

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Context

Epidemiology and public health burden

Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers. The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) [2–4]. HBV-related end stage liver disease or HCC are responsible for over 0.5–1 million deaths per year and currently represent 5–10% of cases of liver transplantation [5–8]. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) together with other co-morbidities including alcohol abuse and obesity, can affect the natural course of HBV infection as well as efficacy of antiviral strategies [2–8]. CHB may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The prevalence of the HBeAg-negative form of the disease has

been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2–4,11–13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14–35% probability of survival at 5 years [2–4,12]. The worldwide incidence of HCC has increased, mostly due to persistent HBV and/or HCV infections; presently it constitutes the fifth most common cancer, representing around 5% of all cancers. The annual incidence of HBV-related HCC in patients with CHB is high, ranging from 2% to 5% when cirrhosis is established [13]. However, the incidence of HBV related HCC appears to vary geographically and correlates with the underlying stage of liver disease and possibly exposure to environmental carcinogens such as aflatoxin. Population movements and migration are currently changing the prevalence and incidence of the disease in several low endemic countries in Europe and elsewhere. Substantial healthcare resources will be required for control of the worldwide burden of disease.

Natural history

Chronic HBV infection is a dynamic process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

- (1) The “immune tolerant” phase is characterised by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of aminotransferases, mild or no liver necroinflammation and no or slow progression of fibrosis [2,3,6,8]. During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent and more prolonged in subjects infected perinatally or in the first years of life. Because of high levels of viremia, these patients are highly contagious.
- (2) The “immune reactive HBeAg-positive phase” is characterised by HBeAg positivity, relatively lower level of replication compared to the immune tolerant phase (as reflected by lower serum HBV DNA levels), increased or

Keywords: Hepatitis B virus; EASL guidelines; Treatment; Interferon alpha; Nucleoside/nucleotide analogues.

Received 28 February 2012; accepted 28 February 2012

Contributors: George Papatheodoridis (Coordinator & EASL Governing Board), Maria Buti, Markus Cornberg, Harry Janssen, David Mutimer, Stanislas Pol, Giovanni Raimondo; **Reviewers:** EASL Governing Board, Geoffrey Dusheiko, Anna Lok, Patrick Marcellin.

* Correspondence: EASL Office, 7 rue des Batoirs, CH-1205 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724.

E-mail address: easloffice@easloffice.eu (European Association for the Study of the Liver).



ELSEVIER

Clinical Practice Guidelines

Table 1. Grading of evidence and recommendations (adapted from the GRADE system) [32–37].

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading of recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption	2

fluctuating levels of aminotransferases, moderate or severe liver necroinflammation and more rapid progression of fibrosis compared to the previous phase [2–4,6,8]. This phase may occur after several years of immune tolerance (partial breakdown of tolerance) and is more frequently and/or more rapidly reached in subjects infected during adulthood, paralleling maturation of specific anti-HBV immunity. It may last for several weeks to several years. The rate of spontaneous HBeAg loss is enhanced. This phase ends with seroconversion to anti-HBe.

- (3) The “inactive HBV carrier state” may follow seroconversion from HBeAg to anti-HBe antibody. It is characterised by very low or undetectable serum HBV DNA levels and normal serum aminotransferases. A minimum follow-up of 1 year with alanine aminotransferase (ALT) levels at least every 3–4 months and serum HBV DNA levels is required before classifying a patient as inactive HBV carrier. ALT levels should remain persistently within the normal range according to traditional cut-off values (approximately 40 IU/ml) [14] and HBV DNA should be below 2000 IU/ml. Some inactive carriers, however, may have HBV DNA levels greater than 2000 IU/ml (usually below 20,000 IU/ml) accompanied by persistently normal ALT levels [14–17]. Patients with HBV DNA <2000 IU/ml and elevated ALT values should be usually advised to undergo liver biopsy for the evaluation of the cause of liver injury. As a result of immunological control of the infection, the inactive HBV carrier state confers a favourable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients [18–20]. HBsAg loss and seroconversion to anti-HBs antibody may occur spontaneously in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA [15]. On the other hand, progression to CHB, usually HBeAg-negative, may also occur [21]. Therefore, inactive HBV carriers should be followed up for life with ALT determinations at least every 6 months after the first year and periodical measurement of HBV DNA levels [14]. The follow-up should be closer in cases with baseline serum HBV DNA levels above 2000 IU/ml, in whom non-invasive evaluation of liver fibrosis may be useful and even liver biopsy might be considered [14]. Inactive carriers have been reported to

have serum HBsAg levels <1000 IU/ml, but such HBsAg levels may occasionally be detected in CHB patients as well [22].

- (4) “HBeAg-negative CHB” may follow seroconversion from HBeAg to anti-HBe antibodies during the immune reactive phase or may develop after years or decades of the inactive carrier state. It represents a later immune reactive phase in the natural history of chronic HBV infection. It is characterised by periodic reactivation with a pattern of fluctuating levels of HBV DNA and aminotransferases and active hepatitis [4,23–25]. These patients are HBeAg-negative and harbour a predominance of HBV virions with nucleotide substitutions in the precore and/or the basal core promoter regions that are hence unable to express or express low levels of HBeAg. HBeAg-negative CHB is associated with low rates of prolonged spontaneous disease remission [4,23]. It is important and sometimes difficult to distinguish true inactive HBV carriers from patients with active HBeAg negative CHB in whom phases of spontaneous remission may occur. The former patients have a good prognosis with a very low risk of complications, while the latter patients have active liver disease with a high risk of progression to advanced hepatic fibrosis, cirrhosis and subsequent complications such as decompensated cirrhosis and HCC. A careful assessment of the patients is needed and, as reported in the inactive carrier state, a minimal follow-up of 1 year with serum ALT levels every 3–4 months and HBV DNA levels usually allows detection of fluctuations of activity in patients with active HBeAg-negative CHB [23].
- (5) In the “HBsAg-negative phase” after HBsAg loss, low-level HBV replication may persist with detectable HBV DNA in the liver [26]. Generally, HBV DNA is not detectable in the serum, while anti-HBc antibodies with or without anti-HBs are detectable. HBsAg loss before the onset of cirrhosis is associated with improvement of the outcome with reduced risk of cirrhosis, decompensation and HCC. The clinical relevance of occult HBV infection [detectable HBV DNA in the liver with low level (<200 IU/ml) or undetectable HBV DNA in blood] is unclear [26]. Immunosuppression may lead to HBV reactivation in these patients [27,28]. If cirrhosis has developed before spontaneous or treatment-induced HBsAg loss, patients remain at risk of

HCC [29–31] and therefore HCC surveillance should continue (C2), although the cost-effectiveness of surveillance has not been determined in this setting.

Methodology

These EASL CPGs represent an update of the last EASL HBV CPGs published in early 2009. They were developed by a CPG Panel of experts chosen by the EASL Governing Board, peer-reviewed by the experts of the 2009 HBV CPGs and approved by the EASL Governing Board. The CPGs have been based as far as possible on evidence from existing publications, and, if evidence was unavailable, on the experts' personal experience and opinion. Manuscripts and abstracts of important meetings published prior to September 2011 have been evaluated. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. The quality of the evidence in these CPGs has been classified in one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The CPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted [32–37]. Grades are not provided for definitions. For practical reasons, months and not weeks were used in parts of the manuscript (e.g. 6 and 12 months instead of 24 and 48/52 weeks, respectively).

The CPG panel members considered the following questions:

- How should liver disease be assessed before therapy?
- What are the goals and end points of treatment?
- What are the definitions of response?
- What is the optimal approach to first-line treatment?
- What are the predictors of response?
- What definitions of resistance should be applied and how should resistance be managed?
- How should treatment be monitored?
- When can treatment be stopped?
- How should special groups be treated?
- What are the current unresolved issues?

Guidelines

Pre-therapeutic assessment of liver disease

As a first step, the causal relationship between chronic HBV infection and liver disease has to be established and an assessment of

the severity of liver disease needs to be performed. In addition, all first degree relatives and sexual partners of patients with chronic HBV infection should be advised to be tested for HBV serological markers (HBsAg, anti-HBc, anti-HBs) and to be vaccinated if they are negative for these markers (A1).

Not all patients with chronic HBV infection have persistently elevated aminotransferases. Patients in the immune tolerant phase and inactive carriers have persistently normal ALT levels, while a proportion of patients with HBeAg-negative CHB may have intermittently normal ALT levels. Therefore, appropriate longitudinal long-term follow-up is crucial.

- (1) The assessment of the severity of the liver disease should include: biochemical markers, including aspartate aminotransferase (AST) and ALT, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, bilirubin, and serum albumin and globulins, blood counts and prothrombin time, and hepatic ultrasound (A1). Usually, ALT levels are higher than those of AST. However, when the disease progresses to cirrhosis, the ratio may be reversed. A progressive decline in serum albumin concentrations and/or increase of (gamma-)globulins and prolongation of the prothrombin time, often accompanied by declining platelet counts, are characteristically observed after cirrhosis has developed.
- (2) HBV DNA detection and HBV DNA level measurement are essential for the diagnosis, decision to treat and subsequent monitoring of patients (A1). Follow-up using real-time PCR quantification assays is strongly recommended because of their sensitivity, specificity, accuracy and broad dynamic range [38–41] (A1). The World Health Organization (WHO) has defined an international standard for normalisation of expression of HBV DNA concentrations [42]. Serum HBV DNA levels should be expressed in IU/ml to ensure comparability; the same assay should be used in the same patient to evaluate antiviral efficacy. All HBV DNA values in this manuscript are reported in IU/ml; values given as copies/ml were converted to IU/ml by dividing by a factor of 5.
- (3) Other causes of chronic liver disease should be systematically looked for including co-infections with HDV, HCV and/or HIV (A1). Patients with chronic HBV infection should be also tested for antibody against hepatitis A virus (anti-HAV) and should be advised to be vaccinated against HAV if they are anti-HAV negative. Co-morbidities, including alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis should be assessed (A1).
- (4) A liver biopsy is often recommended for determining the degree of necroinflammation and fibrosis since hepatic histology can assist the decision to start treatment (A1).

The indications for liver biopsy are reported within the indications for treatment. The biopsy is also useful for evaluating other possible causes of liver disease such as fatty liver disease. Although liver biopsy is an invasive procedure, the risk of severe complications is very low (1/4000–10,000). It is important that the size of the needle biopsy specimen is large enough to accurately assess the degree of liver injury, in particular fibrosis [43] (A1). A liver biopsy is usually not required in patients with clinical evidence of cirrhosis or in those in whom treatment is indicated irrespective of the grade of activity or the stage of

Clinical Practice Guidelines

fibrosis (**A1**). There is growing interest in the use of non-invasive methods, including serum markers and transient elastography, to assess hepatic fibrosis to complement or avoid a liver biopsy [44–51]. Transient elastography, which is a non-invasive method widely used in Europe, offers high diagnostic accuracy for the detection of cirrhosis, although the results may be confounded by severe inflammation associated with high ALT levels and the optimal cut-off of liver stiffness measurements vary among studies [52,53].

Goal of therapy

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients [54] (**B1**). However, chronic HBV infection cannot be completely eradicated due to the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes, which may explain HBV reactivation [26,55,56]. Moreover, the HBV genome integrates into the host genome and might favour oncogenesis and the development of HCC [57–59].

End points of therapy

Therapy must ensure a degree of virological suppression that will then lead to biochemical remission, histological improvement and prevention of complications. The ideal end point is HBsAg loss, which however is infrequently achievable with the currently available anti-HBV agents. A more realistic end point is the induction of sustained or maintained virological remission.

- (1) In HBeAg-positive and HBeAg-negative patients, the ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs. This is associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome (**A1**).
- (2) Induction of sustained off-therapy virological and biochemical response in HBeAg-negative patients (either HBeAg-positive cases at baseline with durable anti-HBe seroconversion or HBeAg-negative cases from baseline) is a satisfactory end point, because it has been shown to be associated with improved prognosis (**A1**).
- (3) A maintained virological remission (undetectable HBV DNA by a sensitive PCR assay) under long-term antiviral therapy in HBeAg-positive patients who do not achieve anti-HBe seroconversion and in HBeAg-negative patients is the next most desirable end point (**A1**).

Definitions of response

Responses can be divided into biochemical, serological, virological and histological. All responses can be estimated at several time points during and after therapy. The definitions of virological responses vary according to the timing (on or after therapy) and type of therapy. Two different types of drugs can be used in the treatment of CHB: conventional or pegylated interferon

alpha (IFN or PEG-IFN) and nucleoside/nucleotide analogues referred to collectively as NAs in this document.

Biochemical response is defined as normalisation of ALT levels. It can be evaluated at several time points on-therapy, at the end and after the end of therapy. Since ALT activity often fluctuates over time, a minimum follow-up of at least 1 year post-treatment with ALT determinations at least every 3 months is required to confirm sustained off-treatment biochemical response (**B1**). It should be noted that the rates of sustained off-treatment biochemical responses may sometimes be difficult to evaluate, as transient (usually ≤ 3 months duration) ALT elevations before long-term biochemical remission may occur in some CHB patients within the first year after treatment discontinuation. In such cases, additional close ALT follow-up of at least 2 years after ALT elevation seems to be reasonable in order to confirm sustained off-therapy biochemical remission (**C2**).

Serological response for HBeAg applies only to patients with HBeAg-positive CHB and is defined as HBeAg loss and seroconversion to anti-HBe.

Serological response for HBsAg applies to all CHB patients and is defined as HBsAg loss and development of anti-HBs.

Virological responses on IFN/PEG-IFN therapy:

- Primary non-response has not been well established.
- Virological response is defined as an HBV DNA concentration of less than 2000 IU/ml. It is usually evaluated at 6 months and at the end of therapy as well as at 6 and 12 months after the end of therapy.
- Sustained off-treatment virological response is defined as HBV DNA levels below 2000 IU/ml for at least 12 months after the end of therapy.

Virological responses on NA therapy:

- Primary non-response is defined as less than 1 \log_{10} IU/ml decrease in HBV DNA level from baseline at 3 months of therapy.
- Virological response is defined as undetectable HBV DNA by a sensitive PCR assay. It is usually evaluated every 3–6 months during therapy depending on the severity of liver disease and the type of NA.
- Partial virological response is defined as a decrease in HBV DNA of more than 1 \log_{10} IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients.
- Virological breakthrough is defined as a confirmed increase in HBV DNA level of more than 1 \log_{10} IU/ml compared to the nadir (lowest value) HBV DNA level on therapy; it may precede a biochemical breakthrough, characterised by an increase in ALT levels. The main causes of virological breakthrough on NA therapy are poor adherence to therapy and/or selection of drug-resistant HBV variants (resistance) (**A1**).
- HBV resistance to NA(s) is characterised by selection of HBV variants with aminoacid substitutions that confer reduced susceptibility to the administered NA(s). Resistance may result in primary non-response or virological breakthrough on therapy (**A1**).
- NA(s) discontinuation is not common practice to date. However, NA(s) may be discontinued in some patients. Sustained off-treatment virological response may be

Table 2. Results of main studies for the treatment of HBeAg-positive chronic hepatitis B at 6 months following 12 months (48 or 52 weeks) of pegylated interferon alpha (PEG-IFN) and at 12 months (48 or 52 weeks) of nucleos(t)ide analogue therapy.

	PEG-IFN		Nucleoside analogues			Nucleotide analogues	
	PEG-IFN-2a	PEG-IFN-2b	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Dose*	180 µg	100 µg	100 mg	600 mg	0.5 mg	10 mg	245 mg
[Ref.]	[63]	[64]	[63, 65-68]	[68]	[67]	[69, 70]	[70]
Anti-HBe seroconversion (%)	32	29	16-18	22	21	12-18	21
HBV DNA <60-80 IU/ml (%)	14	7	36-44	60	67	13-21	76
ALT normalisation# (%)	41	32	41-72	77	68	48-54	68
HBsAg loss (%)	3	7	0-1	0.5	2	0	3

*PEG-IFN were given as percutaneous injections once weekly and nucleos(t)ide analogues as oral tablets once daily.

#The definition of ALT normalisation varied among different trials (i.e. decrease of ALT to <1.25-times the upper limit of normal (ULN) in the entecavir or <1.3-times the ULN in the telbivudine trial).

defined similarly to the definition used for IFN therapy, which requires HBV DNA values below 2000 IU/ml for at least 12 months after treatment discontinuation.

Histological response is defined as decrease in necroinflammatory activity (by ≥ 2 points in HAI or Ishak's system) without worsening in fibrosis compared to pre-treatment histological findings.

Complete response is defined as sustained off-treatment virological response together with loss of HBsAg.

Indications for treatment

The indications for treatment are generally the same for both HBeAg-positive and HBeAg-negative CHB. This is based mainly on the combination of three criteria:

- Serum HBV DNA levels.
- Serum ALT levels.
- Severity of liver disease.

Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy (or non-invasive markers once validated in HBV-infected patients) showing moderate to severe active necroinflammation and/or at least moderate fibrosis using a standardised scoring system (**A1**). In patients who fulfil the above criteria for HBV DNA and histological severity of liver disease, treatment may be initiated even if ALT levels are normal (**A1**). Indications for treatment may also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations.

The need for liver biopsy and treatment should be considered separately in the following subgroups of patients:

- *Immunotolerant patients:* HBeAg-positive patients under 30 years of age with persistently normal ALT levels and a high HBV DNA level, without any evidence of liver disease and without a family history of HCC or cirrhosis, do not require immediate liver biopsy or therapy. Follow-up at least every 3–6 months is mandatory (**B1**). Consider liver biopsy or even therapy in such patients over 30 years of age and/or with a family history of HCC or cirrhosis.

- HBeAg-negative patients with persistently normal ALT levels (ALT determinations at least every 3 months for at least 1 year) and HBV DNA levels above 2000 but below 20,000 IU/ml, without any evidence of liver disease, do not require immediate liver biopsy or therapy (**B1**). Close follow-up with ALT determinations every 3 months and HBV DNA every 6–12 months for at least 3 years is mandatory (**C1**). After 3 years, they should be followed for life like all inactive chronic HBV carriers. Evaluation of the severity of fibrosis by a non-invasive method, such as Fibroscan, might be useful in such cases (**C2**).
- *Patients with obviously active CHB:* HBeAg-positive and HBeAg-negative patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy (**B1**). In such patients, liver biopsy may provide additional useful information, but it does not usually change the decision for treatment. A non-invasive method for the estimation of the extent of fibrosis and most importantly to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy (**B1**).
- Patients with compensated cirrhosis and detectable HBV DNA must be considered for treatment even if ALT levels are normal (**B1**).
- Patients with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NA(s). Significant clinical improvement can be associated with control of viral replication [60–62]. However, antiviral therapy may not be sufficient to rescue some patients with very advanced liver disease who should be considered for liver transplantation at the same time (**A1**).

Results of current therapies

Drugs available for the treatment of CHB include IFN, PEG-IFN and six NAs. NAs for HBV therapy can be classified into nucleosides (lamivudine, telbivudine, emtricitabine, entecavir) and nucleotides (adefovir and tenofovir). PEG-IFN-2b and emtricitabine are not licensed for HBV treatment in most European countries. Lamivudine, adefovir, entecavir, telbivudine and tenofovir have been approved in Europe for HBV treatment, and the combination of tenofovir and emtricitabine in one tablet has been licensed for the treatment of human HIV infection. The efficacy of these drugs has been assessed in randomized controlled trials

Clinical Practice Guidelines

Table 3. Results of main studies for the treatment of HBeAg-negative chronic hepatitis B at 6 months following 12 months (48 weeks) of pegylated interferon alpha (PEG-IFN) and at 12 months (48 or 52 weeks) of nucleos(t)ide analogue therapy.

	PEG-IFN		Nucleoside analogues			Nucleotide analogues	
	PEG-IFN-2a	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir	
Dose*	180 µg	100 mg	600 mg	0.5 mg	10 mg	245 mg	
[Ref.]	[91]	[68, 90-92]	[68]	[92]	[70, 93]	[70]	
HBV DNA <60-80 IU/ml (%)	19	72-73	88	90	51-63	93	
ALT normalisation# (%)	59	71-79	74	78	72-77	76	
HBsAg loss (%)	4	0	0	0	0	0	

*PEG-IFN-2a was given as percutaneous injections once weekly and nucleos(t)ide analogues as oral tablets once daily.

#The definition of ALT normalisation varied among different trials (i.e. decrease of ALT to ≤ 1.25 -times the upper limit of normal (ULN) in the entecavir or ≤ 1.3 -times the ULN in the telbivudine trial).

at 1 year (2 years with telbivudine). Longer-term results are now available from extension of the randomized trials sometimes in patient subgroups and several cohort studies. Tables 2 and 3 show the response rates with these drugs from different trials. These trials used different HBV DNA assays and there are not head-to-head comparisons for all the drugs.

(1) HBeAg-positive patients

Response rates at 6 months following 12 months of PEG-IFN and at 12 months of NA therapy are given in Table 2 [63–70]. Anti-HBe seroconversion rates were of the order of 30% with PEG-IFN and approximately 20% with NAs. A 6-month course of PEG-IFN-2a and/or a lower dose are inferior to the recommended 12-month course [71]. Anti-HBe seroconversion rates are enhanced during the first 6 months following PEG-IFN therapy [63,72]. Anti-HBe seroconversion rates increase with continued NA therapy [73–78], but are affected if resistance occurs [79]. Anti-HBe seroconversion is less durable after discontinuation of NA compared to PEG-IFN therapy [79–82] (**B1**). Durability after anti-HBe seroconversion following treatment with more potent agents, i.e. entecavir and tenofovir, requires further evaluation. In patients adherent to treatment, virological remission rates of >90% can be maintained with ongoing entecavir or tenofovir after ≥ 3 years [78,83–85].

Rates of HBsAg loss following 12 months of treatment were 3–7% with PEG-IFN, 1% with lamivudine, 0% with adefovir, 2% with entecavir, 0.5% with telbivudine, and 3% with tenofovir [63–70]. HBsAg loss rates increase after the end of (PEG-)IFN therapy in patients with sustained off-treatment virological response [72,86–88] and with prolongation of NA(s) therapy [77,78,84,85,89].

(2) HBeAg-negative patients

Response rates at 6 months following 12 months of PEG-IFN and at 12 months of NA therapy are given in Table 3 [68,70,90–93]. Rates of sustained off-treatment virological response were of the order of 20% at 6 months following 12 months of PEG-IFN therapy and <5% following discontinuation of 12 months of NA(s) therapy [90–92,94,95]. In patients adherent to treatment, virological remission rates of >95% can be maintained with entecavir or tenofovir at ≥ 3 –5 years [84,96].

Rates of HBsAg loss following 12 months of treatment were 3% with PEG-IFN-2a (at 6 months after the end of therapy) and 0% with lamivudine, adefovir, entecavir, telbivudine or tenofovir [68,70,90–93]. HBsAg loss rates increase to 9% at 3 years and 12% at 5 years following PEG-IFN-2a therapy [97,98]. In contrast,

HBsAg loss is *exceptionally* observed during the first 4–5 years of NA(s) therapy in HBeAg-negative CHB patients [77,84,99,100].

Predictors of response

Certain general baseline and on-treatment predictors of subsequent response have been identified. Predictors of response for the existing antiviral therapies at various time points vary for different agents. Predictors may be useful to guide initiation and continuation of antiviral therapy.

(1) For IFN/PEG-IFN based treatment

• Pre-treatment factors

In HBeAg-positive CHB, predictors of anti-HBe seroconversion are low viral load (HBV DNA below 2×10^8 IU/ml), high serum ALT levels (above 2–5 times ULN), HBV genotype and high activity scores on liver biopsy (at least A2) [63,64,101,102] (**B2**). HBV genotypes A and B have been shown to be associated with higher rates of anti-HBe seroconversion and HBsAg loss than genotypes D and C, respectively, after treatment with PEG-IFN [63,64,103,104].

In HBeAg-negative CHB, there are no strong pre-treatment predictors of virological response.

• During treatment

In HBeAg-positive CHB, a HBV DNA decrease to <20,000 IU/ml at 12 weeks is associated with a 50% chance of anti-HBe seroconversion [105] and immunologically induced ALT flares followed by a HBV DNA decrease are associated with more frequent anti-HBe seroconversion [106] (**B2**). Recent data showed that decline of HBsAg levels below 1500 IU/ml at 12 weeks is a strong predictor of anti-HBe seroconversion [107,108] (**C2**), while HBsAg levels >20,000 IU/ml or no decline of HBsAg levels at 12 weeks are associated with a very low probability of subsequent anti-HBe seroconversion [107–109] (**C2**). HBeAg levels at week 24 may also predict anti-HBe seroconversion [105] (**B2**).

In HBeAg-negative CHB, HBV DNA decrease to <20,000 IU/ml at 12 weeks has been reported to be associated with a 50% chance of sustained off-treatment response [110]. A combination of no HBsAg decline and $<2 \log_{10}$ IU/ml decline of HBV DNA seems to be a predictor of non-response in European HBeAg-negative patients with genotype D [111,112] (**B2**). Several recent reports showed that HBsAg decline is predictive of sustained off-treatment virological response and HBsAg loss [113–115]. However,

Table 4. Main respective advantages and disadvantages of (pegylated) interferon alpha [(PEG-)IFN] and nucleos(t)ide analogues (NAs) in the treatment of chronic hepatitis B.

	(PEG-)IFN	NAs
Advantages	<ul style="list-style-type: none"> • Finite duration • Absence of resistance • Higher rates of anti-HBe and anti-HBs seroconversion with 12 mo of therapy 	<ul style="list-style-type: none"> • Potent antiviral effect • Good tolerance • Oral administration
Disadvantages	<ul style="list-style-type: none"> • Moderate antiviral effect • Inferior tolerability • Risk of adverse events • Subcutaneous injections 	<ul style="list-style-type: none"> • Indefinite duration • Risk of resistance • Unknown long-term safety

further studies are needed to clarify how to optimise the use of HBsAg levels in the management of patients in clinical practice.

(2) For NAs treatment

- Pre-treatment factors
In HBeAg-positive CHB, pre-treatment factors predictive of anti-HBe seroconversion are low viral load (HBV DNA below 2×10^8 IU/ml), high serum ALT levels, high activity scores on liver biopsy [69,70,77,116] (A1). HBV genotype does not influence the virological response to any NA [117] (A1).
- During treatment
Virological response (undetectable HBV DNA) at 24 weeks during treatment with lamivudine or telbivudine and at 48 weeks during treatment with adefovir is associated with a lower incidence of resistance, i.e. an improved chance of maintained virological response, in both HBeAg-positive and HBeAg-negative patients and with a higher chance of anti-HBe seroconversion in HBeAg-positive patients [77,100,118,119] (B1).
A decline of HBsAg during NA treatment in HBeAg-positive patients may identify cases with subsequent HBeAg or HBsAg loss [120–122] (C2).

Treatment strategies: how-to-treat

Currently, there are two different treatment strategies for both HBeAg-positive and HBeAg-negative CHB patients: treatment of finite duration with (PEG-)IFN or a NA and long-term treatment with NA(s).

The main theoretical advantages of (PEG-)IFN are the absence of resistance and the potential for immune-mediated control of HBV infection with an opportunity to obtain a sustained virological response off-treatment and a chance of HBsAg loss in patients who achieve and maintain undetectable HBV DNA. Frequent side effects and subcutaneous injection are the main disadvantages of (PEG-)IFN treatment. (PEG-)IFN is contraindicated in patients with decompensated HBV-related cirrhosis or autoimmune disease, in patients with uncontrolled severe depression or psychosis, and in female patients during pregnancy (A1).

Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance [67,70,78,85,92,123] (Fig. 1). Thus, they can be confidently used as first-line monotherapies [1] (A1).

The other three NAs may only be used in the treatment of CHB if more potent drugs with high barrier to resistance are not avail-

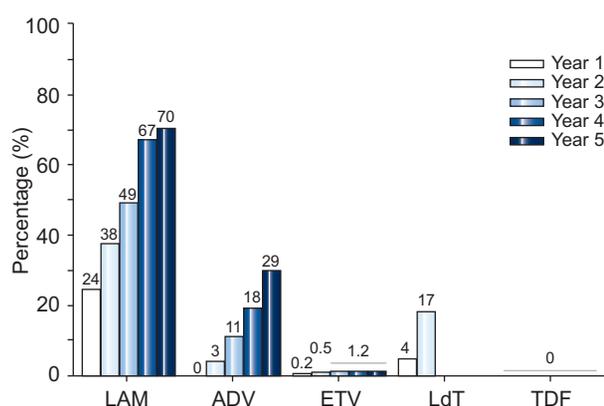


Fig. 1. Cumulative incidence of HBV resistance to lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT) and tenofovir (TDF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. For method of calculation, see Ref. [41]. These trials included different populations, used different inclusion and exclusion criteria and different follow-up end points.

able or appropriate (A1). Lamivudine is an inexpensive agent, but engenders very high rates of resistance with long-term monotherapy [124–127]. Adefovir is less efficacious and more expensive than tenofovir, engendering higher rates of resistance [70,85,100]. Telbivudine is a potent inhibitor of HBV replication, but, due to a lower barrier to resistance, a high incidence of resistance has been observed in patients with high baseline HBV DNA levels and in those with detectable HBV DNA after 6 months of therapy [68,77]; resistance rates to telbivudine are relatively low in patients with low baseline viremia ($<2 \times 10^8$ IU/ml for HBeAg-positive and $<2 \times 10^6$ IU/ml for HBeAg-negative patients) who achieve undetectable HBV DNA at 6 months of therapy [77,128].

(1) Treatment of finite duration with (PEG-)IFN or a NA. This strategy is intended to achieve a sustained off-treatment virological response (A1).

- Finite-duration treatment with (PEG-)IFN. PEG-IFN, if available, has replaced standard IFN in the treatment of CHB mostly due to its easier applicability (once weekly administration). A 48-week course of PEG-IFN is mainly recommended for HBeAg-positive patients with the best chance of anti-HBe seroconversion. It can also be used for HBeAg-negative patients, as it is practically the only option

Clinical Practice Guidelines

Table 5. Cross-resistance data for the most frequent resistant HBV variants. The amino-acid substitution profiles are shown in the left column and the level of susceptibility is given for each drug: S (sensitive), I (intermediate/reduced susceptibility), R (resistant) [139].

HBV variants	Level of susceptibility				
	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild-type	S	S	S	S	S
M204V	R	S	I	I	S
M204I	R	R	I	I	S
L180M + M204V	R	R	I	I	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

that may offer a chance for sustained off-treatment response after a finite duration of therapy. Full information about the advantages, adverse events and inconveniences of (PEG-)IFN versus NAs (Table 4) should be provided so the patient can participate in the decision (**A1**).

The combination of PEG-IFN with lamivudine showed a higher on-treatment virological response but did not show a higher rate of sustained off-treatment virological or serological response [63,64,91]. The combination of PEG-IFN with telbivudine showed a potent antiviral effect, but it is prohibited because of a high risk of severe polyneuropathy [129]. Thus, presently the combinations of PEG-IFN with lamivudine or telbivudine are not recommended (**A1**). There is limited information on the efficacy and safety of combination of PEG-IFN with other NAs and presently this type of combination is not recommended.

- Finite-duration treatment with a NA is achievable for HBeAg-positive patients who seroconvert to anti-HBe on treatment. However, treatment duration is unpredictable prior to therapy as it depends on the timing of anti-HBe seroconversion and the treatment continuation post anti-HBe seroconversion. Anti-HBe seroconversion may not be durable after NAs discontinuation, at least with less potent agents, in a substantial proportion of these patients requiring close virologic monitoring after treatment cessation. An attempt for finite NA treatment should use the most potent agents with the highest barrier to resistance to rapidly reduce levels of viremia to undetectable levels and avoid breakthroughs due to HBV resistance (**A1**). Once anti-HBe seroconversion occurs during NA administration, treatment should be prolonged for an additional 12 months [130]; a durable off-treatment response (persistence of anti-HBe seroconversion) can be expected in 40–80% of these patients [79,80,130–134] (**B1**).

(2) Long-term treatment with NA(s). This strategy is necessary for patients who are not expected or fail to achieve a sustained off-treatment virological response and require extended therapy, i.e. for HBeAg-positive patients who do not develop anti-HBe seroconversion and HBeAg-negative patients. This strategy is also recommended in patients with cirrhosis irrespective of HBeAg status or anti-HBe seroconversion on treatment (**C1**).

The most potent drugs with the optimal resistance profile, i.e. tenofovir or entecavir, should be used as first-line monotherapies (**A1**). It is optimal to achieve and maintain undetectable HBV DNA level tested by real-time PCR, whatever the drug used (**B1**). The long-term effects, safety and tolerability of entecavir and tenofovir are still unknown. Treatment with either tenofovir or entecavir monotherapy for ≥ 3 years achieves maintained virological remission in the vast majority of patients [78,84,85] (**A1**).

There are as yet no data to indicate an advantage of *de novo* combination treatment with NAs in NA naive patients receiving either entecavir or tenofovir [135] (**C1**).

Treatment failure

It is important to distinguish between primary non-response, partial virological response and virological breakthrough [41,136].

(1) *Primary non-response*. Primary non-response is rarely observed with entecavir or tenofovir, telbivudine or lamivudine. In patients with primary non-response to any NA, it is important to check for compliance. In a compliant patient with a primary non-response, genotyping of HBV strains for identification of possible resistance mutations may help in formulating a rescue strategy that must reasonably be based on an early change to a more potent drug that is active against the resistant HBV variant (**B1**).

Primary non-response seems to be more frequent with adefovir (approximately 10–20%) than with other NAs because of suboptimal antiviral efficacy. In NA(s) naive patients with primary non-response to adefovir, a rapid switch to tenofovir or entecavir is recommended (**B1**).

(2) *Partial virological response*. Partial virological response may be encountered with all available NAs. It is always important to check for compliance.

In patients receiving lamivudine or telbivudine (drugs with a low genetic barrier to resistance) with a partial virological response at week 24 or in patients receiving adefovir (moderately potent drug that engenders relatively late emergence of resistance) with a partial response at week 48, change to a more potent drug (entecavir or tenofovir), preferentially without cross-resistance, is recommended (**A1**).

The optimal management of patients with partial virological response under entecavir or tenofovir (highly potent drugs with a high genetic barrier to resistance) is currently debatable. In

such patients with a partial virological response at week 48, the HBV DNA levels at week 48 and their kinetics must be taken into account. Patients with declining serum HBV DNA levels may continue treatment with the same agent (entecavir or tenofovir) given the rise in rates of virological response over time and the very low risk of resistance with long-term monotherapy with both these agents [137] (B1). Some experts would suggest adding the other drug in order to prevent resistance in the long term, particularly in the rare patients without further HBV DNA decline despite drug compliance (C2).

(3) *Virological breakthrough.* Virological breakthrough in compliant patients is related to the development of HBV drug resistance. Testing for genotypic resistance may be performed in compliant patients with confirmed virological breakthroughs, although it is not absolutely necessary for NA naive patients with confirmed virological breakthroughs under monotherapy with lamivudine or telbivudine (B1). Rates of resistance after up to 5 years of administration of the different NAs are shown in Fig. 1. The rates of resistance at 5 years in NA naive patients are <1.5% and 0% for entecavir and tenofovir, respectively [78,123]; thus, virological breakthroughs in NA naive patients receiving entecavir or tenofovir are usually due to poor drug compliance.

The risk of resistance is associated with high baseline HBV DNA levels, a slow decline in HBV DNA and suboptimal previous NA treatment. Resistance should be identified by HBV DNA monitoring as early as possible before biochemical breakthrough (increased ALT), and ideally identification of the pattern of resistance mutations should be used to adapt therapeutic strategies. Indeed, clinical and virological studies have demonstrated the benefit of an early treatment adaptation, as soon as viral load increases [99,138] (B1).

In case of resistance, an appropriate rescue therapy should be initiated with the most effective antiviral agent that does not share cross resistance to minimise the risk of inducing multiple drug-resistant strains (A1). It should be noted that sequential monotherapies with agents with low barriers and hence high or intermediate risk of resistance (lamivudine, adefovir, telbivudine) should be strictly avoided because of the high risk for emergence of multi-drug resistance strains (C1). Table 5 shows cross-resistance data for the most frequent resistant HBV variants [139].

In case of resistance to lamivudine, most experts based on the current evidence suggest that switching to tenofovir is as effective as adding tenofovir to lamivudine [140]. In case of adefovir resistance, a switch to entecavir or tenofovir or tenofovir plus emtricitabine (in a single tablet) is an option [141,142]. The efficacy of tenofovir monotherapy has been reported to be suboptimal in patients with high serum HBV DNA levels due to virological breakthroughs associated with adefovir resistance [140]. In case of telbivudine resistance, a switch to or adding-on tenofovir are the preferred options [136]. There are few data for the treatment of the rare patients with entecavir resistance, and therefore a switch to or adding-on tenofovir may be preferred in such cases [136]. To date, resistance to tenofovir has not been described. It is recommended that genotyping and phenotyping should be done in such cases by an expert laboratory to determine the cross-resistance profile. In case of confirmed tenofovir resistance, an add-on combination with a nucleoside analogue should be preferred, while a switch to entecavir may be sufficient if the patient had no prior lamivudine resistance. In patients with multidrug resistance, genotypic resistance testing is very useful and a combination of a nucleoside and a nucleotide (preferably tenofovir) should be used.

- *Lamivudine resistance:* switch to tenofovir (add adefovir if tenofovir is not available) (B1).
- *Adefovir resistance:* if the patient was NA naive before adefovir, switch to entecavir or tenofovir (B1); entecavir may be preferred in such patients with high viraemia (C2). If the patient had prior lamivudine resistance, switch to tenofovir and add a nucleoside analogue (C1).
- *Telbivudine resistance:* switch to or add tenofovir (add adefovir if tenofovir is not available) (C1).
- *Entecavir resistance:* switch to or add tenofovir (add adefovir if tenofovir is not available) (C1).
- *Tenofovir resistance:* tenofovir resistance has not been detected to date and therefore there is no experience, but it seems reasonable to add entecavir, telbivudine, lamivudine or emtricitabine if tenofovir resistance is confirmed (C2). A switch to entecavir may be sufficient if the patient has not been treated with lamivudine in the past, while adding entecavir may be the preferred option for patients with prior lamivudine resistance (C2).

How to monitor treatment and stopping points

Finite therapy with PEG-IFN

In patients treated with PEG-IFN, full blood counts and serum ALT levels should be monitored monthly and TSH should be monitored every 3 months. All patients should be monitored for safety through 12 months of treatment.

- In HBeAg-positive patients, HBeAg and anti-HBe antibodies and serum HBV DNA levels should be checked at 6 and 12 months of treatment and at 6 and 12 months post-treatment. Sustained off-treatment anti-HBe seroconversion together with ALT normalisation and serum HBV DNA below 2000 IU/ml is the desired outcome (A1). Undetectable serum HBV DNA by real-time PCR during follow-up is the optimal outcome, since it is associated with a significant chance of HBsAg loss (B1). HBeAg-positive patients who develop anti-HBe seroconversion with PEG-IFN require long-term follow-up because of the possibility of HBeAg seroreversion or progression to HBeAg-negative CHB [81,82] (A1). HBsAg should be checked at 12-month intervals after anti-HBe seroconversion if HBV DNA is undetectable, as the rate of HBsAg loss increases over time [87]. Patients who become HBsAg negative should be tested for anti-HBs. Patients treated with PEG-IFN who achieve quick reductions of HBV DNA and/or HBsAg levels through 3 or 6 months of therapy have an increased probability of response. In contrast, HBeAg-positive patients treated with PEG-IFN who fail to achieve serum HBsAg levels below 20,000 IU/ml or any decline in serum HBsAg levels by month 3 have a low probability of achieving anti-HBe seroconversion [107–109]; therefore, stopping PEG-IFN therapy may be considered (C2).
- In HBeAg-negative patients, serum HBV DNA levels should be measured at 6 and 12 months of treatment and at 6 and 12 months post-treatment. A sustained off-treatment virological response with HBV DNA <2000 IU/ml is generally associated with remission of the liver disease. Undetectable HBV DNA by real-time PCR is the ideal desired sustained off-treatment response with a higher probability

Clinical Practice Guidelines

of HBsAg loss in the longer term. HBsAg should be checked at 12-month intervals if HBV DNA remains undetectable (**B1**). Patients who become HBsAg negative should be tested for anti-HBs. HBeAg-negative patients who achieve sustained off-treatment response at 12 months after a PEG-IFN course require long-term follow-up, because there is still a risk of future disease reactivation that seems to diminish over time [143] (**A1**). HBeAg-negative patients, in particular those with genotype D, treated with PEG-IFN who fail to achieve any decline in serum HBsAg levels and a $\geq 2 \log_{10}$ IU/ml decline in serum HBV DNA levels by month 3, have a very low probability of response; therefore, stopping PEG-IFN therapy should be considered [111,112] (**B2**).

Finite treatment with NAs in HBeAg-positive patients

The objective of finite treatment with a NA is sustained off-treatment anti-HBe seroconversion with HBV DNA <2000 IU/ml and normal ALT, or even HBsAg clearance (**A1**). HBeAg and anti-HBe should be checked every 6 months. HBV DNA should be measured by a sensitive PCR assay every 3–6 months during treatment. HBV DNA suppression to undetectable levels in real-time PCR and subsequent anti-HBe seroconversion is associated with biochemical and histological responses. Studies have suggested that NA therapy can be stopped 12 months after anti-HBe seroconversion (**B1**). A proportion of patients who discontinue NA therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response [79,80,131–134]. Therefore, NA treatment may be continued until HBsAg clearance with or without antibodies to HBsAg, particularly in patients with severe fibrosis or cirrhosis (**C1**). HBsAg should be checked at 12-month intervals after anti-HBe seroconversion. HBsAg loss, however, is not observed sufficiently frequently during or after NA therapy (Table 2).

Long-term therapy with NAs

HBV DNA reduction to undetectable levels by real-time PCR (i.e. below 10–15 IU/ml) should ideally be achieved to avoid resistance. HBV DNA monitoring is thus critical to detect treatment failure (**A1**). HBV DNA levels should be monitored at month 3 to ascertain virological response and then every 3–6 months. During therapy with entecavir or tenofovir, agents with high barrier to resistance, the frequency of follow-up measurement of HBV DNA might be decreased once patient compliance and treatment efficacy are confirmed (**C1**).

NAs are cleared by the kidneys, and appropriate dosing adjustments are recommended for patients with creatinine clearance <50 ml/min (**A1**). Therefore, all patients starting NA therapy should be tested for serum creatinine levels and estimated creatinine clearance before treatment (**A1**). In addition, the baseline renal risk should be assessed for all patients. High renal risk includes one or more of the following factors: decompensated cirrhosis, creatinine clearance <60 ml/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation. Minimal rates of renal function decline have been reported with all NAs, except perhaps for telbivudine which seems to improve the creatinine clearance [144] (**C1**). The nephrotoxic potential seems to be higher for nucleotide ana-

logues, particularly adefovir [145] (**B1**). Therefore, it seems appropriate for now to monitor for adverse renal effects with serum creatinine (estimated creatinine clearance) and serum phosphate levels during adefovir or tenofovir therapy in all CHB patients and with serum creatinine levels (estimated creatinine clearance) during nucleoside analogue therapy in CHB patients at high renal risk (**C1**). The frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, in case of no worsening, in patients at low renal risk as well as every month for the first 3 months, every 3 months until the end of the first year and every 6 months thereafter, in case of no worsening, in patients at high renal risk (**C2**). Closer renal monitoring is required in patients who develop creatinine clearance <60 ml/min or serum phosphate levels <2 mg/dl (**C1**).

Drug concentrations are comparable in patients with varying degrees of hepatic impairment, but this has not been fully studied. Decreases in bone mineral density have rarely been reported in HIV-positive patients treated with tenofovir. Studies to evaluate bone densitometry in CHB patients under tenofovir are ongoing. Long-term monitoring for carcinogenesis in CHB patients under entecavir is ongoing. Myopathy has rarely been reported in CHB patients treated with telbivudine. The long-term safety of several NAs combination including tenofovir and entecavir is currently unknown.

Treatment of patients with severe liver disease

Treatment of patients with cirrhosis

PEG-IFN may increase the risk of bacteraemic infection and hepatic decompensation in patients with advanced cirrhosis [146]. However, PEG-IFN in regimens similar to those used in CHB can be used for the treatment of well compensated cirrhosis [147] (**A1**). Among NAs, monotherapies with tenofovir or entecavir are preferred because of their potency and minimal risk of resistance [148,149] (**A1**). Lamivudine should not be used in such patients. Close monitoring of HBV DNA levels every 3 months at least during the first year of therapy and until HBV DNA undetectability is important, as exacerbations of hepatitis B may occur in patients with cirrhosis requiring urgent management. Thus, patients with cirrhosis require long-term therapy, with careful monitoring for resistance and flares.

Clinical studies indicate that prolonged and adequate suppression of HBV DNA can stabilize patients and prevent the progression to decompensated liver disease [54,99] (**A1**). Regression of fibrosis and even reversal of cirrhosis have been reported in patients with prolonged suppression of viral replication [150]. Nonetheless, long-term monitoring for HCC is mandatory despite virological remission under NA(s), since there is still a risk of developing HCC [151,152] (**B1**).

NA therapy should usually be continued indefinitely in cirrhotic patients. After at least 12 months of consolidation therapy, treatment might be stopped in HBeAg-positive patients if they achieve confirmed anti-HBe seroconversion or ideally HBsAg loss and anti-HBs seroconversion and in HBeAg-negative patients if they achieve confirmed HBsAg loss and anti-HBs seroconversion (**B1**).

Treatment of patients with decompensated cirrhosis

Patients with decompensated cirrhosis should be treated in specialised liver units, as the application of antiviral therapy is complex, and these patients may be candidates for liver transplantation. Antiviral treatment is indicated irrespective of HBV DNA level in order to prevent reactivation.

(PEG-)IFN is contraindicated in this setting. Entecavir or tenofovir should be used (A1). The licensed entecavir dose for patients with decompensated cirrhosis is 1 mg (instead of 0.5 mg for patients with compensated liver disease) once daily. Recent studies have shown that both drugs are not only effective but generally safe in these patients, at least in the first years of therapy [60–62]. Lactic acidosis has been reported to develop in some NA, particularly entecavir, treated patients with advanced decompensated cirrhosis (MELD score >20) [153]. Therefore, clinical and laboratory parameters should be closely monitored in this setting (A1). The dose of all NAs needs to be adjusted in patients with low creatinine clearance (<50 ml/min) (A1).

Patients with decompensated cirrhosis may show slow clinical improvement over a period of 3–6 months under NA(s) and then transplantation may be avoided. In such cases, life-long treatment is recommended. The HCC risk is high in these patients even under effective NA therapy and therefore long-term HCC surveillance is mandatory [152] (A1). Some patients with advanced hepatic disease with a high Child–Pugh or MELD score may have progressed beyond the point of no return, and may not benefit, thus requiring liver transplantation [154]. In that situation, treatment with NA(s) inducing HBV DNA undetectability at transplantation will decrease the risk of HBV recurrence in the graft [155].

Prevention of recurrent hepatitis B after liver transplantation

Recurrent HBV infection in the transplanted liver has previously been a major problem. Pre-transplant therapy with a potent NA with a high barrier to resistance is recommended for all HBsAg-positive patients undergoing liver transplantation for HBV-related end-stage liver disease or HCC, to achieve the lowest possible level of HBV DNA before transplantation [155–158] (A1). Lamivudine and/or adefovir in combination with hepatitis B immunoglobulin (HBIG) have reduced the risk of graft infection to less than 10% [155,157,158]. Shorter courses and lower doses of HBIG and other forms of prophylaxis, including tenofovir with emtricitabine or entecavir monotherapy, are being studied. Recently, entecavir prophylaxis without HBIG was shown to be safe and effective in preventing HBV recurrence [159]. Preliminary safety and efficacy data with tenofovir and emtricitabine with or without HBIG have also been reported [160]. In the setting of liver transplantation, nephrotoxicity should be always considered and renal function should be carefully monitored because of the concomitant use of calcineurin inhibitors (C1).

Treatment in special patient groups

HIV co-infected patients

HIV-positive patients with CHB were at increased risk of cirrhosis before HAART and a higher risk of HCC is suggested [161–167]. Treatment of HIV may lead to flares of hepatitis B due to immune reconstitution, but the risk of developing cirrhosis is negligible in HBV/HIV co-infected patients on long-term tenofovir combined with emtricitabine or lamivudine therapy [168]. The indications for therapy are the same as in HIV-negative patients, based on HBV DNA levels, serum ALT levels and histological lesions [169]. In agreement with recent HIV guidelines, it is recommended that most co-infected patients should be simultaneously treated for both HIV and HBV *de novo* [170]. Tenofovir combined with emtricitabine or lamivudine plus a third agent active against HIV are

indicated [170,171] (A1). The strong rationale for early dual anti-HIV and anti-HBV therapy have simplified the recommendations for widening the use of tenofovir and emtricitabine or lamivudine in HBV–HIV co-infected patients, irrespective of immunological, virological or histological considerations [172] (B1).

In a small number of patients with CD₄ count >500/ml, HBV can be treated before the institution of anti-HIV therapy; PEG-IFN, adefovir and telbivudine, which are not proven to be active against HIV, should be preferred [170]. However, if any of these two NAs with a low barrier to resistance does not reach the goal of undetectable HBV DNA after 12 months of therapy, treatment of HIV infection should be envisaged. Lamivudine, entecavir and tenofovir have activity against both HIV and HBV and are contraindicated as single agents for hepatitis B in co-infected patients because of the risk of HIV resistance (A1). Thus, all HBsAg-positive patients should be screened for HIV before these drugs are used in the treatment of HBV infection (A1).

HDV co-infected patients

Severe or fulminant hepatitis is more frequently observed in HBV–HDV co-infection compared to HBV mono-infection [173]. Chronic infection after acute HBV–HDV hepatitis is less common, while chronic delta hepatitis develops in 70–90% of patients with HDV superinfection [173,174]. Active co-infection with HDV is confirmed by detectable HDV RNA, immuno-histochemical staining for HDV antigen, or IgM anti-HDV [174]. However, diagnosis of active HDV infection may be difficult, as HDV RNA assays are not standardised and HDV antigen and IgM anti-HDV assays are not widely available [174,175]. Persistent HDV replication leads to cirrhosis and HCC at annual rates of 4% and 2.8% and is the most important predictor of mortality evidencing the need of antiviral therapy [173,176,177].

(PEG-)IFN is the only drug effective against HDV [178–183] (A1). The efficacy of (PEG-)IFN therapy can be assessed during treatment (after 3–6 months) by measuring HDV RNA levels (C2). More than 1 year of therapy may be necessary, as there may be some benefit from treatment prolongation [183,184] (C2). However, the optimal duration of therapy is not well defined [173,174]. Around 25–40% of treated patients have a sustained off-treatment virological response with undetectable HDV RNA and accompanying improvement in histology, while some also lose HBsAg [173,174,182]. However, it has not been defined how long patients need to be HDV RNA negative after the end of therapy before sustained virological response is achieved. NAs do not impact HDV replication and related disease [173,174]. However, NA treatment might be considered in some patients who have active HBV replication with persistent or fluctuating serum HBV DNA levels above 2000 IU/ml [174,185,186].

HCV co-infected patients

In HBV-infected patients, HCV co-infection accelerates liver disease progression and increases the risk of HCC [187–189]. HBV and HCV replicate in the same hepatocyte without interference [190]. A proportion of these patients may have fluctuating serum HBV DNA levels, thus indicating the need for longitudinal evaluation of viral loads before starting any antiviral therapy in order to clarify the respective pathogenic role of each virus [185]. Nevertheless, HBV DNA level is often low or undetectable and HCV is responsible for the activity of chronic hepatitis in most patients, although this is variable probably due to indirect mechanisms mediated by innate and/or adaptive host immune responses

Clinical Practice Guidelines

[190]. Thus, patients should usually receive treatment for HCV [191] (**B1**). Sustained virological response rates for HCV are broadly comparable with HCV mono-infected patients [187,192–194]. There is a potential risk of HBV reactivation during treatment or after clearance of HCV [191]. Therefore, HBV DNA monitoring is necessary. Any HBV reactivation must then be treated with NA(s) (**B1**).

Acute hepatitis

More than 95–99% of adults with acute HBV infection will recover spontaneously and seroconvert to anti-HBs without antiviral therapy [195] (**A1**). Patients with fulminant or severe hepatitis must be evaluated for liver transplantation (**A1**). These patients may benefit from NA treatment. Support for such a strategy may be found in a small number of reports mainly with lamivudine [196]. As for CHB, entecavir or tenofovir should be used (**C1**). The duration of treatment is not established. However, continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is recommended (**C2**).

Sometimes, the distinction between true severe acute hepatitis B and reactivation of CHB may be difficult and may require liver biopsy. However, NA treatment is the treatment of choice in both cases [196–198] (**B1**).

Children

Chronic hepatitis B runs an asymptomatic course in most children, in whom treatment indications should be very carefully evaluated [199]. In general, a conservative approach is warranted (**A1**). Only conventional IFN, lamivudine and adefovir have been evaluated for safety and efficacy, which were comparable to adults [199–202]. There are ongoing studies with other NAs in children to better define treatment strategies for children.

Healthcare workers

Healthcare workers need special attention, as they may require antiviral therapy even if they do not fulfil the typical indications for treatment to reduce direct transmission during exposure prone procedures to patients. Policies for HBsAg-positive healthcare workers vary among countries. In many countries, healthcare workers, including surgeons, gynaecologists and dentists, who are HBsAg-positive with HBV DNA ≥ 2000 IU/ml should be treated with a potent antiviral agent with a high barrier to resistance (i.e. entecavir or tenofovir), to reduce levels of HBV DNA ideally to undetectable or at least to <2000 IU/ml before resuming exposure-prone procedures (**B1**). Monitoring for compliance and efficacy in practicing surgeons is required. The long-term safety, efficacy, complications and economic implications of such a policy are unknown [203].

Pregnancy

Family planning should be always discussed with women of childbearing age before initiating HBV therapy. The woman should be informed about the safety data of the drugs on a possible pregnancy (**A1**).

(PEG-)IFN is contraindicated during pregnancy (**A1**). Lamivudine, adefovir and entecavir are listed by the FDA as pregnancy category C drugs, and telbivudine and tenofovir as category B drugs [204]. These classifications are based on the risk of teratogenicity in preclinical evaluation. The safety of entecavir in preg-

nancy is not known. There is a considerable body of safety data from the Antiretroviral Pregnancy Registry in pregnant HIV-positive women who have received tenofovir and/or lamivudine or emtricitabine [205,206]. Among them, tenofovir should be preferred, because it has better resistance profile and more extensive safety data in pregnant, HBV positive women [205,206] (**B1**).

In a woman of childbearing age without advanced fibrosis who plans a pregnancy in the near future, it may be prudent to delay therapy until the child is born (**C1**). In a woman of childbearing age with advanced fibrosis or cirrhosis who agrees for a “planned pregnancy” in the future, (PEG-)IFN therapy may be tried as it is given for a finite duration (**C1**). It should be noted that effective contraception is required during (PEG-)IFN therapy. If (PEG-)IFN is not possible or has failed, treatment with a NA has to be initiated and maintained even during a future pregnancy (**C1**). Tenofovir represents the most reasonable choice for such female patients (**B1**).

If female patients become unexpectedly pregnant during anti-HBV therapy, treatment indications should be reevaluated (**C1**). The same treatment indications apply to women who are first diagnosed to have CHB during pregnancy (**C1**). Patients with advanced fibrosis or cirrhosis should definitely continue to be treated, but the treating agent should be reconsidered (**C1**). (PEG-)IFN must be stopped and the patients should continue on a NA, while FDA category C NAs, particularly adefovir and entecavir, should be changed to a FDA category B NA (**C1**). Among FDA category B NAs, tenofovir is preferred because of its high potency, high genetic barrier and available safety data in pregnancy (**C1**).

The prevention of HBV perinatal transmission, which is considered to occur mainly at delivery, is traditionally based on the combination of passive and active immunisation with hepatitis B immunoglobulin (HBIG) and HBV vaccination. Such a strategy, however, may not be effective in a proportion of newborns from highly viremic (serum HBV DNA $>10^{6-7}$ IU/ml), mostly HBeAg-positive, mothers, who carry a $>10\%$ risk of vertical HBV transmission despite HBIG and vaccination [207–210]. Mothers with these high concentrations of HBV DNA should be informed that utilising a NA to reduce their viral loads could add to the effectiveness of HBIG and vaccination (**B1**). Lamivudine and recently telbivudine therapy during the last trimester of pregnancy in pregnant HBsAg-positive women with high levels of viremia have been shown to be safe and to reduce the risk of intra-uterine and perinatal transmission of HBV if given in addition to passive and active vaccination by HBIG and HBV vaccination [208,209,211–213] (**B1**). Thus, telbivudine, lamivudine or tenofovir (as a potent FDA category B agent) may be used for the prevention of perinatal and intra-uterine HBV transmission in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA $>10^{6-7}$ IU/ml) (**B1**). No controlled clinical trial of tenofovir to prevent perinatal transmission has been conducted. If NA therapy is given only for the prevention of perinatal transmission, it may be discontinued within the first 3 months after delivery (**C1**).

If a pregnant woman remains untreated or anti-HBV therapy is discontinued during pregnancy or early after delivery for any reason, close monitoring of the patient is necessary, as there is a risk of hepatic flares, especially after delivery [214,215] (**B1**).

The safety of NA therapy during lactation is uncertain. HBsAg can be detected in breast milk, but breast feeding may not be considered a contraindication in HBsAg-positive mothers. Tenofovir concentrations in breast milk have been reported, but

its oral bioavailability is limited and thus infants are exposed to only small concentrations [216].

Pre-emptive therapy before immunosuppressive therapy or chemotherapy

In HBsAg-positive patients receiving chemotherapy or immunosuppressive therapy including the established and emerging range of biological response modifiers, the risk of reactivation is high, particularly if rituximab is given alone or in combination with steroids [217–220]. Therefore, all candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc prior to initiation of treatment (A1).

Vaccination of HBV seronegative patients is highly recommended (A1). Higher vaccine doses may be required to achieve anti-HBs response in immunocompromised patients.

HBsAg-positive candidates for chemotherapy and immunosuppressive therapy should be tested for HBV DNA levels and should receive pre-emptive NA administration during therapy (regardless of HBV DNA levels) and for 12 months after cessation of therapy (A1). There are limited data on the optimal options. Most experience with pre-emptive treatment has been with lamivudine, which may suffice for patients with low (<2000 IU/ml) HBV DNA levels when a finite and short duration of immunosuppression is scheduled [221,222]. In this setting, prophylactic lamivudine reduces the risk of HBV reactivation and the associated morbidity and mortality (B1). It is, however, recommended that patients, who have a high HBV DNA level and/or may receive a lengthy and repeated cycles of immunosuppression, should be protected with a NA with high antiviral potency and a high barrier to resistance, i.e. entecavir or tenofovir (C1).

HBsAg-negative patients with positive anti-HBc antibodies should be tested for HBV DNA. HBsAg-negative, anti-HBc positive patients with detectable serum HBV DNA should be treated similarly to HBsAg positive patients (C1).

HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA and regardless of anti-HBs status who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV DNA testing and treated with NA therapy upon confirmation of HBV reactivation before ALT elevation (C1). The frequency of monitoring can range from 1–3 months depending on the type of immunosuppressive therapy and comorbidities. Some experts recommend prophylaxis with lamivudine in all HBsAg-negative, anti-HBc positive patients who receive rituximab and/or combined regimens for hematological malignancies, if they are anti-HBs negative and/or if close monitoring of HBV DNA is not guaranteed [220,223–225] (C2). NA prophylaxis is also recommended for anti-HBc positive patients receiving bone marrow or stem cell transplantation [225,226] (C2). The optimal duration of prophylaxis for these indications is not known.

HBsAg-negative recipients of liver grafts from anti-HBc positive donors should receive prophylaxis with lamivudine, which should continue indefinitely [227] (B1).

Dialysis and renal transplant patients

HBV is prevalent in patients with end-stage renal disease including renal transplant patients. Patients with renal disease should be screened for HBV infection. Though vaccine responsiveness is impaired, HBV seronegative patients should be vaccinated. (PEG-)IFN or NAs can be used for CHB patients with renal dysfunction.

All drugs and particularly NAs should be dose-adjusted (A1) and used with caution in patients with renal impairment (B1). According to the approved drug SPCs, there is no recommended tenofovir dose for non-hemodialysed patients with creatinine clearance <10 ml/min. Renal function should be monitored during antiviral treatment. Unexpected deterioration of renal function during antiviral treatment may necessitate a change of treatment or further dose adaptation. Hypertension and coexisting diabetes mellitus should be optimally controlled.

(PEG-)IFN should be avoided in renal transplant patients because of the risk of rejection. Every HBsAg positive patient who undergoes renal transplantation and receives immunosuppressive agents should receive anti-HBV prophylaxis with a NA. The need for antiviral prophylaxis or treatment should be constantly and frequently evaluated for all HBV positive renal transplant patients.

Extrahepatic manifestations

There is decreasing incidence of HBV related extrahepatic manifestations, such as skin manifestations, polyarteritis nodosa and glomerulonephritis. HBsAg positive patients with extra-hepatic manifestations and active HBV replication may respond to antiviral therapy. (PEG-)IFN may worsen some immune mediated extra-hepatic manifestations. Controlled studies of antiviral therapy are limited, but case reports suggest that it may be of benefit. Lamivudine has been most widely used to date. Entecavir and tenofovir are expected to have enhanced efficacy in this group. Plasmapheresis and corticosteroids during the initial phase can be useful in addition to NA therapy in special cases (C2).

Unresolved issues and unmet needs

- (1) Improve knowledge and prognosis of the natural history and indications for treatment, particularly in HBeAg-positive immunotolerant patients and HBeAg-negative patients with serum HBV DNA levels below 20,000 IU/ml.
- (2) Assess the role of non-invasive markers (serum and biochemical) for the evaluation of the severity of liver disease and for the follow-up of treated and untreated patients.
- (3) Further clarify the role of serum HBsAg levels in the evaluation of the natural history, prediction of therapeutic responses and treatment individualisation.
- (4) Assess host genetic and viral markers to determine prognosis and optimise patients' management.
- (5) Assess the impact of early diagnosis and early treatment intervention.
- (6) Assess long-term safety and resistance to the current first-line NAs (entecavir and tenofovir).
- (7) Identify markers that predict successful NA discontinuation.
- (8) Assess the safety and efficacy of the combination of PEG-IFN with a potent NA (entecavir or tenofovir) to increase anti-HBe and anti-HBs seroconversion rates.
- (9) Develop and assess new drugs and therapeutic approaches, particularly immunomodulatory therapies, to enhance loss of HBeAg and HBsAg and subsequent seroconversion.
- (10) Assess long-term impact of therapy on the prevention of cirrhosis and its complications and HCC.
- (11) Develop strategies and identify subgroups for effective HBIG free prophylaxis after liver transplantation for HBV related liver disease.

Clinical Practice Guidelines

- (12) Develop effective and optimum treatment for HDV co-infection.

Conflict of interest

Maria Buti has received research support from Merck/Schering-Plough, Bristol-Myers Squibb, Gilead Sciences and Novartis and has acted as an advisor and lecturer for Bristol-Myers Squibb, Merck/Schering-Plough, Novartis, Gilead Sciences, Glaxo and Roche.

Markus Cornberg has received research support from Merck/Schering-Plough, Roche and has acted as advisor and/or lecturer for GlaxoSmithKline, Gilead, Novartis, Bristol-Myers Squibb, Roche, and Merck/Schering-Plough.

Harry Janssen has received research support from and has acted as advisor and/or lecturer Bristol-Myers Squibb, Gilead, Inogenetics, Merck, Novartis, Roche.

David Mutimer has received lecture fees and consultancy fees from Gilead and Bristol-Myers Squibb.

George Papatheodoridis has received research support from Bristol-Myers Squibb, Gilead and Roche and has acted as an advisor and/or lecturer for Bristol-Myers Squibb, Gilead, Merck/Schering-Plough, Novartis and Roche.

Stanislas Pol has received research support from Bristol-Myers Squibb, Gilead Sciences, Merck/Schering-Plough and Roche, and has acted as an advisor and lecturer for Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead Sciences, Merck/Schering-Plough, Novartis, Roche.

Giovanni Raimondo has received research support from Schering-Plough and GlaxoSmithKline and has acted as an advisor and/or lecturer for Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Novartis and Roche.

References

- [1] European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 2009;50:227–242.
- [2] Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis* 2003;23:47–58.
- [3] McMahon BJ. The natural history of chronic hepatitis B virus infection. *Semin Liver Dis* 2004;24:17–21.
- [4] Hadziyannis SJ, Papatheodoridis GV. Hepatitis Be antigen negative chronic hepatitis B – natural history and treatment. *Semin Liver Dis* 2006;26:130–141.
- [5] Ganem D, Prince AM. Hepatitis B virus infection – natural history and clinical consequences. *N Engl J Med* 2004;350:1118–1129.
- [6] Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007;45:1056–1075.
- [7] Liaw YF. Prevention and surveillance of hepatitis B virus-related hepatocellular carcinoma. *Semin Liver Dis* 2005;25:40–47.
- [8] Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:507–539.
- [9] Zarski JP, Marcellin P, Leroy V, Trepo C, Samuel D, Ganne-Carrie N, et al. Characteristics of patients with chronic hepatitis B in France: predominant frequency of HBe antigen negative cases. *J Hepatol* 2006;45:343–346.
- [10] Funk ML, Rosenberg DM, Lok ASF. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. *J Viral Hepat* 2002;9:52–61.
- [11] Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008;48:335–352.
- [12] Fattovich G, Olivari N, Pasino M, D'Onofrio M, Martone E, Donato F. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. *Gut* 2008;57:84–90.

- [13] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127:S35–S50.
- [14] Papatheodoridis GV, Manolakopoulos S, Liaw Y-F, Lok A. Follow-up and indications for liver biopsy in HBeAg-negative chronic hepatitis B virus infection with persistently normal ALT: a systematic review. *J Hepatol* 2012, in press.
- [15] Martinot-Peignoux M, Boyer N, Colombat M, Akreimi R, Pham B-N, Ollivier S, et al. Serum hepatitis B virus DNA levels and liver histology in inactive HBsAg carriers. *J Hepatol* 2002;36:543–548.
- [16] Manesis E, Papatheodoridis GV, Sevastianos V, Cholongitas E, Papaioannou C, Hadziyannis SJ. Significance of hepatitis B viremia levels determined by a quantitative polymerase chain reaction assay in patients with HBeAg-negative chronic hepatitis B virus infection. *Am J Gastroenterol* 2003;98:2261–2267.
- [17] Papatheodoridis GV, Manesis EK, Manolakopoulos S, Elefsiniotis IS, Goulis J, Giannousis J, et al. Is there a meaningful serum HBV DNA cut-off level for therapeutic decisions in HBeAg-negative chronic hepatitis B virus infection? *Hepatology* 2008;48:1451–1459.
- [18] de Franchis R, Meucci G, Vecchi M, Tatarella M, Colombo M, Del Ninno E, et al. The natural history of asymptomatic hepatitis B surface antigen carriers. *Ann Intern Med* 1993;118:191–194.
- [19] Tai DI, Lin SM, Sheen IS, Chu CM, Lin DY, Liaw YF. Long-term outcome of hepatitis B e antigen-negative hepatitis B surface antigen carriers in relation to changes of alanine aminotransferase levels over time. *Hepatology* 2009;49:1859–1867.
- [20] Chen Y-C, Huang S-F, Chu C-M, Liaw Y-F. Serial HBV DNA levels in patients with persistently normal transaminase over 10 years following spontaneous HBeAg seroconversion. *J Viral Hepat* 2012;19:138–146.
- [21] Papatheodoridis GV, Chrysanthos N, Hadziyannis E, Cholongitas E, Manesis EK. Longitudinal changes in serum HBV DNA levels and predictors of progression during the natural course of HBeAg-negative chronic hepatitis B virus infection. *J Viral Hepat* 2008;15:434–441.
- [22] Brunetto MR, Oliveri F, Colombatto P, Moriconi F, Ciccorossi P, Coco B, et al. Hepatitis B surface antigen serum levels help to distinguish active from inactive hepatitis B virus genotype D carriers. *Gastroenterology* 2010;139:483–490.
- [23] Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2001;34:617–624.
- [24] Brunetto MR, Giarin M, Oliveri F, Saracco G, Barbera C, Parella T, et al. 'e' Antigen defective hepatitis B virus and course of chronic infection. *J Hepatol* 1991;13:S82–S86.
- [25] Brunetto MR, Oliveri F, Coco B, Leandro G, Colombatto P, Gorin JM, et al. 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.
- [26] Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol* 2008;49:652–657.
- [27] Knoll A, Pietrzyk M, Loss M, Goetz WA, Jilg W. Solid-organ transplantation in HBsAg-negative patients with antibodies to HBV core antigen: low risk of HBV reactivation. *Transplantation* 2005;79:1631–1633.
- [28] Marcellin P, Giostra E, Martinotpeignoux M, Lioriot MA, Jaegle ML, Wolf P, et al. Redevelopment of hepatitis-B surface-antigen after renal-transplantation. *Gastroenterology* 1991;100:1432–1434.
- [29] Huo TI, Wu JC, Lee PC, Chau GY, Lui WY, Tsay SH, et al. Sero-clearance of hepatitis B surface antigen in chronic carriers does not necessarily imply a good prognosis. *Hepatology* 1998;28:231–236.
- [30] Chen YC, Sheen IS, Chu CM, Liaw YF. Prognosis following spontaneous HBsAg seroclearance in chronic hepatitis B patients with or without concurrent infection. *Gastroenterology* 2002;123:1084–1089.
- [31] Simonetti J, Bulkow L, McMahon BJ, Homan C, Snowball M, Negus S, et al. Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. *Hepatology* 2010;51:1531–1537.
- [32] Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. *BMJ* 2008;336:1049–1051.
- [33] Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;336:995–998.
- [34] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–926.
- [35] Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, et al. Incorporating considerations of resources use into grading recommendations. *BMJ* 2008;336:1170–1173.

- [36] Jaeschke R, Guyatt GH, Dellinger P, Schunemann H, Levy MM, Kunz R, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ* 2008;337:a744. <http://dx.doi.org/10.1136/bmj.a744>.
- [37] Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336:1106–1110.
- [38] Stelzl E, Muller Z, Marth E, Kessler HH. Rapid quantification of hepatitis B virus DNA by automated sample preparation and real-time PCR. *J Clin Microbiol* 2004;42:2445–2449.
- [39] Thibault V, Pichoud C, Mullen C, Rhoads J, Smith JB, Bitbol A, et al. Characterization of a new sensitive PCR assay for quantification of viral DNA isolated from patients with hepatitis B virus infections. *J Clin Microbiol* 2007;45:3948–3953.
- [40] Chevaliez S, Bouvier-Alias M, Laperche S, Pawlowsky JM. Performance of the Cobas AmpliPrep/Cobas TaqMan real-time PCR assay for hepatitis B virus DNA quantification. *J Clin Microbiol* 2008;46:1716–1723.
- [41] Pawlowsky JM, Dusheiko G, Hatzakis A, Lau D, Lau G, Liang TJ, et al. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach. *Gastroenterology* 2008;134:405–415.
- [42] Saldanha J, Gerlich W, Lelie N, Dawson P, Heermann K, Heath A. An international collaborative study to establish a World Health Organization international standard for hepatitis B virus DNA nucleic acid amplification techniques. *Vox Sanguinis* 2001;80:63–71.
- [43] Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. *Hepatology* 2003;38:1449–1457.
- [44] Myers RP, Tainturier MH, Ratziu V, Piton A, Thibault V, Imbert-Bismut F, et al. Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. *J Hepatol* 2003;39:222–230.
- [45] Poynard T, Morra R, Halfon P, Castera L, Ratziu V, Imbert-Bismut F, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. *BMC Gastroenterol* 2007;7:40.
- [46] Marcellin P, Ziol M, Bedossa P, Douvin C, Poupon R, De LV, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int* 2009;29:242–247.
- [47] Castera L. Transient elastography and other non-invasive tests to assess hepatic fibrosis in patients with viral hepatitis. *J Viral Hepat* 2009;16:300–314.
- [48] Castera L, Bernard PH, Le BB, Foucher J, Trimoulet P, Merrouche W, et al. Transient elastography and biomarkers for liver fibrosis assessment and follow-up of inactive hepatitis B carriers. *Aliment Pharmacol Ther* 2011;33:455–465.
- [49] Fraquelli M, Branchi F. The role of transient elastography in patients with hepatitis B viral disease. *Dig Liver Dis* 2011;43:S25–S31.
- [50] Cardoso AC, Carvalho-Filho RJ, Marcellin P. Transient elastography in chronic viral hepatitis: a critical appraisal. *Gut* 2011;60:759–764.
- [51] Cardoso AC, Carvalho-Filho RJ, Stern C, Dipumpo A, Giuilly N, Ripault MP, et al. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. *Liver Int* 2012;32:612–621.
- [52] Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology* 2008;47:380–384.
- [53] Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011;54:650–659.
- [54] Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521–1531.
- [55] Brechot C, Hadchouel M, Scotto J, Fonck M, Potet F, Vyas GN, et al. State of hepatitis B virus DNA in hepatocytes of patients with hepatitis B surface antigen-positive and -negative liver diseases. *Proc Natl Acad Sci USA* 1981;78:3906–3910.
- [56] Brechot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Brechot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely “occult”? *Hepatology* 2001;34:194–203.
- [57] Brechot C. Pathogenesis of hepatitis B virus-related hepatocellular carcinoma: old and new paradigms. *Gastroenterology* 2004;127:S56–S61.
- [58] Bonilla GR, Roberts LR. The role of hepatitis B virus integrations in the pathogenesis of human hepatocellular carcinoma. *J Hepatol* 2005;42:760–777.
- [59] Pollicino T, Saitta C, Raimondo G. Hepatocellular carcinoma: the point of view of the hepatitis B virus. *Carcinogenesis* 2011;32:1122–1132.
- [60] Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, et al. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010;52:176–182.
- [61] Liaw YF, Sheen IS, Lee CM, Akarca US, Papatheodoridis GV, Suet-Hing WF, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. *Hepatology* 2011;53:62–72.
- [62] Liaw YF, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. *Hepatology* 2011;54:91–100.
- [63] Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005;352:2682–2695.
- [64] Janssen HL, van ZM, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2007;365:123–129.
- [65] Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A one-year trial of lamivudine for chronic hepatitis B. *Asia Hepatitis Lamivudine Study Group*. *N Engl J Med* 1998;339:61–68.
- [66] Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256–1263.
- [67] Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354:1001–1010.
- [68] Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007;357:2576–2588.
- [69] Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B antigen-positive chronic hepatitis B. *N Engl J Med* 2003;348:808–816.
- [70] Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008;359:2442–2455.
- [71] Liaw YF, Jia JD, Chan HL, Han KH, Tanwandee T, Chuang WL, et al. Shorter durations and lower doses of peginterferon alfa-2a are associated with inferior hepatitis B e antigen seroconversion rates in hepatitis B virus genotypes B or C. *Hepatology* 2011;54:1591–1599.
- [72] Van Zonneveld M, Honkoop P, Hansen BE, Niesters HG, Murad SD, de Man RA, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 2004;39:804–810.
- [73] Liaw Y-F, Leung NWY, Chang T-T, Guan R, Tai D-I, Ng K-Y, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. *Gastroenterology* 2000;119:172–180.
- [74] Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;125:1714–1722.
- [75] Leung NW, Lai CL, Chang TT, Guan R, Lee CM, Ni YH, et al. 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.
- [76] Marcellin P, Chang TT, Lim SG, Sievert W, Tong M, Arterburn S, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2008;48:750–758.
- [77] Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009;136:486–495.
- [78] Chang TT, Lai CL, Kew YS, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010;51:422–430.
- [79] Reijnders JG, Perquin MJ, Zhang N, Hansen BE, Janssen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. *Gastroenterology* 2010;139:491–498.
- [80] van Nunen AB, Hansen BE, Suh DJ, Lohr HF, Chemello L, Fontaine H, et al. Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pre-treatment serum hepatitis B virus DNA and alanine aminotransferase. *Gut* 2003;52:420–424.
- [81] Buster EH, Flink HJ, Cakaloglu Y, Simon K, Trojan J, Tabak F, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. *Gastroenterology* 2008;135:459–467.

Clinical Practice Guidelines

- [82] Wong VW, Wong GL, Yan KK, Chim AM, Chan HY, Tse CH, et al. Durability of peginterferon alfa-2b treatment at 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology* 2010;51:1945–1953.
- [83] Yuen MF, Seto WK, Fung J, Wong DK, Yuen JC, Lai CL. Three years of continuous entecavir therapy in treatment-naïve chronic hepatitis B patients: viral suppression, viral resistance, and clinical safety. *Am J Gastroenterol* 2011;106:1264–1271.
- [84] Marcellin P, Buti M, Gane EJ, Krastev Z, Flisiak R, Germanidis G, et al. Five years of treatment with tenofovir DF (TDF) for chronic hepatitis B (CHB) infection is associated with sustained viral suppression and significant regression of histological fibrosis and cirrhosis. *Hepatology* 2011;54:1011A.
- [85] Heathcote EJ, Marcellin P, Buti M, Gane E, de Man RA, Krastev Z, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011;140:132–143.
- [86] Buster EH, Flink HJ, Simsek H, Heathcote EJ, Sharmila S, Kitis GE, et al. Early HBeAg loss during peginterferon alpha-2b therapy predicts HBsAg loss: results of a long-term follow-up study in chronic hepatitis B patients. *Am J Gastroenterol* 2009;104:2449–2457.
- [87] Moucari R, Korevaar A, Lada O, Martinot-Peignoux M, Boyer N, Mackiewicz V, et al. High rates of HBsAg seroconversion in HBeAg-positive chronic hepatitis B patients responding to interferon: a long-term follow-up study. *J Hepatol* 2009;50:1084–1092.
- [88] Piratvisuth T, Lau G, Chao YC, Jin R, Chutaputti A, Zhang QB, et al. Sustained response to peginterferon alfa-2a (40 kD) with or without lamivudine in Asian patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. *Hepatol Int* 2008;2:102–110.
- [89] Gish RG, Chang TT, Lai CL, de MR, Gadano A, Poordad F, et al. Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naïve HBeAg-positive patients with chronic hepatitis B. *J Viral Hepat* 2010;17:16–22.
- [90] Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-p ositive (precore mutant) chronic hepatitis B. *Hepatology* 1999;29:889–896.
- [91] Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004;351:1206–1217.
- [92] Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006;354:1011–1020.
- [93] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Adefovir dipivoxil for the treatment of hepatitis B antigen-negative chronic hepatitis B. *N Engl J Med* 2003;348:800–807.
- [94] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med* 2005;352:2673–2681.
- [95] Shouval D, Lai CL, Chang TT, Cheinquer H, Martin P, Carosi G, et al. Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment: the case for continuous antiviral therapy. *J Hepatol* 2009;50:289–295.
- [96] Shouval D, Lai C-L, Chang T-T, Gadano A, Wu S-S, Halota W, et al. Three years of entecavir (ETV) re-treatment of HBeAg(-) ETV patients who previously discontinued ETV treatment: results from study ETV-901. *Hepatology* 2008;48:722A.
- [97] Marcellin P, Bonino F, Lau GK, Farci P, Yurdaydin C, Piratvisuth T, et al. Sustained response of hepatitis B e antigen-negative patients 3 years after treatment with peginterferon alpha-2a. *Gastroenterology* 2009;136:2169–2179.
- [98] Marcellin P, Piratvisuth T, Brunetto M, Bonino F, Lau GKK, Farci P, et al. Increasing rates of HBsAg clearance and seroconversion in patients with HBeAg-negative disease treated with peginterferon alfa-2a ± lamivudine: results of 5-year post-treatment follow up. *J Hepatol* 2009;50:S336.
- [99] Papatheodoridis GV, Dimou E, Dimakopoulos K, Manolakopoulos S, Rapti I, Kitis G, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. *Hepatology* 2005;42:121–129.
- [100] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology* 2006;131:1743–1751.
- [101] Perrillo RP, Schiff ER, Davis GL, Bodenheimer HC, Lindsay K, Payne J, et al. A randomized, controlled trial of interferon alfa-2B alone and after prednisone withdrawal for the treatment of chronic hepatitis-B. *N Engl J Med* 1990;323:295–301.
- [102] Wong DKH, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 1993;119:312–323.
- [103] Flink HJ, van ZM, Hansen BE, de Man RA, Schalm SW, Janssen HL. Treatment with peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol* 2006;101:297–303.
- [104] Buster EH, Hansen BE, Lau GK, Piratvisuth T, Zeuzem S, Steyerberg EW, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. *Gastroenterology* 2009;137:2002–2009.
- [105] Fried MW, Piratvisuth T, Lau GK, Marcellin P, Chow WC, Cooksley G, et al. HBeAg and hepatitis B virus DNA as outcome predictors during therapy with peginterferon alfa-2a for HBeAg-positive chronic hepatitis B. *Hepatology* 2008;47:428–434.
- [106] Flink HJ, Sprengers D, Hansen BE, van ZM, de Man RA, Schalm SW, et al. Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during peg-interferon (alpha)-2b therapy. *Gut* 2005;54:1604–1609.
- [107] Piratvisuth T, Marcellin P, Popescu M, Kapprell HP, Rothe V, Lu ZM. Hepatitis B surface antigen: association with sustained response to peginterferon alfa-2a in hepatitis B e antigen-positive patients. *Hepatol Int* 2011. PMID: 21701902 [Epub ahead of print].
- [108] Gane E, Jia J, Han K, Tanwadee T, Chuang WL, Chuang WL, et al. Neptune study: on-treatment HBsAg level analysis confirms prediction of response observed in phase 3 study of peginterferon alfa-2a in HBeAg-positive patients. *J Hepatol* 2011;54:S31.
- [109] Sonneveld MJ, Rijckborst V, Boucher CA, Hansen BE, Janssen HL. Prediction of sustained response to peginterferon alfa-2b for hepatitis B e antigen-positive chronic hepatitis B using on-treatment hepatitis B surface antigen decline. *Hepatology* 2010;52:1251–1257.
- [110] Bonino F, Marcellin P, Lau GK, Hadziyannis S, Jin R, Piratvisuth T, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut* 2007;56:699–705.
- [111] Rijckborst V, Hansen BE, Cakaloglu Y, Ferenci P, Tabak F, Akdogan M, et al. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. *Hepatology* 2010;52:454–461.
- [112] Rijckborst V, Hansen BE, Ferenci P, Brunetto MR, Tabak F, Cakaloglu Y, et al. Validation of a stopping rule at week 12 using HBsAg and HBV DNA for HBeAg-negative patients treated with peginterferon alfa-2a. *J Hepatol* 2012;56:1006–1011.
- [113] Brunetto MR, Moriconi F, Bonino F, Lau GK, Farci P, Yurdaydin C, et al. Hepatitis B virus surface antigen levels: a guide to sustained response to peginterferon alfa-2a in HBeAg-negative chronic hepatitis B. *Hepatology* 2009;49:1141–1150.
- [114] Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peignoux M, et al. Early serum HBsAg drop: a strong predictor of sustained virological response to pegylated interferon alfa-2a in HBeAg-negative patients. *Hepatology* 2009;49:1151–1157.
- [115] Moucari R, Martinot-Peignoux M, Mackiewicz V, Boyer N, Ripault MP, Castelnau C, et al. Influence of genotype on hepatitis B surface antigen kinetics in hepatitis B e antigen-negative patients treated with pegylated interferon-alpha2a. *Antivir Ther* 2009;14:1183–1188.
- [116] Perrillo RP, Lai CL, Liaw YF, Dienstag JL, Schiff ER, Schalm SW, et al. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. *Hepatology* 2002;36:186–194.
- [117] Wiegand J, Hasenclever D, Tillmann HL. Should treatment of hepatitis B depend on hepatitis B virus genotypes? A hypothesis generated from an explorative analysis of published evidence. *Antivir Ther* 2008;13:211–220.
- [118] Yuen MF, Sablon E, Hui CK, Yuan HJ, Decraemer H, Lai CL. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. *Hepatology* 2001;34:785–791.
- [119] Zeuzem S, Gane E, Liaw YF, Lim SG, DiBisceglie A, Buti M, et al. Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B. *J Hepatol* 2009;51:11–20.
- [120] Wursthorn K, Jung M, Riva A, Goodman ZD, Lopez P, Bao W, et al. Kinetics of hepatitis B surface antigen decline during 3 years of telbivudine treatment in hepatitis B e antigen-positive patients. *Hepatology* 2010;52:1611–1620.
- [121] Lee JM, Ahn SH, Kim HS, Park H, Chang HY, Kim DY, et al. Quantitative hepatitis B surface antigen and hepatitis B e antigen titers in prediction of treatment response to entecavir. *Hepatology* 2011;53:1486–1493.

- [122] Marcellin P, Heathcote EJ, Buti M, Krastev Z, Jacobson I, de Man RA, et al. HBSAg kinetics in patients with chronic hepatitis B (CHB) treated with tenofovir disoproxil fumarate (TDF) for up to 4 years. *J Hepatol* 2011;54:S297.
- [123] Marcellin P, Heathcote EJ, Corsa A, Liu Y, Miller MD, Kitrinis KM. No detectable resistance to tenofovir disoproxil fumarate (TDF) following up to 240 weeks of treatment in patients with HBeAg+ and HBeAg- chronic hepatitis B virus infection. *Hepatology* 2011;54:480A.
- [124] Lok AS, Hussain M, Cursano C, Margotti M, Gramenzi A, Grazi GL, et al. Evolution of hepatitis B virus polymerase gene mutations in hepatitis B e antigen-negative patients receiving lamivudine therapy. *Hepatology* 2000;32:1145-1153.
- [125] Hadziyannis SJ, Papatheodoridis GV, Dimou E, Laras A, Papaioannou C. Efficacy of long-term lamivudine monotherapy in patients with hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2000;32:847-851.
- [126] Papatheodoridis GV, Dimou E, Laras A, Papadimitropoulos V, Hadziyannis SJ. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. *Hepatology* 2002;36:219-226.
- [127] Di Marco V, Marzano A, Lampertico P, Andreone P, Santantonio T, Almasio PL, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. *Hepatology* 2004;40:883-891.
- [128] Gane EJ, Wang Y, Liaw YF, Hou J, Thongsawat S, Wan M, et al. Efficacy and safety of prolonged 3-year telbivudine treatment in patients with chronic hepatitis B. *Liver Int* 2011;31:676-684.
- [129] Marcellin P, Avila C, Wursthorn K, Chuang WL, Lau GK, Peng CY, et al. Telbivudine (LDT) plus peg-interferon (PEGIFN) in HBeAg-positive chronic hepatitis B - very potent antiviral efficacy but risk of peripheral neuropathy (PN). *J Hepatol* 2010;52:S6-S7.
- [130] Lee HW, Lee HJ, Hwang JS, Sohn JH, Jang JY, Han KJ, et al. Lamivudine maintenance beyond one year after HBeAg seroconversion is a major factor for sustained virologic response in HBeAg-positive chronic hepatitis B. *Hepatology* 2010;51:415-421.
- [131] Song B-C, Suh DJ, Lee HC, Chung Y-H, 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.
- [132] Dienstag JL, Cianciara J, Karayalcin S, Kowdley KV, Willems B, Plisek S, et al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. *Hepatology* 2003;37:748-755.
- [133] Yoon SK, Jang JW, Kim CW, Bae SH, Choi JY, Choi SW, et al. Long-term results of lamivudine monotherapy in Korean patients with HBeAg-positive chronic hepatitis B: response and relapse rates, and factors related to durability of HBeAg seroconversion. *Intervirology* 2005;48:341-349.
- [134] Wu IC, Shiffman ML, Tong MJ, Marcellin P, Mondou E, Lok D, Trinh HN, Carosi G, Akarca US, Gadano A, Habersetzer F, et al. Entecavir (ETV) monotherapy for 96 weeks is comparable to combination therapy with ETV plus tenofovir (TDF) in nucleos(t)ide naive patients with chronic hepatitis B: the BELOW study. *Hepatology* 2011;54:471A.
- [135] Lok AS, Trinh HN, Carosi G, Akarca US, Gadano A, Habersetzer F, et al. Entecavir (ETV) monotherapy for 96 weeks is comparable to combination therapy with ETV plus tenofovir (TDF) in nucleos(t)ide naive patients with chronic hepatitis B: the BELOW study. *Hepatology* 2011;54:471A.
- [136] Lok AS, Zoulim F, Locarnini S, Bartholomeusz A, Ghany MG, Pawlotsky JM, et al. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology* 2007;46:254-265.
- [137] Zoutendijk R, Reijnders JG, Brown A, Zoulim F, Mutimer D, Deterding K, et al. Entecavir treatment for chronic hepatitis B: adaptation is not needed for the majority of naive patients with a partial virological response. *Hepatology* 2011;54:443-451.
- [138] Lampertico P, Vigano P, Manenti E, Iavarone M, Lunghi G, Colombo M. Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine. *Hepatology* 2005;42:1414-1419.
- [139] Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. *Gastroenterology* 2009;137:1593-1608.
- [140] Van Bommel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, et al. Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. *Hepatology* 2010;51:73-80.
- [141] Reijnders JG, Deterding K, Petersen J, Zoulim F, Santantonio T, Buti M, et al. Antiviral effect of entecavir in chronic hepatitis B: influence of prior exposure to nucleos(t)ide analogues. *J Hepatol* 2010;52:493-500.
- [142] Berg T, Marcellin P, Zoulim F, Moller B, Trinh H, Chan S, et al. Tenofovir is effective alone or with emtricitabine in adefovir-treated patients with chronic-hepatitis B virus infection. *Gastroenterology* 2010;139:1207-1217.
- [143] Manesis EK, Hadziyannis SJ. Interferon-alpha treatment and retreatment of hepatitis B e antigen-negative chronic hepatitis B. *Gastroenterology* 2001;121:101-109.
- [144] Gane EJ, Deary G, Piratvisuth T, Chan HL, Zeuzem S, Jia J, et al. Renal function is improved for chronic hepatitis B (CHB) patients treated with telbivudine. *Hepatology* 2011;54:1044A.
- [145] Ha NB, Ha NB, Garcia RT, Trinh HN, Vu AA, Nguyen HA, et al. Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. *Hepatology* 2009;50:727-734.
- [146] Perrillo R, Tamburro C, Regenstein F, Balart L, Bodenheimer H, Silva M, et al. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. *Gastroenterology* 1995;109:908-916.
- [147] Buster EH, Hansen BE, Buti M, Delwaide J, Niederau C, Michielsen PP, et al. Peginterferon alpha-2b is safe and effective in HBeAg-positive chronic hepatitis B patients with advanced fibrosis. *Hepatology* 2007;46:388-394.
- [148] Schiff E, Simsek H, Lee WM, Chao YC, Sette Jr H, Janssen HL, et al. Efficacy and safety of entecavir in patients with chronic hepatitis B and advanced hepatic fibrosis or cirrhosis. *Am J Gastroenterol* 2008;103:2776-2783.
- [149] Buti M, Hadziyannis S, Mathurin P, Urbanek P, Sherman M, Strasser S, et al. Tenofovir disoproxil fumarate is highly active for treatment of chronic hepatitis B in subjects with cirrhosis. *J Hepatol* 2008;48:S33.
- [150] Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010;52:886-893.
- [151] Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* 2010;53:348-356.
- [152] Papatheodoridis GV, Manolakopoulos S, Touloumi G, Vourli G, Raptoulou-Gigi M, Vafiadis-Zoumbouli I, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut* 2011;60:1109-1116.
- [153] Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009;50:2001-2006.
- [154] Fontana RJ, Hann HW, Perrillo RP, Vierling JM, Wright T, Rakela J, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. *Gastroenterology* 2002;123:719-727.
- [155] Papatheodoridis GV, Cholongitas E, Archimandritis AJ, Burroughs AK. Current management of hepatitis B virus infection before and after liver transplantation. *Liver Int* 2009;29:1294-1305.
- [156] Grellier L, Mutimer D, Ahmed M, Brown D, Burroughs AK, Rolles K, et al. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996;348:1212-1215.
- [157] Samuel D. Management of hepatitis B in liver transplantation patients. *Semin Liver Dis* 2004;24:55-62.
- [158] Schiff E, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. *Liver Transpl* 2007;13:349-360.
- [159] Fung J, Cheung C, Chan SC, Yuen MF, Chok KS, Sharr W, et al. Entecavir monotherapy is effective in suppressing hepatitis B virus after liver transplantation. *Gastroenterology* 2011;141:1212-1219.
- [160] Teperman L, Spivey J, Poordad F, Schiano T, Bzowej N, Pungpapong S, et al. Emtricitabine/tenofovir DF combination +/- HBIG post-orthotopic liver transplantation to prevent hepatitis B recurrence in patients with normal to moderate renal impairment: interim results. *J Hepatol* 2010;52:S12-S13.
- [161] Di Martino V, Thevenot T, Colin JF, Boyer N, Martinot M, Degos F, et al. Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B. *Gastroenterology* 2002;123:1812-1822.
- [162] Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. *Lancet Infect Dis* 2007;7:402-409.
- [163] Puoti M, Torti C, Bruno R, Filice G, Carosi G. Natural history of chronic hepatitis B in co-infected patients. *J Hepatol* 2006;44:S65-S70.
- [164] Rockstroh JK. Influence of viral hepatitis on HIV infection. *J Hepatol* 2006;44:S25-S27.

Clinical Practice Guidelines

- [165] Soriano V, Puoti M, Bonacini M, Brook G, Cargnel A, Rockstroh J, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *Aids* 2005;19:221–240.
- [166] Sulkowski MS. Viral hepatitis and HIV coinfection. *J Hepatol* 2008;48:353–367.
- [167] Colin JF, Cazals-Hatem D, Lioriot MA, Martinot-Peignoux M, Pham BN, Auperin A, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;29:1306–1310.
- [168] Tuma P, Medrano J, Resino S, Vispo E, Madejon A, Sanchez-Piedra C, et al. Incidence of liver cirrhosis in HIV-infected patients with chronic hepatitis B or C in the era of highly active antiretroviral therapy. *Antivir Ther* 2010;15:881–886.
- [169] Alberti A, Clumeck N, Collins S, Gerlich W, Lundgren J, Palu G, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005;42:615–624.
- [170] Rockstroh JK, Bhagani S, Benhamou Y, Bruno R, Mauss S, Peters L, et al. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Med* 2008;9:82–88.
- [171] de Vries-Sluijs TE, Reijnders JG, Hansen BE, Zaaier HL, Prins JM, Pas SD, et al. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. *Gastroenterology* 2010;139:1934–1941.
- [172] Piroth L, Pol S, Lacombe K, Mialhes P, Rami A, Rey D, et al. Management and treatment of chronic hepatitis B virus infection in HIV positive and negative patients: the EPIB 2008 study. *J Hepatol* 2010;53:1006–1012.
- [173] Yurdaydin C, Idilman R, Bozkaya H, Bozdayi AM. Natural history and treatment of chronic delta hepatitis. *J Viral Hepat* 2010;17:749–756.
- [174] Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. *Lancet* 2011;378:73–85.
- [175] Mederacke I, Bremer B, Heidrich B, Kirschner J, Deterding K, Bock T, et al. Establishment of a novel quantitative hepatitis D virus (HDV) RNA assay using the Cobas TaqMan platform to study HDV RNA kinetics. *J Clin Microbiol* 2010;48:2022–2029.
- [176] Romeo R, Del NE, Rumi M, Russo A, Sangiovanni A, De FR, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. *Gastroenterology* 2009;136:1629–1638.
- [177] Niro GA, Smedile A, Ippolito AM, Ciancio A, Fontana R, Olivero A, et al. Outcome of chronic delta hepatitis in Italy: a long-term cohort study. *J Hepatol* 2010;53:834–840.
- [178] Farci P. Treatment of chronic hepatitis D: new advances, old challenges. *Hepatology* 2006;44:536–539.
- [179] Farci P, Mandas A, Coiana A, Lai ME, Desmet V, Van EP, et al. Treatment of chronic hepatitis D with interferon alfa-2a. *N Engl J Med* 1994;330:88–94.
- [180] Niro GA, Ciancio A, Gaeta GB, Smedile A, Marrone A, Olivero A, et al. Pegylated interferon alpha-2b as monotherapy or in combination with ribavirin in chronic hepatitis delta. *Hepatology* 2006;44:713–720.
- [181] Yurdaydin C, Bozkaya H, Karaaslan H, Onder FO, Erkan OE, Yalcin K, et al. A pilot study of 2 years of interferon treatment in patients with chronic delta hepatitis. *J Viral Hepat* 2007;14:812–816.
- [182] Wedemeyer H, Yurdaydin C, Dalekos GN, Erhardt A, Kakaloglu Y, Degertekin H, et al. Peginterferon plus adefovir versus either drug alone for hepatitis delta. *N Engl J Med* 2011;364:322–331.
- [183] Castelnau C, Le GF, Ripault MP, Gordien E, Martinot-Peignoux M, Boyer N, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. *Hepatology* 2006;44:728–735.
- [184] Farci P, Roskams T, Chessa L, Peddis G, Mazzoleni AP, Scioscia R, et al. Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology* 2004;126:1740–1749.
- [185] Raimondo G, Brunetto MR, Pontisso P, Smedile A, Maina AM, Saitta C, et al. Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. *Hepatology* 2006;43:100–107.
- [186] Schaper M, Rodriguez-Frias F, Jardi R, Taberner D, Homs M, Ruiz G, et al. Quantitative longitudinal evaluations of hepatitis delta virus RNA and hepatitis B virus DNA shows a dynamic, complex replicative profile in chronic hepatitis B and D. *J Hepatol* 2010;52:658–664.
- [187] Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol* 2008;23:512–520.
- [188] Jamma S, Hussain G, Lau DT. Current concepts of HBV/HCV coinfection: coexistence, but not necessarily in harmony. *Curr Hepat Rep* 2010;9:260–269.
- [189] Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer* 1998;75:347–354.
- [190] Bellecave P, Gouttenoire J, Gajer M, Brass V, Koutsoudakis G, Blum HE, et al. Hepatitis B and C virus coinfection: a novel model system reveals the absence of direct viral interference. *Hepatology* 2009;50:46–55.
- [191] Potthoff A, Wedemeyer H, Boecher WO, Berg T, Zeuzem S, Arnold J, et al. The HEP-NET B/C co-infection trial: a prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. *J Hepatol* 2008;49:688–694.
- [192] 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* 2003;37:568–576.
- [193] Zhou J, Dore GJ, Zhang F, Lim PL, Chen YMA. Hepatitis B and C virus coinfection in the TREAT Asia HIV observational database. *J Gastroenterol Hepatol* 2007;22:1510–1518.
- [194] Saitta C, Pontisso P, Brunetto MR, Fargion S, Gaeta GB, Niro GA, et al. Virological profiles in hepatitis B virus/hepatitis C virus coinfection patients under interferon plus ribavirin therapy. *Antivir Ther* 2006;11:931–934.
- [195] Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou-Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen-positive hepatitis in Greek adults. *Gastroenterology* 1987;92:1844–1850.
- [196] Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat* 2006;13:256–263.
- [197] Lee WM, Squires RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. *Hepatology* 2008;47:1401–1415.
- [198] Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* 2011;53:774–780.
- [199] Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. *Hepatology* 2010;52:2192–2205.
- [200] Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. *Hepatology* 2008;47:1863–1871.
- [201] Jonas MM, Little NR, Gardner SD. Long-term lamivudine treatment of children with chronic hepatitis B: durability of therapeutic responses and safety. *J Viral Hepat* 2008;15:20–27.
- [202] Sokal EM, Kelly D, Wirth S, Mizerski J, Dhawan A, Frederick D. The pharmacokinetics and safety of adefovir dipivoxil in children and adolescents with chronic hepatitis B virus infection. *J Clin Pharmacol* 2008;48:512–517.
- [203] Gunson RN, Shouval D, Roggendorf M, Zaaier H, Nicholas H, Holzmann H, et al. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in health care workers (HCWs): guidelines for prevention of transmission of HBV and HCV from HCW to patients. *J Clin Virol* 2003;27:213–230.
- [204] Anonymous. FDA pregnancy class definitions. <http://en.wikipedia.org/wiki/Pregnancy_category/>; 2010 [accessed 08.10].
- [205] Anonymous. Antiretroviral Pregnancy Registry. <<http://www.apregistry.com/>>; 2010 [accessed 08.10].
- [206] Bzowej NH. Hepatitis B. Therapy in pregnancy. *Curr Hepat Rep* 2010;9:197–204.
- [207] del CR, Grosheide PM, Mazel JA, Heijtkink RA, Hop WC, Gerards LJ, et al. Ten-year neonatal hepatitis B vaccination program, The Netherlands, 1982–1992: protective efficacy and long-term immunogenicity. *Vaccine* 1997;15:1624–1630.
- [208] Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicenter, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009;16:94–103.
- [209] Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, Bai SF, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatol* 2011;55:1215–1221.
- [210] Han L, Zhang HW, Xie JX, Zhang Q, Wang HY, Cao GW. A meta-analysis of lamivudine for interruption of mother-to-child transmission of hepatitis B virus. *World J Gastroenterol* 2011;17:4321–4333.
- [211] van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. *J Viral Hepat* 2003;10:294–297.

- [212] Su GG, Pan KH, Zhao NF, Fang SH, Yang DH, Zhou Y. Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy. *World J Gastroenterol* 2004;10:910–912.
- [213] Shi Z, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. *Obstet Gynecol* 2010;116:147–159.
- [214] Rawal BK, Parida S, Watkins RP, Ghosh P, Smith H. Symptomatic reactivation of hepatitis B in pregnancy. *Lancet* 1991;337:364.
- [215] ter Borg MJ, Leemans WF, de Man RA, Janssen HL. Exacerbation of chronic hepatitis B infection after delivery. *J Viral Hepat* 2008;15:37–41.
- [216] Benaboud S, Pruvost A, Coffie PA, Ekouevi DK, Urien S, Arrive E, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. *Antimicrob Agents Chemother* 2011;55:1315–1317.
- [217] Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991;100:182–188.
- [218] Mindikoglu AL, Regev A, Schiff ER. Hepatitis B virus reactivation after cytotoxic chemotherapy: the disease and its prevention. *Clin Gastroenterol Hepatol* 2006;4:1076–1081.
- [219] Esteve M, Saro C, Gonzalez-Huix F, Suarez F, Forne M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004;53:1363–1365.
- [220] Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011;22:1170–1180.
- [221] Hsu C, Hsiung CA, Su LJ, Hwang WS, Wang MC, Lin SF, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology* 2008;47:844–853.
- [222] Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008;148:519–528.
- [223] Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. *Br J Haematol* 2007;136:699–712.
- [224] Marzano A, Angelucci E, Andreone P, Brunetto M, Bruno R, Burra P, et al. Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis* 2007;39:397–408.
- [225] Cornberg M, Protzer U, Petersen J, Wedemeyer H, Berg T, Jilg W, et al. Prophylaxis, diagnosis and therapy of hepatitis B virus infection – the German guideline. *Z Gastroenterol* 2011;49:871–930.
- [226] Viganò M, Vener C, Lampertico P, Annaloro C, Pichoud C, Zoulim F, et al. Risk of hepatitis B surface antigen seroreversion after allogeneic hematopoietic SCT. *Bone Marrow Transplant* 2011;46:125–131.
- [227] Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors: a systematic review. *J Hepatol* 2010;52:272–279.