

REVIEWS

A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States

EMMET B. KEEFFE,* DOUGLAS T. DIETERICH,† STEVE-HUY B. HAN,§ IRA M. JACOBSON,|| PAUL MARTIN,¶ EUGENE R. SCHIFF,# HILLEL TOBIAS,** and TERESA L. WRIGHT*†

*Division of Gastroenterology and Hepatology, Stanford University Medical Center, Stanford; §Division of Digestive Diseases, University of California at Los Angeles; ¶Liver Transplant Program, Cedars-Sinai Medical Center, Los Angeles; **Division of Gastroenterology, University of California at San Francisco, San Francisco, California; †Department of Medicine, The Mount Sinai Medical Center; ||Division of Gastroenterology and Hepatology, Weill Medical College of Cornell University; **Liver Transplant Service, New York University Medical Center, New York, New York; and #Center for Liver Diseases, University of Miami School of Medicine, Miami, Florida

Background & Aims: Chronic hepatitis B is an important public health problem worldwide and in the United States. A treatment algorithm for chronic hepatitis B virus (HBV) infection was developed by a panel of US hepatologists based on new developments in the understanding of the virology of HBV, availability of more sensitive molecular diagnostic testing, and advantages and disadvantages of currently approved therapies. **Methods:** This algorithm is based on available evidence, but where data are lacking, the panel relied on clinical experience and consensus expert opinion. **Results:** Serum HBV DNA can be detected at levels as low as 100–1000 copies/mL by using molecular assays and should be determined to establish a baseline level before treatment, monitor response to antiviral therapy, and survey for the development of drug resistance. The primary aim of antiviral therapy is durable suppression of serum HBV DNA to the lowest level possible. The threshold level of HBV DNA for determination of candidacy for therapy is $\geq 10^5$ copies/mL for patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. A lower serum HBV DNA threshold is appropriate for patients with HBeAg-negative chronic hepatitis B and those with decompensated cirrhosis, and the panel recommends thresholds of 10^4 copies/mL and 10^3 copies/mL, respectively. **Conclusions:** Interferon alfa-2b, lamivudine, and adefovir dipivoxil are all approved as initial therapy for chronic hepatitis B and have certain advantages and disadvantages. Issues for consideration include efficacy, safety, incidence of resistance, method of administration, and cost. Studies are under way to explore the safety and efficacy of combination therapy, which may prove to be more effective than monotherapy in suppressing viral replication and may decrease or delay the incidence of drug resistance.

This hepatitis B virus (HBV) treatment algorithm was developed by a panel of US hepatologists. The aim is to develop a practical and comprehensive algo-

gorithm for the diagnosis, treatment, and monitoring of patients with chronic HBV infection in the United States. The panel analyzed existing data on available therapies, as well as published guidelines.^{1,2} When possible, the panel's recommendations are based solidly on evidence, but where data are lacking, the panel relied on their own clinical experience and expert opinion. The algorithm aims to assist treating physicians in answering the practical questions of what tests to order and how to interpret them, which patients to treat, when and how long to treat, what the available treatment options are, and how to monitor patients.

Burden of Disease

It is estimated that worldwide, at least 350 million people are chronically infected with HBV.³ Although the prevalence of HBV infection in the United States is less than that in many other countries, an estimated 1.25 million individuals are infected with the virus.⁴ Despite the availability of hepatitis B vaccine programs, new infections with HBV remain common. Approximately 100,000 people in the United States become acutely infected each year.⁵ Individuals with chronic hepatitis B are at increased risk for developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC). It is estimated that up to 5000 people

Abbreviations used in this paper: AFP, α -fetoprotein; ALT, alanine aminotransferase; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; PCR, polymerase chain reaction; US, ultrasound; YMDD, tyrosine-methionine-aspartate-aspartate.

© 2004 by the American Gastroenterological Association

1542-3565/04/\$30.00

PII: 10.1053/S1542-3565(03)00312-4

Table 1. Definitions and Diagnostic Criteria Used in HBV Infection

Definitions	Diagnostic criteria
Chronic hepatitis B	
Chronic necroinflammatory disease of the liver caused by persistent HBV infection	<ol style="list-style-type: none"> 1. HBsAg positive > 6 mo 2. Serum HBV DNA > 10⁵ copies/mL 3. Persistent or intermittent elevation of ALT/AST levels 4. Liver biopsy showing chronic hepatitis (necroinflammatory score ≥ 4)^a
Chronic hepatitis B can be subdivided into:	
HBeAg-positive chronic hepatitis B	HBeAg positive, anti-HBe negative
HBeAg-negative chronic hepatitis B	HBeAg negative, anti-HBe positive ^b
Inactive HBsAg carrier state	
Persistent HBV infection of the liver without significant ongoing necroinflammatory disease	<ol style="list-style-type: none"> 1. HBsAg positive > 6 mo 2. HBeAg negative, anti-HBe positive 3. Serum HBV DNA < 10⁵ copies/mL 4. Persistently normal ALT/AST levels 5. Liver biopsy showing absence of significant hepatitis (necroinflammatory score < 4)^a
Resolved hepatitis B	
Previous HBV infection without further virological, biochemical, or histological evidence of active virus infection or disease	<ol style="list-style-type: none"> 1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs 2. HBsAg negative 3. Undetectable serum HBV DNA^c 4. Normal ALT levels

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg; anti-HBs, antibody to HBsAg; anti-HBc, antibody to hepatitis B core antigen.

^aLiver biopsy optional.

^bMost of these patients have precore or core promoter variants.

^cVery low levels may be detectable by polymerase chain reaction.

Adapted with permission from the American Association for the Study of Liver Diseases.¹

die each year in the United States from complications of HBV infection, including cirrhosis and HCC.⁶

Natural History and Terminology

After acute HBV infection, ~3%–5% of adults and up to 95% of children fail to produce an immune response adequate to clear the infection^{3,7,8}; in these persons, chronic HBV infection develops. Clinical terms used for the stages of chronic HBV infection and criteria used in their diagnosis, adopted at The National Institutes of Health Workshop on Management of Hepatitis B,^{1,9} are listed in Table 1. Other clinical terms relating to HBV infection are listed in Table 2.

The onset of chronic HBV infection is marked by the continued presence of hepatitis B surface antigen (HBsAg), high levels of HBV DNA, and the presence of hepatitis B e antigen (HBeAg) in serum. In adult-acquired disease, the early phase of infection often is accompanied by marked disease activity, with elevated alanine aminotransferase (ALT) levels, whereas in perinatally acquired disease, patients tend to have normal ALT levels (immune tolerant phase). The activity of disease can accelerate in the latter group, with increased ALT levels, but this usually does not occur until adulthood. HBeAg seroconversion (defined as loss of HBeAg

and gain of antibody to HBeAg [anti-HBe], occurring either spontaneously or related to treatment) is most common in the phases in which ALT levels are elevated. Loss of HBeAg and seroconversion to anti-HBe usually

Table 2. Definitions of Other Clinical Terms Used in the Course of HBV Infection

Acute exacerbation or flare of hepatitis B
Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than 2 times the baseline value
Reactivation of hepatitis B
Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B
HBeAg clearance
Loss of HBeAg in a person who was previously HBeAg positive
HBeAg seroconversion
Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative, associated with a decrease in serum HBV DNA levels to < 10 ⁵ copies/mL
HBeAg reversion
Reappearance of HBeAg in a person who was previously HBeAg negative and anti-HBe positive

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg.

Adapted with permission from the American Association for the Study of Liver Diseases.¹

are preceded by a marked decrease in serum HBV DNA levels to $<10^5$ copies/mL¹⁰ and typically are followed by normalization of ALT levels. Thus, HBeAg seroconversion represents a transition from chronic hepatitis B to an “inactive HBsAg carrier state,” in which there is little clinical evidence of hepatitis and lower serum HBV DNA levels. Some patients also lose HBsAg, which is referred to as “resolution” of HBV infection.

A proportion of patients who undergo HBeAg seroconversion experience a return of high HBV DNA levels and persistent or intermittent ALT level elevations. These patients have a naturally occurring mutant form of HBV that does not produce HBeAg, usually because of mutation in the precore or core promoter region. This form of chronic HBV infection is called “HBeAg-negative chronic hepatitis B.” Hence, chronic hepatitis B can be divided into 2 major forms: HBeAg positive and HBeAg negative.

Spontaneous flares of disease activity can occur during the natural course of chronic hepatitis B,¹¹ and repeated exacerbations may lead to progressive fibrosis and cirrhosis, as well as carcinogenesis. For patients with chronic hepatitis B, mortality rates at 5 years are 16% for those with compensated cirrhosis^{12,13} and 65%–86% for those with decompensated cirrhosis (in the absence of liver transplantation).^{13,14} The presence of HBeAg and HBV DNA is associated with an increased risk for HCC. A recent study found that men who are positive for both HBsAg and HBeAg have a relative risk for progression to HCC of 60.2 (9.6 for HBsAg alone) compared with those without HBsAg.¹⁵ This study also showed that the likelihood of HCC in individuals with detectable serum HBV DNA by a branched-chain DNA assay (Quantiplex; Chiron, Emeryville, CA) is 3.9-fold that of individuals without detectable HBV DNA, and the risk increases with increasing HBV DNA levels.¹⁵ Because HBeAg and HBV DNA are both markers of HBV replication, these findings implicate viral replication in the outcome of HBV infection and provide a rationale for antiviral therapy to arrest progression of liver disease.

HBV Mutants

HBV has a mutation rate ~ 10 times greater than that of other DNA viruses, and the reverse transcriptase lacks a proofreading function that is common to most other polymerases. Mutations may occur in any of the HBV genes; several viral mutants occur naturally or by selective pressure of antiviral therapy. Four forms of HBV are relevant in current clinical practice: wild-type HBV and 3 commonly occurring mutant viruses; precore mutants, core promoter mutants, and tyrosine-methio-

nine-aspartate-aspartate (YMDD) mutants. Other mutants are likely to be identified as newer drugs are used long term for the treatment of HBV infection (e.g., an adefovir-resistant mutation [N236T] recently was identified in 2 of 124 patients treated for 2 yr).¹⁶

Precore and Core Promoter Mutants

HBeAg generally is regarded as a marker of HBV replication, and in the past, patients found to be HBeAg negative were considered to have nonreplicative HBV infection. Patients with normal ALT levels were referred to as “healthy carriers” but are now called “inactive carriers.” A number of studies were conducted in patients with elevated ALT levels to investigate other possible causes of hepatitis. In the early 1980s, an increasing number of patients in the Mediterranean region were recognized as HBeAg negative, but had active HBV replication.¹⁷ In 1989, specific mutations were identified in the HBV genome that prevented HBeAg formation in an otherwise normally replicating HBV.¹⁸ The most common mutation, a G to A substitution at nucleotide 1896 in the precore region, results in a stop codon, preventing HBeAg production, and is termed the precore mutant. A second dual mutation, the double basic core promoter mutant involving 2 nucleotide substitutions (A₁₇₆₂T and G₁₇₆₄A), leads to downregulation of HBeAg production.¹⁹

HBeAg-negative chronic hepatitis B is not acquired as a de novo infection.²⁰ Rather, the precore mutant form emerges as the predominant species during the course of typical HBV infection with wild-type virus and is selected during the immune clearance phase (HBeAg seroconversion). The development of HBeAg-negative chronic hepatitis B can occur either close to HBeAg seroconversion or many years or even decades later.²¹ There tend to be 2 main patterns of disease activity. Approximately 30%–40% of patients experience persistently elevated ALT levels (3–4-fold increase), but 45%–65% of patients have an erratic pattern of ALT level elevations, with frequent flares of disease activity.^{22,23} Serum HBV DNA levels also tend to be high, particularly before ALT level elevations.²¹ Sustained spontaneous remission is uncommon in patients with HBeAg-negative chronic hepatitis B (6%–15%),^{22,23} and the long-term prognosis is poor compared with HBeAg-positive patients.²²

YMDD Mutants

The YMDD mutation is a specific mutation occurring in the tyrosine-methionine-aspartate-aspartate portion of the HBV P gene associated with the active site of the DNA polymerase. The mutation is caused by

selective pressure of L-nucleoside analogue antivirals, such as lamivudine, emtricitabine, and telbivudine that result in the production of a viral polymerase with an altered active site and confers resistance to certain antiviral agents. The emergence and clinical relevance of YMDD mutants are described in more detail in a later section.

HBV Genotypes

HBV is classified into 8 genotypes (A–H) based on DNA sequence differences, and their geographic distribution varies.^{24,25} Genotype A is found mainly in North America, northern Europe, India, and Africa; genotypes B and C, in Asia; genotype D, in southern Europe, the Middle East, and India; genotype E, in West Africa and South Africa; genotype F, in South America and Central America; and genotype G, in the United States and Europe. An additional genotype (H) recently was identified in persons from Central America and California,²⁴ but this finding has not been verified. HBeAg-negative (precore mutant) HBV is most common in genotypes B, C, and D, which explains why precore mutant HBV infection is more common in Asia and southern Europe.

Preliminary data suggest that HBV genotype may be related to clinical outcome. Some studies in Asia suggest that genotype C is associated more frequently with severe liver disease and HCC than is genotype B,^{26–28} although other studies contradict the latter finding.^{26,28} Genotype B appears to be associated with seroconversion from HBeAg to anti-HBe at a younger age than genotype C.^{26,29} Genotype also may affect response to antiviral therapy because genotypes A and B appear to have greater rates of antiviral response to interferon (IFN)-alpha therapy than D and C.^{30,31} The role of HBV genotype in outcome of liver disease deserves further study. Testing for HBV genotype is not yet performed in clinical practice because the clinical relevance of genotyping remains controversial and uncertain.

Diagnostic Markers in HBV Infection

The diagnosis of chronic HBV infection typically is based on evaluation of serological and virological markers of HBV infection in serum and biochemical and histological markers of liver disease.

Serological Markers

HBsAg is the first serological marker to appear after infection. Its persistence for >6 months indicates chronic HBV infection. Antibody to HBsAg (anti-HBs)

implies recovery and/or immunity to HBV. Anti-HBs also is detectable after immunity conferred by hepatitis B vaccination. Occasionally, anti-HBs and HBsAg are both detectable in patients with chronic infection. The presence of HBeAg indicates active replication of HBV. However, its absence cannot be assumed to equate to absent viral replication because HBeAg is not detectable in patients with HBeAg-negative (precore or core promoter mutant) HBV infection. The presence of anti-HBe generally indicates HBeAg seroconversion, although it also is found in patients with HBeAg-negative infection. HBeAg seroconversion (HBeAg loss and detection of anti-HBe) generally has been considered the end point for HBV therapy for HBeAg-positive patients because it has been associated with a lower risk for disease progression,³² although not protective against the later development of HCC.

Virological Markers

The amount of HBV DNA in serum is a measure of the level of viral replication. Until recently, serum HBV DNA testing was performed using nonamplified hybridization assays. These assays have limited sensitivity, with a lower limit of quantification of 10^5 – 10^6 copies/mL (Table 3). The National Institutes of Health Workshop on Management of Hepatitis B recommended that treatment be considered for patients with detectable HBV DNA by nonamplified assays (i.e., with serum HBV DNA > 10^5 copies/mL).⁹ However, some HBeAg-positive patients and many HBeAg-negative patients have fluctuating HBV DNA levels that decrease to < 10^5 copies/mL.³³ Furthermore, the threshold HBV DNA level associated with progressive liver disease is unknown. In the panel's experience, patients can have advanced liver disease even if they have serum HBV DNA levels persistently < 10^5 copies/mL; the clinical significance of low HBV DNA levels is uncertain. As listed in Table 3, the current target amplification assays, such as polymerase chain reaction (PCR) assays, have a much lower limit of detection (as low as 100–1000 copies/mL). These assays are becoming more widely available and are preferable in the initial evaluation of patients and, even more importantly, monitoring of both treated and untreated patients.

Biochemical Markers

Elevated serum ALT levels (i.e., greater than the upper limit of the normal range) are an indicator of necroinflammatory activity. Hence, a normal ALT level often is considered predictive of histological quiescence, and HBV-infected patients with persistently normal ALT levels generally have milder inflammation seen on

Table 3. Comparison of HBV DNA Quantification Assays

Assay (manufacturer)	Volume of sample	Sensitivity ^a		Linearity (<i>copies/mL</i>)	Genotype independent	Coefficient of variation (%)	
		(<i>pg/mL</i>)	(<i>copies/mL</i>)				
Branched DNA (Bayer)	10 μ L	2.1	7×10^5	7×10^5 – 5×10^9	A, B, C, D, E, F	6–15	
Hybrid capture (Digene)	30 μ L	0.5	1.4×10^5	2×10^5 – 1×10^9	A, B, C, D	10–15	
	1 mL	0.02	5×10^3	5×10^3 – 3×10^6			
Liquid hybridization (Abbott)	100 μ L	1.6	4.5×10^5 [8×10^6] ^b	5×10^5 – 1×10^{10}	Detects genotype D better than A	12–22	
PCR (Roche)	50 μ L	0.001	4×10^2		(A), B, C, D, E	14–44	
				Amplicor Monitor			4×10^2 – 1×10^7
				Amplicor Cobas			2×10^2 – 10^5
Taqman		2×10^2 – 10^{10}					
Molecular beacons	10–50 μ L	-	<50	50 – 1×10^9	A–F	5–10	

HBV, hepatitis B virus.

^a1 μ g/mL HBV DNA = 283,000 copies ($\approx 3 \times 10^5$ viral genome equivalents).

^bCorrected limit of detection.

Adapted with permission from the American Association for the Study of Liver Diseases.¹

liver biopsy than patients with elevated ALT levels. Moreover, patients with normal ALT levels tend to have a poor serological response to antiviral therapy and often are not considered for treatment. However, some patients with normal ALT levels and elevated HBV DNA levels have significant inflammation and fibrosis on biopsy.³⁴ In such cases, treatment may be indicated.

Histological Markers

Histological evaluation of liver biopsy specimens is a more sensitive and accurate indicator of liver disease than ALT level. It is useful to establish the baseline status of liver histological characteristics at initial evaluation before initiation of therapy and exclude other causes of liver disease. However, liver biopsy is not always used as a method of diagnosis and is resisted by some patients because of its invasive nature.

Patient Evaluation

Table 4 lists tests that should be performed at the initial evaluation of patients with chronic HBV infection and the suggested follow-up for patients not considered for treatment. The initial evaluation should include a thorough history and physical examination, with particular attention to family history of HBV infection and liver cancer, risk factors for coinfection, and alcohol use. Laboratory tests should include assessment of liver disease, markers of HBV replication, and tests for coinfection with other viruses for those at risk. A liver biopsy also is recommended for patients with intermittent or persistent elevation in ALT levels, but it is not mandatory. Screening for HCC should be considered in high-risk individuals (discussed next). Patients also should be counseled on precautions to prevent transmission of

HBV infection and vaccination of sexual and household contacts. All patients should be discouraged from heavy alcohol use, and abstinence from alcohol is recommended for those with cirrhosis. All individuals with chronic HBV infection and not immune to hepatitis A should be vaccinated according to the Centers for Disease Control and Prevention recommendations (i.e., 2 doses of hepatitis A vaccine, with an initial injection at baseline and booster injection at 6–18 mo).

Table 4. Evaluation of Patients With Chronic HBV Infection

Initial evaluation
History and physical examination
Laboratory tests to assess liver disease: complete blood cell count with platelets, hepatic panel, and prothrombin time
Tests for HBV replication: HBeAg/anti-HBe, HBV DNA
Tests to rule out other causes of liver disease: anti-HCV, anti-HDV
Tests to screen for HCC: AFP and US in high-risk patients
Liver biopsy to grade and stage liver disease: for patients who meet criteria for chronic hepatitis
Suggested follow-up for patients not considered for treatment
HBeAg-positive chronic hepatitis B with HBV DNA $\geq 10^5$ copies/mL and normal ALT level
ALT every 3 to 6 mo
Consider liver biopsy and/or treatment when ALT levels become elevated
Consider screening for HCC in relevant populations
Inactive HBsAg carrier state
ALT every 6–12 mo
If ALT levels become elevated, check serum HBV DNA and exclude other causes of disease
Consider screening for HCC in relevant populations

HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; anti-HBe, antibody to HBeAg; AFP, α -fetoprotein; US, ultrasound; anti-HCV, antibody to hepatitis C virus; anti-HDV, antibody to hepatitis D virus; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen. Adapted with permission from the American Association for the Study of Liver Diseases.¹

Screening for HCC

HBV carriers are at increased risk for the development of HCC.^{35,36} In most patients, HCC generally begins as an encapsulated single tumor. Doubling time of the tumor ranges from 2 to 12 months (median, 4 mo).^{37,38} HCC can be detected early with periodic α -fetoprotein (AFP) and ultrasound (US) screening. Periodic screening studies using AFP and US in HBV-infected subjects detected small tumors (<5 cm) in 64% and 83% of persons with HCC, respectively.^{39,40} The combination of AFP and US appears superior to either modality alone. Data suggest that screening every 6 months with AFP and US is more effective than annual screening in detecting HCC, but there appears to be no difference between screening every 3 or 6 months.^{39–44}

The standard approach to HCC screening is outlined in the American Association for the Study of Liver Diseases Practice Guideline¹ and the European Association for the Study of the Liver HBV Consensus Guidelines.⁴⁵ HCC screening should be considered for HBV carriers at high risk for HCC (i.e., men > 45 yr, persons with cirrhosis, and those with a family history of HCC). It is important to be aware that in patients with hepatitis B, HCC can occur in the absence of cirrhosis.^{35,36} Screening should be every 6 months using AFP and US. Magnetic resonance imaging and computed tomography, although more expensive, generally are considered to be more sensitive than US and may be preferred by clinicians for some patients (e.g., those with cirrhosis resulting in poor US sensitivity). Although AFP is less sensitive than US, it has a high negative predictive value (99%).^{39,46} Periodic screening for HCC by using AFP should be considered in low-risk individuals from endemic areas.¹

Candidates for Therapy

Although there is general agreement on the tests that should be ordered in the initial evaluation of patients with chronic HBV infection (Table 4), there are some controversial issues on how these are used in determining candidates for therapy.

Normal Versus Elevated ALT Levels

ALT level commonly is used as an assessment of liver disease and has been important in defining which patients are candidates for therapy. However, reliance on elevated ALT levels as a prerequisite to treatment candidacy has limitations. The extent of liver cell necrosis and degree of elevated ALT level do not always correlate, and ALT measurements may fail to identify patients with necroinflammatory activity or fibrosis, as seen in hepatitis C.^{47,48} In addition, ALT activity may be indepen-

dently related to body mass index, sex, abnormal lipid and carbohydrate metabolism, and whether a patient is receiving dialysis therapy.⁴⁸ Moreover, ALT level elevations occur in different circumstances, such as during spontaneous HBeAg loss, in association with some antiviral therapies or with infection with other viruses.¹¹

ALT level has been an important influence on the decision to treat because of its value in predicting a serological response to lamivudine^{49,50} and IFN.^{51,52} The predictive value of ALT level has been reinforced by the observation that despite the generally lower response rates seen in Asian patients, those with elevated ALT levels respond as well as white patients with equivalent degrees of ALT level elevation to lamivudine⁵⁰ and IFN.⁵²

Geographic origin and genotype also affect the usefulness of ALT level as a determinant for treatment. The majority of Asian patients have normal ALT levels, but up to one third have active hepatitis B nonetheless.⁵² The non-A genotypes found in Asia and elsewhere are predisposed to HBeAg-negative (precore and core promoter) mutants with immune-tolerant HBV infection with normal ALT levels. These patients have the ability to significantly replicate HBV in the face of normal ALT levels and presence of anti-HBe.

The use of ALT levels to define patients with chronic hepatitis B who are candidates for treatment derives from the historic experience with IFN therapy and helps define a cohort more likely to respond to that medication, not a disease state appropriately in need of effective therapy. On the basis of the natural history of the disease, a treatment algorithm should define the patient disease state that requires treatment and then identify the drug treatment options. Although it is helpful to know a patient's ALT level, a normal ALT level does not always help determine who should be treated. A patient's ALT level needs to be considered in conjunction with his or her serum HBV DNA level. Hence, in patients with detectable HBV DNA ($\geq 10^5$ copies/mL) and normal ALT levels, a liver biopsy might be considered; if significant disease is found, the patient should be considered for treatment. Patients with HBV DNA level $\geq 10^5$ copies/mL and elevated ALT levels generally should be treated, regardless of whether liver biopsy is performed.

Viral Threshold

Historically, the presence (i.e., levels greater than the assay limit of detection) or absence (i.e., levels less than the assay limit) of HBV DNA by hybridization techniques was a major determinant of treatment candidacy. This was chosen because in most patients who have undergone HBeAg seroconversion, HBV DNA levels

decrease to less than the detection limit of unamplified hybridization assays ($<10^5$ copies/mL), ALT level normalizes, and necroinflammation decreases.^{53,54} However, patients with chronic hepatitis B have fluctuating HBV DNA levels that may, at times, decrease to less than that level. In addition, the threshold HBV DNA level that is associated with progressive liver disease is unknown. In the past, undetectable HBV DNA by hybridization techniques has been considered clinically insignificant; however, HBV DNA levels $<10^5$ copies/mL are associated with significant intrahepatic HBV DNA and covalently closed circular DNA levels.⁵⁵ Furthermore, HBV DNA has been detected by PCR in the serum and liver of patients with cirrhosis and HCC who have been found to have undetectable HBV DNA by hybridization (and negative HBsAg).^{56,57} Target amplification assays, such as PCR, can detect 100–1000 copies/mL. Although the clinical significance of low levels of HBV DNA is unclear, patients with $<10^5$ copies/mL may be still at risk for biochemical, histological, and clinical progression of disease, although to a lesser extent than those with $\geq 10^5$ copies/mL.

With the advent of new techniques, serum HBV DNA is evolving as the most useful measurement for the follow-up of patients with chronic hepatitis B. A review of 26 prospective studies found significant correlations between viral load levels or viral load changes and various accepted markers of disease activity (histological grading and biochemical and serological response).⁵⁸ To determine whether there is a clinically significant threshold for HBV DNA, Chu et al.³³ analyzed sequential samples (by PCR) from 165 Chinese patients with different stages of chronic hepatitis B. Serum HBV DNA levels decreased by a mean of 3 \log_{10} in patients who had spontaneous or IFN-related HBeAg loss, but no threshold HBV DNA level was associated with HBeAg loss. Also, serum HBV DNA level at the time of HBeAg loss was not a predictor of the durability of HBeAg loss. HBeAg-positive patients tended to have greater HBV DNA levels (10^5 – 10^8 copies/mL) than HBeAg-negative patients, but levels as high as 10^8 copies/mL were detected in some HBeAg-negative patients. Moreover, approximately one third of HBeAg-negative patients had HBV DNA levels persistently $>10^5$ copies/mL. Interestingly, two thirds of HBeAg-negative patients and all inactive carriers had levels persistently $<10^5$ copies/mL, indicating that it is not possible to define a single cutoff HBV DNA value to distinguish inactive carriers from patients with HBeAg-negative chronic hepatitis B. ALT levels and liver biopsy results can be used to differentiate

among these patients, although the latter is not used routinely.

Optimal management of chronic hepatitis B requires the use of PCR assays to establish an accurate baseline HBV DNA level, then continued use of PCR assays during antiviral therapy to most accurately measure response and viral rebound associated with viral resistance. Use of non-PCR assays may allow significant viral replication to go undetected, with potentially injurious clinical consequences in both the pretreatment and on-treatment settings.

Patient Populations

The majority of chronic HBV infections result from perinatal transmission in Asia. In these patients, persistence of HBeAg is lengthier (immune tolerant phase), ALT levels tend to be normal, and serum HBV DNA levels may be high.^{59,60} The majority of patients do not clear HBeAg or seroconvert until the fourth decade of infection. Those who remain HBeAg positive can either remain immune tolerant or subsequently develop a Western pattern of hepatitis and experience either persistent or intermittent elevations of ALT levels.^{61–63} Even patients who clear HBeAg remain at high risk for HBeAg-negative hepatitis B, which has serious implications.

Asians tend to develop complications of chronic hepatitis B (e.g., HCC) in their sixth to seventh decade of infection, often after HBeAg seroconversion.¹⁵ Whereas Asian patients with elevated ALT levels respond to IFN⁵² and lamivudine⁵⁰ therapy as well as white patients, most Asian patients have normal ALT levels. IFN therapy does not seem to result in a permanent clearance of HBV in Asian patients. A recent study that followed up a cohort of Chinese patients after treatment with IFN showed that even after HBeAg seroconversion, 91% of patients had detectable HBV DNA by PCR.⁶⁴ Furthermore, these patients still had a high incidence of cirrhosis and HCC. Conversely, in the white population, IFN therapy increased the chance of HBeAg clearance, which was associated with better clinical and survival outcomes.³²

A second serological pattern of hepatitis is seen in Africa, Mediterranean countries, and Alaska, where HBV transmission tends to be from person to person during childhood.^{7,65} Most HBeAg-positive children have elevated ALT levels, and seroconversion tends to occur in late childhood or teens. The natural history of this population is between that of the Asian and Western populations. The third pattern of hepatitis, seen in individuals in Western developed countries, is different from that in the Asian population. HBV is acquired during

Table 5. Comparison of Interferon, Lamivudine, and Adefovir Dipivoxil in HBeAg-Positive Chronic Hepatitis B

Parameter	Interferon (untreated) 12–24 wk	Lamivudine (placebo) 52 wk	Adefovir dipivoxil (placebo) 48 wk
Serum HBV DNA loss ^a (%)	37 (17)	44 (16)	21 (0)
Serum HBV DNA log ₁₀ reduction	Not available	Not available	3.52 log (0.55)
HBeAg loss (%)	33 (12)	32 (11)	24 (11), 44 at 72 wk
HBeAg seroconversion (%)	18 ^b	16–18 (4–6), 50 at 5 yr	12 (6), 23 at 72 wk
HBsAg loss (%)	11–25 at 5 yr in white patients	Insufficient data	Insufficient data
ALT normalization (%)	23 ^b	41–72 (7–24)	48 (16)
Histological improvement (%)	Poor data	49–56 (23–25)	53 (25)
Development of resistance (%)	No	14–32, increasing to 69 at 5 yr	1.6 at 2 yr
Durability of response after HBeAg seroconversion (%)	80–90 at 4–8 yr	77 at 37 mo	Not available
Defined treatment course	Yes	Unclear	Unclear
Safety	Poor	Same as placebo	Same as placebo
Tolerability	Poorly tolerated	Well tolerated	Well tolerated
Dosing regimen	5 MU/d or 10 MU 3 times wk for at least 16 wk (injection)	100 mg once daily (oral)	10 mg once daily (oral)
Cost/mo. (\$)	1420	260 ¹²⁴	450 ¹²⁴

NOTE. All data are at 1 year unless otherwise stated.

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; MU, million units; LLD, lower limit of detection.

^aInterferon and lamivudine, hybridization assay (LLD, 10⁵ copies/mL); adefovir, polymerase chain reaction assay (LLD, 400 copies/mL).

^bDifference between treated and untreated.

adulthood, and transmission is through sexual exposure, intravenous drug use, or transfusion. The incidence of chronicity is lowest in this group at <5%.⁷ Western patients with chronic hepatitis B tend to have greater ALT and HBV DNA levels and respond better overall to antiviral treatment.

Goals of Therapy

The goal of therapy for chronic hepatitis B is to eliminate or significantly suppress HBV replication and prevent the progression of liver disease to cirrhosis with the potential development of liver failure or HCC. Hence, the primary aim of treatment should be to reduce the HBV DNA level and maintain it at the lowest possible levels (i.e., durable HBV DNA suppression). This, in turn, will lead to the other aims of therapy, such as histological improvement and ALT level normalization. In patients who are HBeAg positive before therapy, an additional goal of treatment is loss of HBeAg with seroconversion to anti-HBe positivity. The latter is preferable because attainment of complete HBeAg seroconversion indicates that antiviral therapy may be stopped, and the likelihood is high that the benefit will persist off therapy. Loss of HBsAg, although highly desirable, rarely is achieved with short-term antiviral therapy and hence is not a common goal for antiviral trials.

Approved HBV Therapies

Currently, there are 3 approved treatments for chronic HBV infection in the United States: IFN alfa-2b,

lamivudine, and adefovir dipivoxil (Table 5). Several new antiviral agents and immunomodulatory therapies are under investigation, but are not yet commercially available.

Treatment and Management of Chronic HBV

HBeAg-Positive Patients

IFN, lamivudine, and adefovir are all approved for first-line therapy in patients with HBeAg-positive chronic HBV infection.

Summary of key clinical data. *IFN.* A meta-analysis of data from 15 trials showed HBeAg loss and HBeAg seroconversion in treated patients (Table 5).⁶⁶ Elevated ALT levels and low serum HBV DNA levels are the best predictors of response to treatment.⁶⁷ Most Asian patients with chronic HBV infection have normal ALT levels, even in the presence of high HBV DNA levels,⁵² and respond poorly to IFN therapy.⁵¹ In European studies, HBsAg loss has been observed in 5%–10% of patients within 1 year of the start of IFN treatment; among sustained responders, this increases to 11%–25% by 5 years.^{32,68,69} This has not been observed in Asian studies.

IFN is administered by subcutaneous injection, and therapy is associated with many adverse effects, such as flu-like symptoms, fatigue, anorexia, depression, and leukopenia.⁷⁰

Lamivudine. One year of lamivudine therapy results in histological improvement, HBeAg seroconver-

sion, suppression of serum HBV DNA, and ALT level normalization (Table 5).^{34,71,72} If therapy is stopped before HBeAg seroconversion, viral replication returns; hence, long-term therapy is required in most patients. HBeAg seroconversion increases with duration of lamivudine treatment from 17% at year 1 to 27%, 40%, 47%, and 50% at years 2, 3, 4, and 5, respectively.^{34,73–76} HBeAg seroconversion rates also increase with increasing pretreatment ALT levels.^{49,50} In an analysis of 4 lamivudine trials, HBeAg loss occurred in 56% of patients with pretreatment ALT levels >5 times the upper limit of normal.⁵⁰ Unfortunately, the incidence of YMDD mutant increases with duration of therapy from 14% to 32% at 1 year to 69% at 5 years.^{71,77} In patients who develop lamivudine-resistant HBV, HBV DNA and ALT levels tend to rebound toward pretreatment levels. More recent data have shown that some patients experience reversal of their initial histological improvement.^{74,78} Furthermore, in some patients, the development of lamivudine-resistant HBV has been associated with severe ALT level flares and even rapid decompensation.⁷⁹ Lamivudine is well tolerated and has an excellent safety profile.

Adefovir dipivoxil. One year of adefovir therapy with 10 mg once daily resulted in histological improvement, reduced serum HBV DNA and ALT levels, and increased rates of HBeAg seroconversion (Table 5).⁸⁰ Patients treated beyond 48 weeks appear to derive continued virological, serological, and clinical benefit. By week 72, 46% of patients had undetectable serum HBV DNA by PCR, 75% had ALT level normalization, 44% had lost HBeAg, and 23% had HBeAg seroconversion.⁸⁰ The 30-mg dose gave no additional benefit over the 10-mg dose, except for the magnitude of HBV DNA suppression.

The safety profile of adefovir is similar to that of placebo. No patient in the 10-mg group had serum creatinine level increases ≥ 0.5 mg/dL, as seen at higher adefovir doses (8% of patients in the 30-mg group).⁸⁰ Beyond 1 year, there is no comparator, but the incidence of abnormalities in serum creatinine levels was not different from the first year. Increases in serum creatinine levels in the 30-mg group limit the long-term use of this dose. Renal toxicity was seen at greater doses of adefovir in the early drug discovery phase.

In contrast to lamivudine, no adefovir resistance mutation has been observed after 1 year of treatment. Recent resistance surveillance data have shown the emergence of adefovir resistance mutation N236T in 1.6% of patients (2 of 124 patients) at 2 years (across several studies).¹⁶ Adefovir-resistant HBV with N236T has been shown to be susceptible to lamivudine.¹⁶ A recent case report

described a patient who developed adefovir resistance.⁸¹ This was associated with a rebound in serum HBV DNA and ALT levels to near-pretreatment levels. The patient responded to lamivudine therapy. There are insufficient data on the impact of adefovir resistance on other clinical end points.

Combination therapy. Some trials suggest there is additive benefit of lamivudine-IFN combination therapy,^{72,82} but large well-designed studies are needed to confirm these initial observations. Several large studies are under way exploring combinations of nucleosides and/or nucleotides and peginterferon.

Durability of response. HBeAg loss induced by IFN treatment has been durable in 80%–90% of patients after 4–8 years of follow-up.^{1,83–87} Data on durability of response after lamivudine treatment are limited. In a follow-up study of patients who had HBeAg seroconverted during lamivudine treatment, seroconversion was durable in 77% of patients (30 of 39 patients) after a median follow-up of 37 months (range, 5–46 mo).⁸⁸ Most clinicians consider HBeAg seroconversion preferable to HBeAg loss alone, but it still remains uncertain if the durability of treatment response to lamivudine is affected by this distinction. Durability of lamivudine-induced HBeAg seroconversion may be affected by duration of treatment after HBeAg seroconversion. In a study from Korea, patients who received lamivudine for at least 4 months after seroconversion had a lower relapse rate at 2 years (32%) compared with those administered only up to 2 months' treatment after seroconversion (74%).⁸⁹ These data support the continuation of treatment for at least 4–6 months after HBeAg seroconversion. In a recent study of 61 patients in whom serum HBeAg and HBV DNA (solution hybridization) had been persistently negative for at least 24 months of lamivudine therapy, cumulative reappearance rates of serum HBV DNA after cessation of lamivudine therapy were 15%, 21%, and 31% at 6 months, 1 year, and 2 years, respectively.⁹⁰ Cumulative reappearance rates for serum HBeAg were 11%, 13%, and 16%, respectively, suggesting that long-term additional administration of lamivudine might enhance the durability of HBeAg seroconversion. There are no published data on durability of response after adefovir treatment.

Predictors of response. A number of clinical, biochemical, and serological factors have been identified as predictive of a good response to IFN therapy. However, the best predictors are high pretreatment ALT and low HBV DNA levels.^{67,70,91} These parameters also are associated with a greater rate of spontaneous HBeAg seroconversion. Recent studies have shown that HBV

Table 6. Recommendations for Treatment: HBeAg-Positive Patients

HBeAg status	HBV DNA ^a	ALT	Treatment strategy
Positive	<10 ⁵	Normal	No treatment Monitor every 6–12 mo ^b Consider therapy in patients with known significant histological disease, even if low-level replication
Positive	≥10 ⁵	Normal	Low rate of HBeAg seroconversion for IFN, lamivudine, adefovir Consider biopsy; treat if disease If treated, lamivudine or adefovir preferred (more potent HBV suppressive agents with fewer side effects)
Positive	≥10 ⁵	Elevated	Adefovir, lamivudine, or IFN are first-line options If “high” HBV DNA, adefovir or lamivudine preferred

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; IFN, interferon.

^aCopies/mL.

^bOn initial diagnosis and every 3 months for 1 year to ensure stability.

genotype may influence IFN response.^{26,30,31} High pretreatment ALT level also is the best predictor of a response to lamivudine treatment.^{49,50}

Treatment recommendations: HBeAg-positive patients. Recommendations for treatment of HBeAg-positive patients are listed in Table 6. The panel recommends ≥10⁵ copies/mL as a reasonable threshold for determining candidates for treatment in HBeAg-positive patients. Patients with <10⁵ copies/mL currently are not recommended for treatment, but they still may be at risk for biochemical, histological, and clinical progression of disease and should be actively monitored by PCR assay. On a case-by-case basis, liver biopsy may be performed on such patients, and therapy may be considered when there is histological evidence of significant liver disease. Patients who are not treated should initially be monitored every 3 months for 1 year to ensure stability, then every 6–12 months.

HBeAg-positive patients with a serum HBV DNA level ≥ 10⁵ copies/mL should be considered for treatment, depending on their ALT levels. Patients with normal ALT levels appear to experience viral suppression similar to that of patients with elevated ALT levels, but efficacy is low in terms of HBeAg seroconversion. However, because the former group of patients may have significant liver disease and viral suppression is associated with histological response, biopsy should be considered, and the patient should be treated if disease is found. Additional studies are required to investigate the efficacy of antiviral therapy in patients with HBV DNA levels ≥ 10⁵ copies/mL and normal ALT levels. For patients with serum HBV DNA levels ≥ 10⁵ copies/mL and elevated ALT levels, adefovir, lamivudine, or IFN are all recommended as first-line options; however, adefovir or lamivudine are preferred for patients with high serum HBV DNA and/or normal ALT levels because response to IFN therapy is low. Although serum HBV DNA can be suppressed effectively with adefovir and lamivudine in

patients with normal ALT levels, which may confer benefit, HBeAg seroconversion is infrequent.

Duration of therapy and on-treatment monitoring. Patients should be monitored at least every 6 months while on therapy with either lamivudine or adefovir and possibly more frequently on lamivudine therapy to facilitate early detection of resistance. Taking into account the available data,^{89,90} the panel recommends that patients be treated after HBeAg seroconversion as long as HBV levels are decreasing until they have undetectable HBV DNA levels by PCR. Treatment then should be continued for an additional 6 months. In patients who have HBeAg seroconversion, but in whom HBV DNA levels are detectable and stable, treatment should be continued for 6 months. Seroconversion should be documented again, then consideration should be given to stopping treatment (in noncirrhotic patients). Patients who experience relapse can be retreated. HBeAg-positive patients who fail to lose HBeAg should be treated indefinitely because the chance of HBeAg seroconversion increases with time. Adefovir should be considered for long-term use in patients who were treated initially with lamivudine because of the lower chance of resistance.

HBeAg-Negative Patients

The end point of therapy for HBeAg-negative patients with chronic HBV infection is more difficult to assess than for HBeAg-positive patients because HBeAg seroconversion cannot be used. Thus, HBV DNA suppression and ALT level normalization are the only practical measures of response to therapy.

Summary of key clinical data. *IFN.* IFN treatment of HBeAg-negative patients has resulted in end-of-treatment responses ranging from 40% to 90%,⁹ but relapse rates are high at 30%–90%.²⁰ Overall, sustained virological response rates range from 15%–25%.⁹ Responses appear to be more durable in patients who un-

Table 7. Recommendations for Treatment: HBeAg-Negative Patients

HBeAg status	HBV DNA ^a	ALT	Treatment strategy
Negative	<10 ⁴	Normal	No treatment Monitor every 6–12 mo ^b Consider therapy in patients with known significant histological disease, even if low-level replication
Negative	≥10 ⁴	Normal	Low “efficacy” for lamivudine, IFN, adefovir Consider biopsy; treat if disease
Negative	≥10 ⁴	Elevated	Adefovir, lamivudine, or IFN are first-line options Long-term treatment required Adefovir preferred (low rate of resistance)

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; IFN, interferon.

^aCopies/mL.

^bOn initial diagnosis and every 3 months for 1 year to ensure stability.

dergo treatment for >12 months.⁹² Also, up to 32% of patients who achieve a sustained virological response go on to clear HBsAg.⁹² IFN-treated patients with a sustained virological response seem to have significantly better and complication-free survival than nonresponders or untreated patients.^{93,94}

Lamivudine. Overall, approximately two thirds of patients have a biochemical and virological response after 6–12 months of lamivudine therapy,^{95–97} with necroinflammation improving in a similar proportion. However, most patients relapse after therapy is stopped, and the majority relapse after lamivudine resistance develops.^{96,97} Longer treatment durations can maintain normal ALT levels and undetectable HBV DNA, but biochemical and virological breakthroughs occur as a result of the emergence of lamivudine-resistant YMDD mutant HBV. A study of long-term lamivudine therapy showed that although ALT and HBV DNA level responses were seen in 96% and 68% of patients at 12 months, respectively, responses then steadily decreased with duration of therapy. Only ~40% of patients maintained normal ALT levels and undetectable HBV DNA at >30 months.⁹⁷ The incidence of lamivudine resistance increases with time; 19%–27% of patients have YMDD mutant HBV at 1 year,^{95,98} increasing to 44% at 2 years⁹⁵ and 60% at 4 years.^{21,97} The emergence of YMDD mutants in this population can be associated with clinically significant hepatitis,⁹⁷ which significantly limits the role of lamivudine in treating HBeAg-negative chronic HBV infection.

Adefovir dipivoxil. One year of therapy with adefovir resulted in histological improvement in 64% of patients compared with 33% of placebo patients.⁹⁹ Serum HBV DNA levels were reduced by a median of 3.91 log₁₀ copies/mL compared with 1.35 log₁₀ copies/mL for placebo, and HBV DNA was <400 copies/mL (by PCR) in 51% of treated patients and none of the placebo patients. ALT levels normalized in 72% of treated pa-

tients compared with 29% of placebo patients. Adefovir was well tolerated and had a safety profile similar to that of placebo. Significantly, no adefovir-resistant mutations were observed at up to 48 weeks of therapy. Recent data show that after 2 years of therapy, 2 of 79 patients in this study developed an adefovir-resistant mutation (N236T) that is not cross-resistant to lamivudine.¹⁶

Treatment recommendations: HBeAg-negative patients. Recommendations for treatment of HBeAg-negative patients are listed in Table 7. Chu et al.³³ showed that approximately half the HBeAg-negative patients had serum HBV DNA levels persistently <10⁵ copies/mL on initial testing at the time of presentation. Because HBeAg-negative patients tend to have lower serum HBV DNA levels than HBeAg-positive patients, but may still have disease, the panel recommends treating patients who have serum HBV DNA levels ≥10⁴ copies/mL. Otherwise, recommendations are similar to those for HBeAg-positive patients. Adefovir, lamivudine, and IFN can be considered first-line options. Long-term treatment is required in most cases (unless HBsAg seroconversion occurs), and adefovir would be preferred over lamivudine for long-term treatment because of its low level of resistance and good tolerability.

Duration of therapy and on-treatment monitoring. Patients on therapy should be monitored every 6 months. Duration of therapy for IFN remains unclear, although a longer treatment duration (12 mo) appears more beneficial in terms of sustained virological response. However, tolerability clearly is an issue for patients with long treatment durations. Lamivudine and adefovir need to be administered long term; however, because long-term lamivudine therapy is limited by the emergence of YMDD mutant HBV, adefovir would be preferred. On-treatment monitoring of serum HBV DNA by PCR assay and ALT levels should be performed every 6 months.

Lamivudine-Resistant Patients

Development of resistance is associated with HBV DNA rebound, followed by ALT level elevation and eventual reversion of histological improvement and, in some cases, progressive liver disease associated with severe exacerbations.^{73,74,78,79,97} Lamivudine resistance has been described in all patient groups, including compensated and decompensated patients, transplant recipients, and human immunodeficiency virus (HIV)-coinfected patients. In cirrhotic patients, the development of resistance is associated with increased ALT levels, which can be severe, and a decline in liver synthetic function, leading to decompensation of liver disease.¹⁰⁰ Predictors of lamivudine resistance include high pretreatment HBV DNA levels, non-Asian ethnicity, male sex, and high body mass index.¹⁰¹ Resistance can be diagnosed accurately clinically by an increase in serum HBV DNA levels in a patient on prolonged antiviral therapy who experienced an initial decrease in viral levels after initiation of therapy. This increase in HBV DNA levels typically is associated with liver damage (increase in serum ALT levels). There is a strong correlation between this clinical diagnosis of resistance and genotypic markers of polymerase mutations, making direct sequencing of HBV for resistance unnecessary.

Summary of key clinical data. *Adefovir dipivoxil.* Several studies have evaluated the use of adefovir in lamivudine-resistant HBV. Two studies that included patients with compensated and decompensated lamivudine-resistant HBV and a study of HBV-HIV-coinfected patients are discussed in later sections.

Another study measured the independent contribution of adefovir monotherapy for patients with compensated lamivudine-resistant HBV.¹⁰² Adefovir monotherapy and adefovir in combination with continued lamivudine therapy resulted in similar reductions in serum HBV DNA levels, in contrast to continued lamivudine therapy, which did not reduce HBV DNA levels. No patients experienced clinically significant ALT level elevations when they were switched from lamivudine to adefovir monotherapy. Combination therapy was well tolerated.

Treatment recommendations: patients with lamivudine-resistant HBV. Currently, the recommended treatment for lamivudine-resistant HBV is adefovir. Whether this is administered as monotherapy or in combination with continued lamivudine therapy depends on the status of the patient's liver disease. Data for compensated patients showed mild increases in ALT levels in some patients when switching from lamivudine to adefovir therapy, but no patient experienced clinically significant ALT level elevations.¹⁰² This suggests that switching

patients from lamivudine to adefovir therapy is a safe strategy. Because the consequences of returning wild-type HBV are potentially more hazardous in decompensated patients, the addition of adefovir to continued lamivudine therapy should be considered. Continued lamivudine therapy also will treat adefovir-resistant mutants if they develop.

Duration of therapy and on-treatment monitoring. The recommendation for duration of therapy with adefovir and monitoring also depends on the status of the patient. Generally, compensated HBeAg-positive patients should be treated until HBeAg seroconversion and undetectable HBV DNA by PCR assay occur, then for an additional 6 months. (Refer to other sections for other patient categories.)

Patients With Cirrhosis (or End-Stage Liver Disease)

Before the advent of effective antiviral therapy, 5-year survival rates were 84% for compensated cirrhosis and 14%–35% for decompensated cirrhosis.^{12–14} Various clinical parameters, such as bilirubin level and older age, were shown to predict survival. In addition, in compensated cirrhosis, patients who had lost HBeAg had a 97% survival rate at 5 years compared with 72% in HBeAg-positive patients, implicating viral replication in adverse outcomes.¹³

Summary of key clinical data. *IFN.* IFN has been difficult to use in patients with clinically decompensated cirrhosis. Although patients have shown post-treatment responses to IFN therapy, with some patients clearing HBsAg, their disease tends to deteriorate during therapy, and it may take months for liver chemistry test results to return to normal after completion of therapy. In addition, there is a high risk for serious complications, including serious bacterial infections and exacerbations of hepatitis.¹⁰³ Among decompensated patients, response appears to be better in those with Child-Turcotte-Pugh class A (100%) compared with classes B (33%) and C (0%).¹⁰⁴ The occurrence of bacterial infections, even at low doses, in non-class A cirrhotic patients suggests that IFN should not be used for these patients.¹⁰⁴ IFN appears to be safe and effective for patients with compensated cirrhosis, although there is a risk of hepatic decompensation with prolonged therapy.

Lamivudine. Lamivudine considerably improved the treatment options for patients with decompensated cirrhosis. Several studies have shown that lamivudine is well tolerated and results in clinical improvement in many patients. In 27 nontransplantation patients treated for a median of 869 days with lamivudine, there was a rapid decline in serum HBV DNA levels and normaliza-

Table 8. Recommendations for Treatment: Compensated Cirrhotic Patients

HBeAg status	HBV DNA ^a	Cirrhosis	Treatment strategy
Positive or negative	<10 ⁴	Compensated	May choose to treat or observe Adefovir or lamivudine preferred
Positive or negative	≥10 ⁴	Compensated	Adefovir or lamivudine are first-line options Long-term treatment required Adefovir preferred (low rate of resistance) Combination adefovir plus lamivudine has theoretical advantage because of low likelihood of resistance to either virus

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

^aCopies/mL.

tion of ALT levels, with some patients clearing HBeAg.¹⁰⁵ Serum albumin and bilirubin levels also were improved. In a similar study by Villeneuve et al.,¹⁰⁶ improvement was seen in treated patients beyond ~9 months of therapy. Serum HBV DNA levels decreased, aspartate aminotransferase and ALT levels normalized, and there were improvements in albumin level, prothrombin time, and Child-Turcotte-Pugh score. Both studies also showed that survival was improved compared with historic controls. However, YMDD mutant HBV emerges after 6–12 months of therapy, indicated by increases in HBV DNA and ALT levels.¹⁰⁵ In decompensated cirrhotic patients, YMDD mutant HBV has been associated with biochemical dysfunction and a reduction in efficacy. Some cirrhotic patients cannot tolerate the development of YMDD mutant HBV and may deteriorate very rapidly after YMDD develops.⁷⁹

Adefovir dipivoxil. A compassionate-use study of adefovir, 10 mg/d, included patients with chronic hepatitis B with either compensated or decompensated cirrhosis and clinical evidence of lamivudine resistance who either were listed for liver transplantation (n = 128) or were posttransplantation (n = 196).¹⁰⁷ By week 48, serum HBV DNA levels had decreased by ~4 log₁₀ copies/mL in both pretransplantation and posttransplantation patients; this reduction was maintained to week 96. HBV DNA levels were reduced to <400 copies/mL in 34% of posttransplantation patients and 81% of pretransplantation patients, and ALT levels normalized in 49% and

76%, respectively. Child-Turcotte-Pugh scores remained stable or improved in the majority of patients, and 38% of pretransplantation patients were taken off the liver transplant list. Survival rates were >80% and >90% after 1 year of treatment in pretransplantation and posttransplantation patients, respectively. The safety profile of adefovir was consistent with the stage of liver disease and comorbidities of this population. Serum creatinine level increases ≥0.5 mg/dL were observed in ~13% of patients. No adefovir resistance has been reported in the pretransplantation group or posttransplantation group after 48 weeks.

Another study of patients with compensated or decompensated lamivudine-resistant HBV showed similar results. The addition of adefovir to lamivudine resulted in significant reductions in serum HBV DNA levels (~4–5 log₁₀ copies/mL after 48 weeks of therapy).¹⁰⁸ Decompensated patients showed significant improvements in biochemical parameters and hepatic functional status.

Treatment recommendations: patients with cirrhosis. Recommendations for treatment for compensated and decompensated HBeAg-positive or HBeAg-negative cirrhotic patients are listed in Tables 8 and 9. The treatment strategy for compensated cirrhotic patients with serum HBV DNA levels <10⁴ copies/mL is either to monitor the patient or treat with lamivudine or adefovir. The panel believes that in the absence of currently available data to guide this choice, the upside potential for clinical improvement outweighed the

Table 9. Recommendations for Treatment: Decompensated Cirrhotic Patients

HBeAg status	HBV DNA ^a	Cirrhosis	Treatment strategy
Positive or negative	<10 ³ or ≥10 ³	Decompensated	Adefovir or lamivudine are first-line options Long-term treatment required Adefovir preferred (low rate of resistance) Combination therapy may be preferred because of low likelihood of resistance to either virus Waiting list for liver transplantation

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

^aCopies/mL.

Table 10. Dosing Recommendations in Patients With or at Risk for Renal Impairment

Creatinine clearance (mL/min) ^a				
≥50	20–49	10–19	Hemodialysis patients	
Adefovir dipivoxil				
10 mg every 24 hr	10 mg every 48 hr	10 mg every 72 hr	10 mg every 7 d posthemodialysis	
Creatinine clearance (mL/min) ^a				
≥50	30–49	15–29	5–14	<5
Lamivudine				
100 mg once daily	100 mg first dose, then 50 mg once daily	100 mg first dose, then 25 mg once daily	35 mg first dose, then 15 mg once daily	35 mg first dose, then 10 mg once daily

NOTE. Creatinine clearance should be established at baseline to select appropriate initial dosing. Patients should be monitored throughout therapy, and dosing should be adjusted, if required. No additional dosing required after routine (4-hr) hemodialysis treatment.

^aCreatinine clearance calculated by Cockcroft-Gault method using lean or ideal body weight.

Data from Hepsera (Gilead Sciences, Foster City, CA) product information and Eпивir-HBV (GlaxoSmithKline, Research Triangle Park, NC) product information.

downside low risk for drug toxicity and cost in patients with significant liver disease, albeit compensated. In patients with HBV DNA levels $\geq 10^4$ copies/mL, lamivudine or adefovir are first-line options because of their proven efficacy and good tolerability. The panel believes that IFN is contraindicated in these patients because of the potential for decompensation with a flare of disease induced by IFN. Adefovir is preferred over lamivudine for long-term treatment because of the high risk for resistance to lamivudine, which could lead to decompensation. Combination therapy with adefovir plus lamivudine has the theoretical benefit of reducing the development of resistance to either and/or both viruses by the concomitant administration of a second antiviral with activity against the mutant that might emerge as a consequence of therapy with either drug alone.

All decompensated cirrhotic patients (serum HBV DNA $< 10^3$ copies/mL or $\geq 10^3$ copies/mL) should be considered for treatment. Adefovir or lamivudine are first-line options, although adefovir is preferred for long-term treatment. Adefovir also is preferred for patients with Child-Turcotte-Pugh class B or C because they may not tolerate the development of YMDD mutant HBV. The aim in decompensated patients is to improve patient status such that they might even be removed from the transplant list. Combination therapy is likely to be more effective than monotherapy in suppressing viral replication and may decrease or delay the incidence of drug resistance; hence, consideration should be given to the combination of adefovir with lamivudine as the first-line treatment option for patients with decompensated liver function. A study comparing combination adefovir-lamivudine therapy with monotherapy in decompensated cirrhotic patients is warranted.

Duration of therapy and on-treatment monitoring.

The panel believes that therapy in cirrhotic patients should be long term and indefinite. Although there are no data on the benefit of continuation of treatment in compensated cirrhotic patients after HBeAg seroconversion, data from China showed that patients who experience HBeAg seroconversion may still develop HCC or have progression of their liver disease.¹⁰⁹ This may be caused by persistent low levels of HBV and/or events in oncogenesis that are initiated and propagated despite the suppression of viral replication. In the absence of data on benefit and given the favorable safety profile of nucleoside/nucleotide analogues, therapy should be continued until the patient becomes PCR negative and has lost HBsAg. On-treatment monitoring should be performed every 3 months. With lamivudine therapy, monitoring might be more frequent (every 1–2 mo) so that the emergence of lamivudine resistance is not missed because of the potential risk for decompensation.

Monitoring renal function before and during therapy is particularly important in patients who have multiple risk factors for renal impairment. Adjustments to the dosing of adefovir should be made, as listed in Table 10. Similarly, adjustments to the dosing of lamivudine should be made, also listed in Table 10.

Patients Coinfected With HIV-HBV and Hepatitis C Virus–HBV

HIV-HBV–coinfected patients. In the United States and Europe, $\sim 10\%$ of all HIV-infected patients are coinfecting with HBV.¹¹⁰ Data from the Multicenter AIDS Cohort Study, which include data before and after the availability of highly active antiretroviral therapy, showed that liver-related mortality in HIV-HBV–coin-

ected patients is 14-fold greater than that for either virus alone.¹¹¹ Approximately 80% of HIV-positive patients are administered lamivudine (300 mg/d) as part of their antiretroviral medication.

Summary of key clinical data. *Lamivudine.* Lamivudine has been shown to be effective and well tolerated in patients coinfecting with HBV and HIV,¹¹² resulting in significant reductions in serum HBV DNA levels. The rate of emergence of lamivudine-resistant HBV is greater in coinfecting patients than in those with HBV infection alone, reaching 90% at 4 years.¹¹³

Adefovir dipivoxil. Adefovir, 10 mg/d, has been effective in HIV-HBV-coinfecting patients with lamivudine-resistant HBV, resulting in a 4-log₁₀ decrease in HBV DNA levels and ALT level normalization by 48 weeks.¹¹⁴ No adefovir-resistant reverse-transcriptase mutations developed in any of the 11 patients tested. Because adefovir at the 10-mg dose is not effective against HIV, it therefore is unlikely to select adefovir- or tenofovir-resistant HIV mutants. Serum creatinine level increases ≥ 0.5 mg/dL without changes in serum phosphorus levels were seen in 2 patients. Both resolved and were considered unrelated to adefovir.

Tenofovir. Several studies confirmed that tenofovir is effective against both HIV and HBV. A study by Cooper et al.¹¹⁵ showed that tenofovir resulted in 0.6-log decrease in HIV level and 5-log decrease from baseline for HBV level. Similarly, another coinfection study showed a 4-log decrease in HBV DNA level by week 24 and an increase of ~ 80 CD4 cells.¹¹⁶ However, there have been reports of renal toxicity and hypophosphatemia associated with tenofovir therapy.^{117,118}

Treatment recommendations. Therapy for HIV-HBV-coinfecting patients needs to be individualized according to the status of the patient. Tenofovir and adefovir are equally potent against HBV, but adefovir has no activity against HIV at the 10-mg dose. If a patient's HIV infection is not being treated, the patient should not be administered tenofovir or lamivudine monotherapy. Adefovir, 10 mg monotherapy is an option because this will treat HBV, but have no activity against the HIV reverse transcriptase. Tenofovir or lamivudine monotherapy is not recommended at this stage because of the risk for HIV resistance. If a patient is being treated for HIV infection, a highly active antiretroviral therapy regimen containing tenofovir or tenofovir-lamivudine combination is an option. For patients who are on a stable HIV treatment regimen, it may be preferred to add adefovir, rather than switch to tenofovir, to cover both viruses.

Hepatitis C virus-HBV-coinfecting patients. Injecting drug users often are coinfecting with HBV and hepatitis C virus (HCV).¹¹⁹ Various studies have shown that the outcome of combined infection is more severe than that of infection with either virus alone.^{119,120} In most patients, one infection tends to predominate, and the other is dormant. In a situation in which HCV infection is the dominant disease, HCV RNA is detectable and HBV DNA is not. The converse is true for HBV-dominant disease. Many HBV-HCV-coinfecting patients tend to be HBeAg negative and have low HBV DNA levels, with HCV infection being dominant.

Treatment recommendations. Patients should be assessed to determine which virus appears to be dominant, then treated accordingly. Hence, patients with HBV DNA levels $\geq 10^3$ copies/mL and undetectable HCV RNA should be treated for HBV infection. However, because most tend to have low HBV DNA levels and detectable HCV RNA, the panel recommends that HCV-HBV-coinfecting patients be treated for 3 months with peginterferon and ribavirin in standard doses. If HBV DNA does not begin to respond or levels increase on therapy, lamivudine or adefovir can be added. A recent study showed that patients with HCV-HBV coinfection treated for predominant HCV infection responded as well as patients with chronic HCV infection alone; only a few patients have activation of HBV infection during therapy.¹²¹

Chemotherapy

All patients with chronic HBV infection, as well as those who are positive for hepatitis B core antibody, should be given short-term therapy with either lamivudine or adefovir while receiving chemotherapy as prophylaxis against reactivation of HBV. Patients who are HBsAg negative and anti-HBs positive can reactivate; hence, the recommendation is to treat all patients with hepatitis B core antibody. Because this is short-term therapy, lamivudine resistance is less of a concern.¹²²

Pregnancy

Lamivudine and adefovir are classified as category C; therefore, standard category C recommendations should be followed. Both drugs can be continued during pregnancy, but the stage of the mother's liver disease and potential benefit of treatment must be weighed against the small risk to the fetus. Because this mostly concerns young women who are likely to have only mild liver disease, treatment of the disease could be postponed. Treatment during the third trimester to prevent transmission to the newborn may be considered. Although some success has been reported in preventing transmis-

sion of HBV to the newborn by using lamivudine, other reports suggested that babies have still been infected with HBV.¹²³ Any patient treated with lamivudine or adefovir should be reported to the respective pregnancy registry.

Resistance Monitoring

Resistance can be defined clinically (i.e., genotyping is not required) as “confirmed” by a $\geq 1\text{-log}_{10}$ increase in serum HBV DNA level from the patient’s lowest on-treatment level occurring on 2 sequential occasions.

Patients administered lamivudine should be monitored every 3–6 months for resistance. Because of adefovir’s significantly lower rate of resistance, adefovir-treated patients should be monitored every 6 months for resistance after the first year of therapy.

Conclusion

The goal of therapy for patients with chronic HBV infection is to prevent the progression of liver disease to cirrhosis and HCC. Because HBV replication is implicated in the outcome of chronic HBV infection, the primary aim of therapy is durable suppression of serum HBV DNA to the lowest levels possible. The advent of such molecular diagnostic assays as PCR enables the accurate monitoring of HBV DNA at levels as low as 100–1000 copies/mL and should be used to establish a patient’s baseline HBV DNA level before treatment and monitor response to antiviral therapy or viral rebound associated with resistance.

The threshold HBV DNA level for determination of candidates for therapy is $\geq 10^5$ copies/mL for patients with HBeAg-positive chronic HBV infection. Patients also should have elevated ALT levels and/or evidence of hepatitis on liver biopsy. An individualized approach to liver biopsy and consideration of therapy in viremic patients with normal ALT levels is warranted, and future studies of this population of HBV-infected patients are needed. A lower serum HBV DNA threshold is needed for patients with HBeAg-negative chronic hepatitis B and those with decompensated cirrhosis,² and the panel recommends thresholds $\geq 10^4$ copies/mL and $\geq 10^3$ copies/mL for these patient groups, respectively.

IFN, lamivudine, and adefovir are all approved as initial therapy for chronic hepatitis B. However, in choosing a therapy, consideration should be given to the advantages and disadvantages of the 3 therapies. The issues to consider are efficacy, safety, resistance, method of administration, and cost. Although IFN has the advantage of a finite duration of treatment, durable re-

sponse (in patients who respond), and lack of resistance, it is expensive to use, has to be administered by injection, and has many side effects. Lamivudine is well tolerated, with an excellent safety profile and good efficacy, but its long-term use is limited by the development of resistance. Thus, it might be a good choice for patients with high baseline ALT levels with a $\geq 50\%$ chance of HBeAg loss with only 1 year of therapy and for patients receiving short-term antiviral prophylaxis during chemotherapy. Patients requiring therapy for longer than 1 year probably are treated best with adefovir, with its much lower incidence of resistance. Adefovir has similar efficacy to lamivudine and is well tolerated. It has the advantage of a delayed and very low rate of resistance development and therefore is preferred for long-term use. However, its cost is greater than that of lamivudine.

Several areas require further study. Combination therapy may prove to be more effective than monotherapy in suppressing viral replication and may decrease or delay the incidence of drug resistance. Several large studies are under way exploring the use of 2 nucleoside/nucleotide antivirals or an antiviral plus peginterferon in compensated patients. Combination therapy with oral agents could be of particular value in decompensated cirrhosis, and a study comparing combination adefovir-lamivudine therapy with monotherapy in this patient group clearly is needed.

References

1. Lok ASF, McMahon B. Chronic hepatitis B. *Hepatology* 2001; 34:1225–1241.
2. Conjeevaram HS, Lok ASF. Management of chronic hepatitis B. *J Hepatol* 2003;38:S90–S103 (suppl).
3. Lee W. Hepatitis B virus infection. *N Engl J Med* 1997;337: 1733–1745.
4. McQuillan GM, Coleman PJ, Kruszon-Moran D, Moyer LA, Lambert SB, Margolis HS. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health* 1999;89: 14–18.
5. Hepatitis B Foundation. What is hepatitis B? Statistics. Available at: <http://www.hepb.org/index.html>. Accessed: February 2003.
6. Poterucha JJ, Wiesner RH. Liver transplantation and hepatitis B. *Ann Intern Med* 1997;126:805–807.
7. McMahon BJ, Alward WLM, Hall DB, Heyward WL, Bender TR, Francis DP, Maynard JE. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985;151:599–603.
8. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Karayannis AR, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology* 1987;92:1844–1850.
9. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000—summary of a workshop. *Gastroenterology* 2001; 120:1828–1853.
10. Di Bisceglie AM, Waggoner JG, Hoofnagle JH. Hepatitis B virus

- deoxyribonucleic acid in liver of chronic carriers: correlation with serum markers and changes associated with loss of hepatitis B e antigen after antiviral therapy. *Gastroenterology* 1987;93:1236–1241.
11. Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. *Gastroenterology* 2001;120:1009–1022.
 12. Realdi G, Fattovich G, Hadziyannis S, Schalm SW, Almasio P, Sanchez-Tapias J, Christensen E, Giustina G, Noventa F. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. *J Hepatol* 1994;21:656–666.
 13. de Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW, van Blankenstein M. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. *Gastroenterology* 1992;103:1630–1635.
 14. Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, Christensen E, Krogsgaard K, Degos F, de Moura MC, Solinas A, Noventa F, Realdi G. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. *Hepatology* 1995;21:77–82.
 15. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, Hsiao CK, Chen PJ, Chen DS, Chen CJ. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002;347:168–174.
 16. Xiong S, Yang H, Westland CE, Delaney WE 4th, Colledge D, Bartholomeusz A, Thibault V, Benhamou Y, Angus P, Wulfsohn M, Gibbs CS, Fry J, Borosgart CL, Locarnini S. Resistance surveillance of HBeAg-chronic hepatitis B (CHB) patients treated for two years with adefovir dipivoxil (ADV) (abstr). *J Hepatol* 2003;(suppl 2):182A.
 17. Hadziyannis SJ, Lieberman HM, Karvountzis GG, Shafritz DA. Analysis of liver disease, nuclear HBeAg, viral replication, and hepatitis B virus HBV DNA in liver and serum of HBeAg vs. anti-HBe positive carriers of hepatitis B virus. *Hepatology* 1983;3:656–662.
 18. Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, Thomas HC. Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection. *Lancet* 1989;2:588–591.
 19. Okamoto H, Tsuda F, Akahane Y, Sugai Y, Yoshida M, Moriyama K, Tanaka T, Miyakawa Y, Mayumi M. Hepatitis B virus with mutations in the core promoter for an e antigen-negative phenotype in carriers with antibody to e antigen. *J Virol* 1994;68:8102–8110.
 20. Hadziyannis SJ. Hepatitis B e antigen negative chronic hepatitis B: from clinical recognition to pathogenesis and treatment. *Viral Hepatitis Rev* 1995;1:7–36.
 21. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2001;34:617–624.
 22. Hadziyannis SJ, Bramou T, Alexopoulou A, Makris A. Immunopathogenesis and natural course of anti-HBe positive chronic hepatitis with replicating B virus. In: Hollinger FB, Lemon SM, Margolis HS, eds. *Viral hepatitis and liver disease*. Baltimore, MD: Williams & Wilkins, 1991:673–676.
 23. Brunetto MR, Giarin MM, Oliveri F, Chiaberge E, Baldi M, Alfarano A, Serra A, Saracco G, Verme G, Will H. Wild-type and e antigen-minus hepatitis B viruses and course of chronic hepatitis. *Proc Natl Acad Sci U S A* 1991;88:4186–4190.
 24. Arauz-Ruiz P, Norder H, Robertson BH, Magnus LO. Genotype H: a new Amerindian genotype of hepatitis B virus revealed in Central America. *J Gen Virol* 2002;83:2059–2073.
 25. Kidd-Ljunggren K, Miyakawa Y, Kidd AH. Genetic variability in hepatitis B viruses. *J Gen Virol* 2002;83:1267–1280.
 26. Chu CJ, Lok AS. Clinical significance of hepatitis B virus genotypes. *Hepatology* 2002;35:1274–1276.
 27. Kao JH, Chen PJ, Lai MY, Chen DS. Genotypes and clinical phenotypes of hepatitis B virus in patients with chronic hepatitis B virus infection. *J Clin Microbiol* 2002;40:1207–1209.
 28. Fujie H, Moriya K, Shintani Y, Yotsuyanagi H, Iino S, Koike K. Hepatitis B virus genotypes and hepatocellular carcinoma in Japan. *Gastroenterology* 2001;120:1564–1565.
 29. Chu CJ, Hussain M, Lok AS. Hepatitis B virus genotype B is associated with earlier seroconversion compared with hepatitis B virus genotype C. *Gastroenterology* 2002;122:1756–1762.
 30. Kao JH, Wu NH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes and the response to interferon therapy. *J Hepatol* 2000;33:998–1002.
 31. Zhang X, Zoulim F, Habersetzer F, Xiong S, Trepo C. Analysis of hepatitis B virus genotypes and pre-core region variability during interferon treatment of HBe antigen negative chronic hepatitis B. *J Med Virol* 1996;48:8–16.
 32. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Haussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996;334:1422–1427.
 33. Chu CJ, Hussain M, Lok ASF. Quantitative serum HBV DNA levels during different stages of chronic hepatitis B infection. *Hepatology* 2002;36:1408–1415.
 34. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, Wu PC, Dent JC, Barber J, Stephenson SL, Gray DF. A one-year trial of lamivudine for chronic hepatitis B. *N Engl J Med* 1998;339:61–68.
 35. Beasley RP. Hepatitis B virus: the major etiology of hepatocellular carcinoma. *Cancer* 1988;61:1942–1956.
 36. McMahon BJ. Hepatocellular carcinoma and viral hepatitis. In: Wilson RA, ed. *Viral hepatitis*. New York: Dekker, 1997:315–330.
 37. Johnson PJ, Williams R. Serum alpha-fetoprotein estimations and doubling time in hepatocellular carcinoma: influence of therapy and possible value in early detection. *J Cancer Inst* 1980;64:1329–1332.
 38. Sheu JC, Sung JL, Chen DS, Yang PM, Lai MY, Lee CS, Hsu HC, Chuang CN, Yang PC, Wang TH. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterology* 1985;89:259–266.
 39. Sherman M, Peltekian KM, Lee CL. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. *Hepatology* 1995;22:432–437.
 40. Sheu JC, Sung JL, Chen DS, Lai MY, Wang TH, Yu JY, Yang PM, Chuang CN, Yang PC, Lee CS. Early detection of hepatocellular carcinoma by real-time ultrasonography. *Cancer* 1985;56:660–666.
 41. Zoli M, Magalotti D, Bianchi G, Gueli C, Marchesini G, Pisi E. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. *Cancer* 1996;78:977–985.
 42. Oka H, Kurioka N, Kim K, Kanno T, Kuroki T, Mizoguchi Y, Kobayashi K. Prospective study of early detection of hepatocellular carcinoma. *Cancer* 1990;12:680–687.
 43. Cottone M, Turri M, Caltagirone M, Parisi P, Orlando A, Fiorentino G, Virdone R, Fusco G, Grasso R, Simonetti RG. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8 year prospective study by ultrasound and alpha-fetoprotein. *J Hepatol* 1994;21:1029–1034.
 44. Colombo M, De Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, Donato MF, Piva A, Di Carlo V, Dioguardi N. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991;325:675–680.
 45. EASL Jury. EASL International Consensus Conference on Hepatitis B. 13-14 September, 2002: Geneva, Switzerland. Consensus statement (short version). *J Hepatol* 2003;38:533–540.
 46. McMahon BJ, Bulkow L, Harpster A. Screening for hepatocellular carcinoma in Alaska Natives infected with chronic hepatitis

- B: a 16-year population-based study. *Hepatology* 2000;32:842–846.
47. Puoti C, Magrini A, Stati T, Rigato P, Montagnese F, Rossi P, Aldegheri L, Resta S. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. *Hepatology* 1997;26:1393–1398.
 48. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, Vianello L, Zanuso F, Mozzi F, Milani S, Conte D, Colombo M, Sirchia G. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002;137:1–9.
 49. Chien RN, Liaw YF, Atkins M. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. *Hepatology* 1999;30:770–774.
 50. Perrillo RP, Lai CL, Liaw YF, Dienstag JL, Schiff ER, Schalm SW, Heathcote EJ, Brown NA, Atkins M, Woessner M, Gardner SD. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. *Hepatology* 2002;36:186–194.
 51. Lok ASF, Lai CL, Wu PC, Leung EK. Long-term follow-up in a randomised trial of recombinant alpha₂-interferon in Chinese patients with chronic hepatitis B infection. *Lancet* 1988;2:298–302.
 52. Lok ASF, Wu PC, Lai CL, Lau JY, Leung EK, Wong LS, Ma OC, Lauder IJ, Ng CP, Chung HT. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. *Gastroenterology* 1992;102:2091–2097.
 53. Hoofnagle JH, Dusheiko GM, Seeff LB, Jones EA, Waggoner JG, Bales ZB. Seroconversion from hepatitis B e antigen to antibody in chronic type B hepatitis. *Ann Intern Med* 1981;94:744–748.
 54. Fattovich G, Ruggie M, Brollo L, Pontisso P, Noventa F, Guido M, Alberti A, Realdi G. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. *Hepatology* 1986;6:167–172.
 55. Werle B, Wursthorn K, Petersen J, Bowden S, Locarnini S, Lau G, Trepo C, James C, Brosgart C, Xiong S, Delaney V, Gibbs C, Zoulim F. Quantitative analysis of hepatic HBV cccDNA during the natural history of chronic hepatitis B and adefovir dipivoxil therapy: an international multicenter study (abstr). *Hepatology* 2002;36(suppl 4):296A.
 56. Bréchet C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Bréchet P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely “occult”? *Hepatology* 2001;34:194–203.
 57. Conjeevaram HS, Lok AS. Occult hepatitis B virus infection: a hidden menace? *Hepatology* 2001;34:204–206.
 58. Mommeja-Marin H, Mondou E, Blum R, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2002;37:1309–1319.
 59. Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. *Hepatology* 1988;8:1130–1133.
 60. Chang MH, Hsu HY, Hsu HC, Ni YH, Chen JS, Chen DS. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis e antigen before 3 years of age. *Hepatology* 1995;22:1387–1392.
 61. Lok ASF, Lai CL, Wu PC, Leung EKY, Lam TS. Spontaneous hepatitis e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. *Gastroenterology* 1987;92:1839–1843.
 62. Lee PI, Chang MH, Lee CY, Hsu HY, Chen JS, Chen PJ, Chen DS. Changes in serum hepatitis B DNA and aminotransferase levels during the course of chronic hepatitis B virus infection in children. *Hepatology* 1990;12:657–660.
 63. Lok ASF, Lai CL. Acute exacerbations in Chinese patients with chronic hepatitis B virus (HBV) infection: incidence, predisposing factors and etiology. *J Hepatol* 1990;10:29–34.
 64. Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology* 2001;34:139–145.
 65. Bortolotti F, Cadrobbi P, Crivellaro C, Guido M, Ruggie M, Noventa F, Calzia R, Realdi G. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B infection in childhood. *Gastroenterology* 1990;99:805–810.
 66. Wong DKH, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. *Ann Intern Med* 1993;119:312–323.
 67. Schiff ER. Treatment algorithms for hepatitis B and C. *Gut* 1993;34:S148–S149 (suppl 2).
 68. Bortolotti F, Jara P, Barbera C, Gregorio GV, Vegnente A, Zancan L, Hierro L, Crivellaro C, Vergani GM, Iorio R, Pace M, Con P, Gatta A. Long term effect of alpha interferon in children with chronic hepatitis B. *Gut* 2000;46:715–718.
 69. Fattovich G, Giustina G, Sanchez-Tapias J, Quero C, Mas A, Olivetto PG, Solinas A, Almasio P, Hadziyannis S, Degos F, de Moura MC, Krogsgaard K, Pantalena M, Realdi G, Corrocher R, Schalm SW. Delayed clearance of serum HBsAg in compensated cirrhosis B: relation to interferon alpha therapy and disease prognosis. *Am J Gastroenterol* 1998;93:896–900.
 70. Hoofnagle JH, DiBisceglie AM. The treatment of chronic viral hepatitis. *N Engl J Med* 1997;336:347–356.
 71. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, Crowther L, Condreay LD, Woessner M, Rubin M, Brown NA. Lamivudine as initial treatment for chronic hepatitis B virus in the United States. *N Engl J Med* 1999;341:1256–1263.
 72. Schalm SW, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, Dhillon A, Moorat A, Barber J, Gray DF. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B virus infection: a randomised trial. *Gut* 2000;46:562–568.
 73. Liaw YF, Leung NWY, Chang TT, Guan R, Tai DI, Ng KY, Chien RN, Dent J, Roman L, Edmundson S, Lai CL. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. *Gastroenterology* 2000;119:172–180.
 74. Leung NWY, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, Lim SG, Wu PC, Dent JC, Edmundson S, Condreay LD, Chien RN. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001;33:1527–1532.
 75. Chang TT, Lai CL, Liaw YF, Guan R, Lim SG, Lee CM, Ng KY, Leung NWY, Nicholls GJ, Pearce MA, Dent JC. Incremental increases in HBeAg seroconversion and continued ALT normalization in Asian chronic HBV (CHB) patients treated with lamivudine for four years (abstr). *Antivir Ther* 2000;5(suppl 1):44.
 76. Guan R, Lai CL, Liaw YF, Lim SG, Lee CM. Efficacy and safety of 5 years lamivudine treatment of Chinese patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2001;16:A60–A61 (abstr) (suppl 1).
 77. Liaw YF. Results of lamivudine in Asian trials. In: *Proceedings of EASL International Consensus Conference on Hepatitis B: 2002 September 13–14; Geneva*. Geneva: European Association for the Study of the Liver, 2002.
 78. Dienstag JL, Goldin RD, Heathcote EJ, Hann HW, Woessner M, Stephenson SL, Gardner S, Gray DF, Schiff ER. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105–117.
 79. Liaw Y. Management of YMDD mutations during lamivudine therapy in patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2002;17:S333–S337 (suppl).

80. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;348:808–816.
81. Angus P, Vaughn R, Xiong S, Yang H, Delaney W, Gibbs C, Brosgart C, Colledge D, Edwards R, Ayres A, Bartholomeusz A, Locarnini S. Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. *Gastroenterology* 2003;125:292–297.
82. Barbarini G, Zechini F, Pellicelli A, Spallanzani L, Francavilla R, Scotto G, Bacca D, Bruno M, Babudieri S, Matarazzo F, Annese M, DiStefano G, Barbaro G. Long-term efficacy of interferon alpha-2b and lamivudine in combination compared to lamivudine monotherapy in patients with chronic hepatitis B: an Italian multicenter randomized trial (abstr). *Hepatology* 2001;34:318A.
83. Korenman J, Baker B, Waggoner J, Everhart JE, Di Bisceglie AM, Hoofnagle JH. Long-term remission of chronic hepatitis B after alpha-interferon therapy. *Ann Intern Med* 1991;114:629–634.
84. Krogsgaard K. The long-term effect of treatment with interferon-alpha 2a in chronic hepatitis B. *J Viral Hepat* 1998;5:389–397.
85. Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999;29:971–975.
86. Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schmid P, Hoofnagle JH. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology* 1997;113:1660–1667.
87. Lok AS, Chung HT, Liu VW, Ma OC. Long-term follow-up of chronic hepatitis B patients treated with interferon alfa. *Gastroenterology* 1993;105:1833–1838.
88. Dienstag JL, Cianciara J, Karayalcin S, Kowdley KV, Willems B, Plisek S, Woessner M, Gardner S, Schiff E. Durability of serologic response after lamivudine treatment of chronic hepatitis B. *Hepatology* 2003;37:748–755.
89. Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. *Hepatology* 2000;32:803–806.
90. Ryu SH, Chung YH, Choi MH, Kim JA, Shin JW, Jang MK, Park NH, Lee HC, Lee YS, Suh DJ. Long-term additional lamivudine therapy enhances durability of lamivudine-induced HBeAg loss: a prospective study. *J Hepatol* 2003;39:614–619.
91. Brook MG, Karayiannis P, Thomas HC. Which patients with chronic hepatitis B virus infection will respond to alpha-interferon therapy? A statistical analysis of predictive factors. *Hepatology* 1989;10:761–763.
92. Manesis EK, Hadziyannis SJ. Interferon alpha treatment and retreatment of hepatitis B e antigen-negative chronic hepatitis B. *Gastroenterology* 2001;121:101–109.
93. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol* 2001;34:306–313.
94. Brunetto MR, Oliveri F, Coco B, Leandro G, Colombatto P, Gorin JM, Bonino F. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long term cohort study. *J Hepatol* 2002;36:263–270.
95. Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, Hawley S, Barber J, Condreay L, Gray DF. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B. *Hepatology* 1999;29:889–896.
96. Santantonio T, Mazzola M, Iacovazzi T, Miglietta A, Guastadisegni A, Pastore G. Long-term follow-up of patients with anti-HBe/HBV DNA-positive chronic hepatitis B treated for 12 months with lamivudine. *J Hepatol* 2000;32:300–306.
97. Hadziyannis SJ, Papatheodoridis GV, Dimou E, Laras A, Papatheodoridis C. Efficacy of long-term lamivudine monotherapy in patients with hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2000;32:847–851.
98. Buti M, Cotrina M, Jardi R, de Castro EC, Rodriguez-Frias F, Sanchez-Avila F, Esteban R, Guardia J. Two years of lamivudine therapy in anti-HBe-positive patients with chronic hepatitis B. *J Viral Hepatol* 2001;8:270–275.
99. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ. Adefovir dipivoxil for the treatment of HBeAg-negative chronic hepatitis B. *N Engl J Med* 2003;348:800–807.
100. Perrillo R, Rakela J, Dienstag J, Levy G, Martin P, Wright T, Caldwell S, Schiff E, Gish R, Villeneuve JP, Farr G, Anschuetz G, Crowther L, Brown N. Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology* 1999;29:1581–1586.
101. Atkins M, Hunt CM, Brown N, Gray F, Sanathanan L, Woessner M, Lai CL, Dusheiko G, Dienstag J, Wright T, Barnard J, Bourne E, Condreay L. Clinical significance of YMDD mutant hepatitis B virus in a large cohort of lamivudine-treated hepatitis B patients (abstr). *Hepatology* 1998;28:319A.
102. Peters MG, Hann HW, Martin P, Heathcote EJ, Buggisch P, Rubin R, Bourliere M, Kowdley K, Trepo C, Gray DF, Sullivan M, Kleber K, Ebrahimi R, Xiong S, Brosgart C. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2004;126:91–101.
103. Hoofnagle JH, DiBisceglie AM, Waggoner JG, Park Y. Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. *Gastroenterology* 1993;104:1116–1121.
104. Perrillo R, Tamburro C, Regenstein F, Balart L, Bodenheimer H, Silva M, Schiff E, Bodicky C, Miller B, Denham C. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology* 1995;109:908–916.
105. Perrillo RP, Wright T, Rakela J, Levy G, Schiff E, Gish R, Martin P, Dienstag J, Adams P, Dickson R, Anschuetz G, Bell S, Condreay L, Brown N. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001;33:424–432.
106. Villeneuve JP, Condreay LD, Willems B, Pomier-Layrargues G, Fenyves D, Bilodeau M, Leduc R, Peltekian K, Wong F, Margulies M, Heathcote EJ. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. *Hepatology* 2000;31:207–210.
107. Schiff ER, Lai CL, Neuhaus P, Tillman H, Samuel D, Villeneuve JP, Hadziyannis S, Xiong S, Lama N, James C, Fry J, Namini H, Van Doren S, Brosgart C. Adefovir dipivoxil (ADV) for the treatment of chronic hepatitis B in patients pre- and post-liver transplantation (OLT) with lamivudine resistant (LAM-R) hepatitis B virus (HBV) (abstr). *Hepatology* 2002;36:371A.
108. Perrillo R, Hann HW, Mutimer D, Willems B, Leung N, Lee W, Moorat A, Gardner S, Woessner M, Bourne E, Brosgart C, Schiff E. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. *Gastroenterology* 2004;126:81–90.
109. Yuen MF, Sablon E, Yuan HJ, Wong DK, Hui CK, Wong BC, Chan AO, Lai CL. Significance of hepatitis B genotype in acute exacerbation, HBeAg seroconversion, cirrhosis-related complications, and hepatocellular carcinoma. *Hepatology* 2003;37:562–567.
110. Homann C, Krogsgaard K, Pedersen C, Andersson P, Nielsen JO. High incidence of hepatitis B infection and evolution of chronic hepatitis B infection in patients with advanced HIV infection. *J Acquir Immune Defic Syndr* 1991;4:416–420.
111. Thio CL, Seaberg EC, Skolasky R, Jr, Phair J, Visscher B, Munoz A, Thomas DL. HIV-1, hepatitis B virus, and risk of liver-related

- mortality in the Multicenter AIDS Cohort Study (MACS). *Lancet* 2002;360:1921–1926.
112. Benhamou Y, Katlama C, Lunel F, Coutellier A, Dohin E, Hamm N, Tubiana R, Herson S, Poynard T, Opolon P. Effects of lamivudine on replication of hepatitis B virus in HIV-infected men. *Ann Intern Med* 1996;125:705–712.
 113. Benhamou Y, Bochet M, Thibault V, Di Martino V, Caumes E, Bricaire F, Opolon P, Katlama C, Poynard T. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology* 1999;30:1302–1306.
 114. Benhamou Y, Bochet M, Thibault V, Calvez V, Fievet MH, Vig P, Gibbs CS, Brosgart C, Fry J, Namini H, Katlama C, Poynard T. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* 2001;358:718–723.
 115. Cooper D, Cheng A, Coakley D, Sayre J, Zhong L, Chen SS, Westland C, Miller MD, Brosgart C. Anti-hepatitis B virus (HBV) activity of tenofovir disoproxil fumarate (TDF) in lamivudine (LAM) experienced HIV/HBV co-infected patients (poster 6015). 14th International AIDS Conference, Barcelona, Spain, 2002.
 116. Benhamou Y, Bochet M, Tubiana R, Thibault V, Suffisseau L, Sullivan M, Rooney J, Brosgart C, Bricaire F, Katlama C, Poynard T. Tenofovir disoproxil fumarate (TDF) suppresses lamivudine-resistant HBV replication in patients co-infected with HIV/HBV (abstr 7527). 14th International AIDS Conference, Barcelona, Spain, 2002.
 117. Reynes J, Peyrière H, Merle De Boever C, Le Moing V. Renal tubular injury and severe hypophosphatemia (Fanconi Syndrome) associated with tenofovir therapy (abstr 717). 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, 2003.
 118. Blick G, Greiger-Zanlungo P, Garton T, Hatton E, Lopez RJ. Tenofovir may cause severe hypophosphatemia in HIV/AIDS patients with prior adefovir-induced renal tubular acidosis (abstr 718). 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, 2003.
 119. Roudot-Thoraval F, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. *Hepatology* 1997;26:485–490.
 120. Fong TL, Di Bisceglie AM, Waggoner JG, Banks SM, Hoofnagle JH. The significance of antibody to hepatitis C virus in patients with chronic hepatitis B. *Hepatology* 1991;14:64–67.
 121. Liu CJ, Chen PJ, Lai MY, Kao JH, Jeng YM, Chen DS. Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients. *Hepatology* 2002;37:568–576.
 122. Simpson ND, Simpson PW, Ahmed AM, Nguyen MH, Garcia G, Keeffe EB, Ahmed A. Prophylaxis against chemotherapy-induced reactivation of hepatitis B virus infection with lamivudine. *J Clin Gastroenterol* 2003;37:68–71.
 123. Van Zonneveld M, Van Nunen AB, Niesters HGM, De Man RA, Schalm SW, Janssen HLA. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. *J Viral Hepat* 2003;10:294–297.
 124. Mailliard ME, Gollan JL. Suppressing hepatitis B without resistance—so far, so good. *N Engl J Med* 2003;348:848–850.

Address requests for reprints to: Emmet B. Keeffe, Stanford University Medical Center, 750 Welch Road, Suite 210, Palo Alto, California 94304-1509. ekeeffe@stanford.edu; fax: (650) 498-5692.

The meeting at which this algorithm was developed was supported by an unrestricted educational grant from Gilead Sciences.