimen be modified based on this new information?
- Treatment should be discontinued.
  - Ribavirin dosage should be increased to 600 mg twice daily.
  - Treatment should be continued at the current dosages for a total of 48 weeks.
  - PegIFN should be changed to IFN alfacon 9 mcg subcutaneously daily.
17. H.B. is a 42-year-old woman with chronic HBV infection. Her laboratory test results are: HBsAg, positive; HBeAg, negative; hepatitis B core antibody, positive; HBV DNA 132,000 IU/mL; and ALT 55 IU/L. According to the results of the REVEAL-HBV study group trial, which laboratory test is a strong, independent risk predictor of hepatocellular carcinoma in patients like J.K.?
- Serum ALT concentration.
  - Serum bilirubin concentration.
  - HBeAg.
  - Serum HBV DNA.
18. D.B. is a 45-year-old man with nucleos(t)ide-naïve chronic HBV infection and compensated cirrhosis. His laboratory tests were reported as: HBsAg, positive; HBeAg, negative; HBV DNA 4,000 IU/ml; ALT 40 IU/L; and serum creatinine 0.9 mg/dL. Which one of the following is the best long-term treatment option for D.B.?
- Lamivudine 100 mg daily.
  - Telbivudine 600 mg daily.
  - Entecavir 0.5 mg daily.
  - PegIFN- $\alpha$ 2a 180 mcg subcutaneously once weekly.
19. L.K., a 53-year-old woman with chronic HBV infection, is seen in the hepatology clinic for a follow-up visit. Her laboratory tests completed 3 months ago were reported as: HBsAg, positive; HBeAg, negative; HBV DNA, negative; ALT 23 IU/L; and serum creatinine 0.8 mg/dL. Laboratory tests performed 2 weeks before her current appointment were reported as: HBsAg, positive; HBeAg, negative; HBV DNA 21,000 IU/mL; and ALT 260 IU/L. Her current antiviral treatment, telbivudine 600 mg daily, was started 2 years ago. L.K.'s hepatologist suspects genotypic resistance to telbivudine. While awaiting the results of genotypic resistance testing, which one of the following is the most appropriate treatment option for L.K.?
- Continue telbivudine and add lamivudine 100 mg daily.
  - Discontinue telbivudine and start entecavir 0.5 mg daily.

- C. Continue telbivudine and add tenofovir disoproxil fumarate 300 mg daily.
  - D. Continue telbivudine and add adefovir dipivoxil 30 mg daily.
20. F.A., a 57-year-old African American man (weight 117 kg) with chronic HCV, is referred to the hepatology clinic for antiviral treatment. His medical history is significant for hypertension and type 2 diabetes mellitus. His current drugs are glipizide XL (extended release) 10 mg daily, hydrochlorothiazide 50 mg daily, and lisinopril 10 mg daily. His recent laboratory tests were reported as: ALT 180 IU/L; aspartate aminotransferase 165 IU/L; total bilirubin 2.4 g/dL; HCV RNA 900,000 IU/mL; HCV genotype 1b; serum creatinine 1.1 g/dL; hemoglobin 15.6 g/dL; hematocrit 47%; white blood cell count  $6.4 \times 10^3/\text{mm}^3$ ; and platelet count 170,000/ $\text{mm}^3$ . After completing additional testing, F.A. will be initiated on combination therapy with pegIFN alfa-2b and ribavirin. According to the results of the Weight-Based Dosing of PEG-Intron and Rebetol (WIN-R) study, what would be the most appropriate ribavirin dose for F.A.?
- A. 800 mg in the morning, 800 mg in the evening.
  - B. 600 mg in the morning, 800 mg in the evening.
  - C. 600 mg in the morning, 600 mg in the evening.
  - D. 400 mg in the morning, 600 mg in the evening.