Clinical Practice Guidelines

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EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Summary

Hepatitis B virus (HBV) infection remains a global public health problem with changing epidemiology due to several factors including vaccination policies and migration. This Clinical Practice Guideline presents updated recommendations for the optimal management of HBV infection. Chronic HBV infection can be classified into five phases: (I) HBeAg-positive chronic infection, (II) HBeAg-positive chronic hepatitis, (III) HBeAg-negative chronic infection, (IV) HBeAg-negative chronic hepatitis and (V) HBsAg-negative phase. All patients with chronic HBV infection are at increased risk of progression to cirrhosis and hepatocellular carcinoma (HCC), depending on host and viral factors. The main goal of therapy is to improve survival and quality of life by preventing disease progression, and consequently HCC development. The induction of long-term suppression of HBV replication represents the main endpoint of current treatment strategies, while HBsAg loss is an optimal endpoint. The typical indication for treatment requires HBV DNA >2,000 IU/ml, elevated ALT and/or at least moderate histological lesions, while all cirrhotic patients with detectable HBV DNA should be treated. Additional indications include the prevention of mother to child transmission in pregnant women with high viremia and prevention of HBV reactivation in patients requiring immunosuppression or chemotherapy. The long-term administration of a potent nucleos(t)ide analogue with high barrier to resistance, *i.e.*, entecavir, tenofovir disoproxil or tenofovir alafenamide, represents the treatment of choice. Pegylated interferon-alfa treatment can also be considered in mild to moderate chronic hepatitis B patients. Combination therapies are not generally recommended. All patients should be monitored for risk of disease progression and HCC. Treated patients should be monitored for therapy response and adherence. HCC remains the major concern for treated chronic hepatitis B patients. Several subgroups of patients with HBV infection require specific focus. Future treatment strategies to achieve 'cure' of disease and new biomarkers are discussed.

Keywords: Hepatitis B; EASL guidelines; Treatment; Interferon; Entecavir; Tenofovir; TAF; HBsAg; Hepatocellular carcinoma; HBV DNA; HBV reactivation; Mother to child transmission.
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Introduction

Infection with hepatitis B virus (HBV) remains an important global public health problem with significant morbidity and mortality.[1–3] New information on the pathogenesis and management of HBV infection has become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2011 and published in 2012.[1] The objective of this manuscript is to update the recommendations for the optimal management of HBV infection. In order to keep the manuscript and particularly the reference list within a reasonable length, only references published after 2012 have been considered, since the readers can find the older supportive references in the 2012 EASL HBV CPGs.[1] The CPGs do not fully address prevention including vaccination. In addition, despite increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients and public health authorities must continue to make choices based on the evolving evidence.

Background

Epidemiology and public health burden

Approximately 240 million people are chronic HBV surface antigen (HBsAg) carriers, with a large regional variation of HBsAg-positive patients between low (<2%) and high (>8%) endemicity levels.[2,4] The prevalence is decreasing in several highly endemic countries due to improvements in the socioeconomic status, universal vaccination programs and perhaps effective antiviral treatments.[5] However, population movements and migration are currently changing the prevalence and incidence in several low endemic countries in Europe (*e.g.*, Italy, Germany), owing to the higher HBsAg prevalence rates in migrants and refugees from outside Europe compared with the indigenous population.[6,7] Even with universal vaccination programs, it has been impossible to substantially prevent acute cases of HBV infection, especially in high risk populations.[8,9] The number of HBV related deaths due to liver cirrhosis and/or hepatocellular carcinoma (HCC)

increased between 1990 and 2013 by 33%, relating to >686,000 cases in 2013 worldwide.[10]

Virology and immunopathogenesis

The viral life cycle

Human HBV belongs to the *Hepadnaviridae* family of small, enveloped, primarily hepatotropic DNA viruses. In the host, the virus replicates and assembles exclusively in hepatocytes, and virions are released non-cytopathically through the cellular secretory pathway. The viral genome shows an extremely compact organisation. The small (3.2 kb), partially double-stranded, relaxed-circular (rc) DNA features 4 open reading frames encoding 7 proteins: HBeAg (HBV e antigen, secreted dimeric protein), HBcAg (HBV core antigen, viral capsid protein), HBV Pol/RT (polymerase, reverse transcriptase activity), PreS1/PreS2/HBsAg (large, medium, and small surface envelope glycoproteins), and HBx (HBV x antigen, regulator of transcription required for the initiation of infection).[11,12] Upon viral uptake into hepatocytes, the HBV nucleocapsid is transported to the nucleus to release the rcDNA genome. In the nucleoplasm, the rcDNA is converted into a covalently closed circular DNA (cccDNA), which is wrapped by histones to form an episomal chromatinized structure. It then serves as a transcription template for all viral transcripts that are translated into the different viral proteins.[13] Besides encoding the capsid protein and the viral polymerase, the pregenomic RNA is reverse transcribed into new rcDNA within the viral capsid. The DNA containing nucleocapsids in the cytoplasm are either recycled into the nucleus to maintain cccDNA reservoir, or enveloped and secreted via the endoplasmic reticulum.[11] In addition to complete infectious virions (diameter of 42 nm), infected cells produce a large excess of genome-free, non-infectious sub-viral spherical or filamentous particles of 22 nm.[11] Viral genome integration in the host genome can occur randomly; it is not required for viral replication, but is one of the important mechanisms involved in hepatocyte transformation.[14]

Genetic variability of HBV

The lack of reverse transcriptase proofreading activity leads to frequent mutations of the viral genome. This results in the coexistence of genetically distinct viral species in infected individuals, also called viral quasispecies, which evolve depending on the pressure from the host environment. The interplay between the virus, hepatocyte and the immune response or antiviral treatment is thought to drive the emergence of HBV mutants that have the capacity to escape immune responses or antiviral treatments. Analysis of genome-wide nucleotide divergence has allowed for the identification of nine genotypes (A-I) and several sub-genotypes.[12,15]

Immunopathogenesis

In acute resolving infections, the response of the innate and adaptive immune system to HBV is efficient and timely. Viral clearance involves the induction of a robust adaptive T cell reaction inducing both a cytolytic dependent and independent antiviral effect via the expression of antiviral cytokines, as well as the induction of B cells producing neutralizing antibodies preventing the spread of the virus.[16,17] Hepatocyte turnover resulting from infected cell death leads to cccDNA dilution.

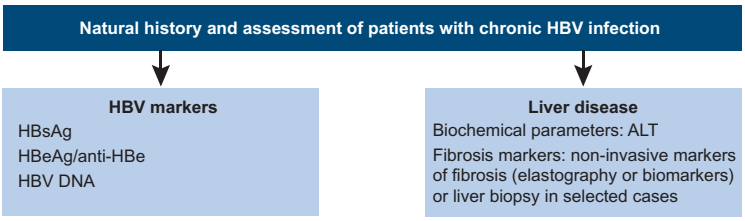
When the acute infection becomes chronic, there is a progressive impairment in HBV specific T cell function. Chronic HBV infection progresses through distinct disease phases that are strongly associated with age. It has been observed that children and young adults with chronic HBV infection have an immune profile that is less compromised than that observed in older patients, challenging the concept of 'immune tolerance'.[16] Several studies showed that HBV persists with virus-specific and global T cell dysfunction mediated by multiple regulatory mechanisms, but without distinct T cell–based immune signatures for clinical phenotypes (or clinical phase of infection).[16,17] Genome-wide association studies recently identified the *INTS10* gene at 8p21.3 as a novel locus contributing to the susceptibility to persistent HBV infection among Chinese subjects, and being causative for HBV clearance by activation of *IRF3* and then expression of anti-virus interferons hereby highlighting the role of innate immunity in viral clearance.[18]

Natural history and new nomenclature for the chronic states

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and the host immune response and not all patients with chronic HBV infection have chronic hepatitis (CHB). The natural history of chronic HBV infection has been schematically divided into five phases, taking into account the presence of HBeAg, HBV DNA levels, alanine aminotransferase (ALT) values and eventually the presence or absence of liver inflammation (Fig. 1). The new nomenclature is based on the description of the two main characteristics of chronicity: infection *vs.* hepatitis. However, despite this nomenclature, in a significant number of patients, a single determination of HBV replication markers as well as disease activity markers does not allow an immediate classification to one of the phases. Serial monitoring of serum HBeAg, HBV DNA and ALT levels is required in most instances but even after a complete assessment, some subjects fall into an indeterminate grey area and management needs to be individualised. The phases of chronic HBV infection are not necessarily sequential:

Phase 1: HBeAg-positive chronic HBV infection, previously termed "immune tolerant" phase; characterised by the presence of serum HBeAg, very high levels of HBV DNA and ALT persistently within the normal range according to traditional cut-off values [upper limit of normal (ULN) approximately 40 IU/L].[1] In the liver, there is minimal or no liver necroinflammation or fibrosis but a high level of HBV DNA integration and clonal hepatocyte expansion suggesting that hepatocarcinogenesis could be already underway in this early phase of the infection.[1,19] This phase is more frequent and prolonged in subjects infected perinatally and is associated with preserved HBV specific T cell function at least until young adulthood.[20] The rate of spontaneous HBeAg loss is very low in this phase. These patients are highly contagious due to the high levels of HBV DNA.

Phase 2: HBeAg-positive chronic hepatitis B is characterised by the presence of serum HBeAg, high levels of HBV DNA and elevated ALT. In the liver, there is moderate or severe liver necroinflammation and accelerated progression of fibrosis[1]. It may occur after several years of the first phase and is more frequently and/or rapidly reached in subjects infected during adulthood. The outcome of this phase is variable. Most patients can achieve HBeAg seroconversion and HBV DNA suppression and enter the HBeAg-negative infection phase. Other patients may fail to control HBV and progress to the HBeAg-negative CHB phase for many years.



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

Fig. 1. Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers. *Persistently or intermittently. °°HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without sings of chronic hepatitis.

Phase 3: HBeAg-negative chronic HBV infection, previously termed 'inactive carrier' phase, is characterised by the presence of serum antibodies to HBeAg (anti-HBe), undetectable or low (<2,000 IU/ml) HBV DNA levels and normal ALT according to traditional cut-off values (ULN ~40 IU/L). Some patients in this phase, however, may have HBV DNA levels >2,000 IU/ml (usually <20,000 IU/ml) accompanied by persistently normal ALT and only minimal hepatic necroinflammatory activity and low fibrosis. These patients have low risk of progression to cirrhosis or HCC if they remain in this phase, but progression to CHB, usually in HBeAg-negative patients, may occur.[1] HBsAg loss and/or seroconversion may occur spontaneously in 1–3% of cases per year.[1] Typically, such patients may have low levels of serum HBsAg (<1,000 IU/ml).[21]

Phase 4: HBeAg-negative chronic hepatitis B is characterised by the lack of serum HBeAg usually with detectable anti-HBe, and persistent or fluctuating moderate to high levels of serum HBV DNA (often lower than in HBeAg-positive patients), as well as fluctuating or persistently elevated ALT values. The liver histology shows necroinflammation and fibrosis.[1] Most of these subjects harbour HBV variants in the precore and/or the basal core promoter regions that impair or abolish HBeAg expression. This phase is associated with low rates of spontaneous disease remission.[1]

Phase 5: HBsAg-negative phase is characterised by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). This phase is also known as "occult HBV infection". In rare cases, the absence of HBsAg could be related to the sensitivity of the assay used for detection.[22] Patients in this phase have normal ALT values and usually, but not always, undetectable serum HBV DNA. HBV DNA (cccDNA) can be detected frequently in the liver.[1] HBsAg loss before the onset of cirrhosis is associated with a minimal risk of cirrhosis, decompensation and HCC, and an improvement on survival. However, if cirrhosis has developed before HBsAg loss, patients remain at risk of HCC therefore HCC surveillance should continue. Immunosuppression may lead to HBV reactivation in these patients.[1]

Factors related to progression to cirrhosis and HCC

The risk of progression to cirrhosis and HCC is variable and is affected by the host's immune response. The 5-year cumulative incidence of cirrhosis ranges from 8% to 20% in untreated CHB patients and, among those with cirrhosis, the 5-year cumulative risk of hepatic decompensation is 20%.[1] The annual risk of HCC in patients with cirrhosis has been reported to be 2–5%.[23]

HCC is currently the main concern for diagnosed CHB patients and may develop even in patients who have been effectively treated.[24] The risk of developing HCC is higher in patients with one or more factors that relate to the host (cirrhosis, chronic hepatic necroinflammation, older age, male sex, African origin, alcohol abuse, chronic co-infections with other hepatitis viruses or human immunodeficiency virus [HIV], diabetes or metabolic syndrome, active smoking, positive family history) and/or to HBV properties (high HBV DNA and/or HBsAg levels, HBV genotype C > B, specific mutations).[24] The above factors seem to affect the progression to cirrhosis in untreated CHB patients.[1]

Several risk scores have been recently developed for HCC prediction in CHB patients. Most of them, such as GAG-HCC, CU-HCC and REACH-B, have been developed and validated in Asian untreated CHB patients,[25] but they do not seem to offer good predictability in most studies including Caucasian CHB patients.[26,27] A recently developed and validated new score, PAGE-B, offers good predictability for HCC during the first 5 years of entecavir or tenofovir therapy in Caucasian, mostly European, CHB patients and can be easily applied in clinical practice, as it is based on widely available parameters (platelets, age, gender).[28] The PAGE-B score appears to predict HCC development even in untreated CHB patients.[29,30]

Initial assessment of subjects with chronic HBV infection

The initial evaluation of a subject with chronic HBV infection should include a complete history, a physical examination, assessment of liver disease activity and severity and markers of HBV infection (Fig. 1). In addition, all first degree relatives and sexual partners of subjects with chronic HBV infection should be advised to be tested for HBV serological markers (HBsAg, anti-HBs, anti-HBc) and to be vaccinated if they are negative for these markers.

(1) The assessment of the severity of liver disease is important to identify patients for treatment and HCC surveillance. It is based on a physical examination and biochemical parameters (aspartate aminotransferase [AST] and ALT, gamma-glutamyl transpeptidase [GGT], alkaline phosphatase, bilirubin, and serum albumin and gamma globulins, full blood count and prothrombin time). An abdominal hepatic ultrasound is recommended in all patients. A liver biopsy or a non-invasive test should be performed to determine disease activity in cases where biochemical and HBV markers reveal inconclusive results.[31] Of the non-invasive methods, which include liver stiffness measurements and serum biomarkers of liver fibrosis, the use of transient elastography has been mostly studied and seems to offer a higher diagnostic accuracy for the detection of cirrhosis. The diagnostic accuracy of all non-invasive methods is better at excluding than confirming advanced fibrosis or cirrhosis.[31,32] The results of transient elastography may be confounded by severe inflammation associated with high ALT levels.[31,32]
(2) HBeAg and anti-HBe detection are essential for the determination of the phase of chronic HBV infection.
(3) Measurement of HBV DNA serum level is essential for the diagnosis, establishment of the phase of the infection, the decision to treat and subsequent monitoring of patients.
(4) Serum HBsAg quantification can be useful, particularly in HBeAg-negative chronic HBV infection and in patients to be treated with interferon-alfa (IFNα).
(5) HBV genotype is not necessary in the initial evaluation, although it may be useful for selecting patients to be treated with IFNα offerering prognostic information for the probability of response to IFNα therapy and the risk of HCC.
(6) Co-morbidities, including alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis and other causes of chronic liver disease should be systematically excluded including co-infections with hepatitis D virus (HDV), hepatitis C virus (HCV) and HIV.
(7) Testing for antibodies against hepatitis A virus (anti-HAV) should be performed, and patients with negative anti-HAV should be advised to be vaccinated against HAV.

Methodology

These CPGs were developed by a CPG panel of experts chosen by the EASL Governing Board, peer-reviewed by three external experts 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 since the last CPG and prior to December 2016 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[33] (Table 1). The strength of recommendations (strong: 1, weak: 2) thus reflects the quality (grade) of underlying evidence (I, II-1, II-2, II-3, III). Grades are not provided for statements and 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).

Guidelines

Goals of therapy

The main goal of therapy for patients with chronic HBV infection is to improve survival and quality of life by preventing disease progression, and consequently HCC development. Additional goals of antiviral therapy are to prevent mother to child transmission, hepatitis B reactivation and the prevention and treatment of HBV-associated extrahepatic manifestations.

The likelihood of achieving these goals depends on the timing of therapy during the natural course of the infection but also on the stage of the disease and the patients' age when treatment is started. Regression of fibrosis and cirrhosis can be regarded as a further goal of treatment in patients with established advanced fibrosis or cirrhosis, although its impact has not been fully clarified in clinical outcomes. Treatment strategies to prevent HCC development may differ in some ways from those that are needed to prevent fibrosis progression.

In patients with HBV-induced HCC, the goals of nucleos(t)ide analogue (NA) therapy are firstly to suppress HBV replication to induce the stabilisation of HBV-induced liver disease and to prevent disease progression, and secondly to reduce the risk of HCC recurrence after potentially curative HCC therapies. Stabilising the HBV-induced liver disease can be also regarded as a prerequisite for the safe and effective applications of HCC treatments.

In patients with acute hepatitis B, preventing the risk of acute or subacute liver failure is the main treatment goal. Improving the quality of life by shortening the duration of the disease associated symptoms as well as lowering the risk of chronicity may be also regarded as relevant goals of treatment.

Endpoints of therapy

Recommendations

- The induction of long-term suppression of HBV DNA levels represents the main endpoint of all current treatment strategies (Evidence level I, grade of recommendation 1).
- The induction of HBeAg loss, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a valuable endpoint, as it often represents a partial immune control of the chronic HBV infection (Evidence level II-1, grade of recommendation 1).
- A biochemical response defined as ALT normalisation should be considered as an additional endpoint, which is achieved in most patients with long-term suppression of HBV replication (Evidence level II-1, grade of recommendation 1).
- HBsAg loss, with or without anti-HBs seroconversion, is an optimal endpoint, as it indicates profound suppression of HBV replication and viral protein expression (Evidence level II-1, grade of recommendation 1).

Table 1. Grading evidence and recommendations (adapted from GRADE system).

Grade evidence	
I	Randomised, controlled trials
II-1	Controlled trials without randomisation
II-2	Cohort or case-control analytical studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology
Grade recommendation	
1	Strong recommendation: Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
2	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

The level of HBV replication represents the strongest single predictive biomarker associated with disease progression and the long-term outcome of chronic HBV infection. The inhibition of viral replication by antiviral treatment has been shown to achieve the elimination of chronic HBV-induced necroinflammatory activity and progressive fibrotic liver processes in the vast majority of patients, in turn reducing the risk of HCC. It therefore represents the cornerstone endpoint of all our current therapeutic attempts.[1,25,34–40] The level of HBV DNA suppression that should be attained in order to achieve these benefits is not well defined, but inferred that the lower, the better.

Treatment-induced HBeAg loss and seroconversion to anti-HBe characterises the induction of a partial immune control often leading to a low replicative phase of the chronic HBV infection. Whether this is a durable phase is only proven after treatment cessation. After stopping therapy, HBeAg seroreversion, as well as the development of HBeAg-negative CHB, may also occur (even after NA consolidation treatment), making this endpoint less reliable.[41,42] Hence, continuing oral antiviral therapy irrespective of the HBeAg response until HBsAg loss has become an alternative strategy.

Suppression of HBV DNA to undetectable levels is normally associated with normalisation of ALT levels. Persistence of elevated ALT levels in patients with complete suppression of viral replication is associated with a lower chance of fibrosis regression and can be a reason for histologic disease progression.[43] The most likely explanation for these findings is the presence of concomitant liver injury such as alcoholic or non-alcoholic fatty liver disease.[34,44] In contrast, transient ALT flares may indicate some level of immune reconstitution and can be associated with favourable outcomes.[1,45,46]

The loss of HBsAg is regarded as the optimal treatment endpoint, termed 'functional cure', but it is only rarely achieved with our current antiviral armamentarium. Spontaneous HBsAg seroreversion with reactivation of the inflammatory liver process after HBsAg loss is rare and may occur in patients with a significant impairment of their immune function.[47–52] The main advantage of HBsAg loss is that it allows a safe discontinuation of antiviral therapy. As chronic HBV infection cannot be completely eradicated due to the persistence of cccDNA and integrated HBV DNA,[1] it remains unclear whether HBsAg loss adds to the prevention of the long-term complications of chronic HBV infection beyond what can be achieved by the suppression of HBV DNA replication alone. HCC may still develop even after spontaneous HBsAg loss (annual rate approximately 0.55%).[53] The risk, however, is lower if HBsAg loss is achieved at a younger age and/or in the absence of significant fibrosis.[1,54] In an Asian cohort followed for 287 patient-years after NA treatment induced HBsAg seroclearance, only two patients with baseline cirrhosis developed HCC or died (0.7% annual risk), which was a significantly lower rate compared with propensity score-matched patients without HBsAg seroclearance (HR 0.09, p <0.01).[47]

Indications for treatment

Recommendations

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

The indications for treatment are generally the same for both HBeAg-positive and HBeAg-negative CHB (Fig. 2). This is based mainly on the combination of three criteria:

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

Patients without cirrhosis should be considered for treatment when they have HBV DNA levels above 2,000 IU/ml, serum ALT levels above the traditional ULN (~40 IU/L) and severity of liver disease assessed traditionally by liver biopsy showing at least moderate necroinflammation and/or at least moderate fibrosis. Patients with HBV DNA >20,000 IU/ml and ALT >2x ULN can start treatment even without a liver biopsy. 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 critically from a monitoring perspective, to confirm or rule out cirrhosis is useful in patients who start treatment without liver biopsy.

In patients who have HBV DNA >2,000 IU/ml and at least moderate fibrosis, treatment may be initiated even if ALT levels are normal. In patients who cannot or are reluctant to undergo liver biopsy, non-invasive markers of fibrosis may also be used for decisions on treatment indications.

As explained in more detail in the EASL-ALEH CPGs on "non-invasive tests for evaluation of liver disease severity and prognosis",[32] patients with chronic HBV infection either with normal ALT and liver stiffness >9 kPa, or with elevated ALT but below 5x ULN and liver stiffness >12 kPa at a reliable transient elastography can be considered to have severe fibrosis or cirrhosis. Equivalent cut-offs from other elastographic or serological methods of assessment of liver fibrosis may also be used once validated in chronic HBV patients.

Indications for treatment may also take into account the patients' age, health status, risk of HBV transmission, family history of HCC or cirrhosis and extrahepatic manifestations (Fig. 2).

Monitoring of patients currently not treated

Recommendations

- Patients with HBeAg-positive chronic HBV infection who are younger than 30 years and do not fulfill any of the above treatment indications should be followed at least every 3–6 months (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-negative chronic HBV infection and serum HBV DNA <2,000 IU/ml who do not fulfill any of the above treatment indications should be followed every 6–12 months (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-negative chronic HBV infection and serum HBV DNA ⩾2,000 IU/ml who do not fulfill any of the above treatment indications should be followed every 3 months for the first year and every 6 months thereafter (Evidence level III, grade of recommendation 1).

Patients who are not candidates for antiviral therapy should be monitored with periodical assessments of serum ALT and HBV DNA levels as well as for liver fibrosis severity by non-invasive markers (Fig. 2). Patients with HBeAg-positive chronic HBV infection who remain untreated should ideally have ALT determinations at least every 3 months, HBV DNA determinations every 6–12 months and assessment of liver fibrosis every 12 months.[1]

Patients with HBeAg-negative chronic HBV infection and HBV DNA <2,000 IU/ml should have ALT determinations every 6–12 months and periodical HBV DNA and liver fibrosis assessments, perhaps every 2–3 years. A quantitative determination of HBsAg levels can be helpful in the decision on the frequency of follow-up in such patients.[21] Patients can be followed for ALT levels every 12 months and HBV DNA and liver fibrosis assessments every 3 years if they have HBsAg levels <1,000 IU/ml, while follow-up with ALT every 6 months and HBV DNA and liver fibrosis assessment at least every 2 years is advised for patients with HBsAg levels ⩾1,000 IU/ml.[1,21,55]

Patients with HBeAg-negative chronic HBV infection and HBV DNA ⩾2,000 IU/ml should be followed with ALT determinations at least every 3 months for the first year and every 6 months thereafter, as well as with assessments of HBV DNA and liver fibrosis by a non-invasive method every year for at least 3 years. If they do not fulfill any treatment indication within the first 3 years of follow-up, they should be consequently followed for life, like all patients in this phase.[55]

Treatment strategies

Currently, there are two main treatment options for CHB patients: treatment with a NA or with IFNα, currently pegylated (PegIFNα) (Table 2).[1,56] The NAs that have been approved in Europe for HBV treatment include lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (TBV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), and can be classified into those associated with low barrier against HBV resistance (LAM, ADV, TBV) and those with high barrier to HBV resistance (ETV, TDF, TAF) (Fig. 3).[1,56,57]

The main advantage of treatment with a potent NA with high barrier to resistance (*i.e.*, ETV, TDF, TAF) is its predictable high long-term antiviral efficacy leading to undetectable HBV DNA levels in the vast majority of compliant patients as well as its favourable safety profile (Table 2).[1,56,57] These drugs can be safely used in any HBV infected patient and represent the only treatment option for several patient subgroups including those with decompensated liver disease, liver transplants, extrahepatic manifestations, acute hepatitis B or severe chronic HBV exacerbation.[57–61] NAs are also the only option for prevention of HBV reactivation in patients under immunosuppression. In addition, preventing HBV transmission in patients with high viremia who do not fulfill the typical criteria for treatment initiation represents further indications in which only NAs should be used.[1,49,50,52,56,57]

The rationale for a PegIFNα based approach is to induce long-term immunological control with a finite duration treatment. The main disadvantages of PegIFNα treatment is the high variability of response and its unfavourable safety profile making a significant number of patients ineligible or unwilling for this type of treatment (Table 2).[1,56] Patient selection according to disease activity, HBV genotype, stage of the disease, as well as levels of HBV DNA, HBsAg and HBeAg status can be helpful indicators to predict the individual response probability.[1,56] Early on-treatment predictors are established and can be used as additional tools (*e.g.* stopping rules) to individualise the treatment strategy, this helps to discontinue PegIFNα early in those with a low likelihood of long-term response.[1]

Theoretically, a combined NA and PegIFNα approach may provide advantages by combining the potent antiviral effect of NA plus the immune modulation of IFNα.[1,56,62,63] The evidence for

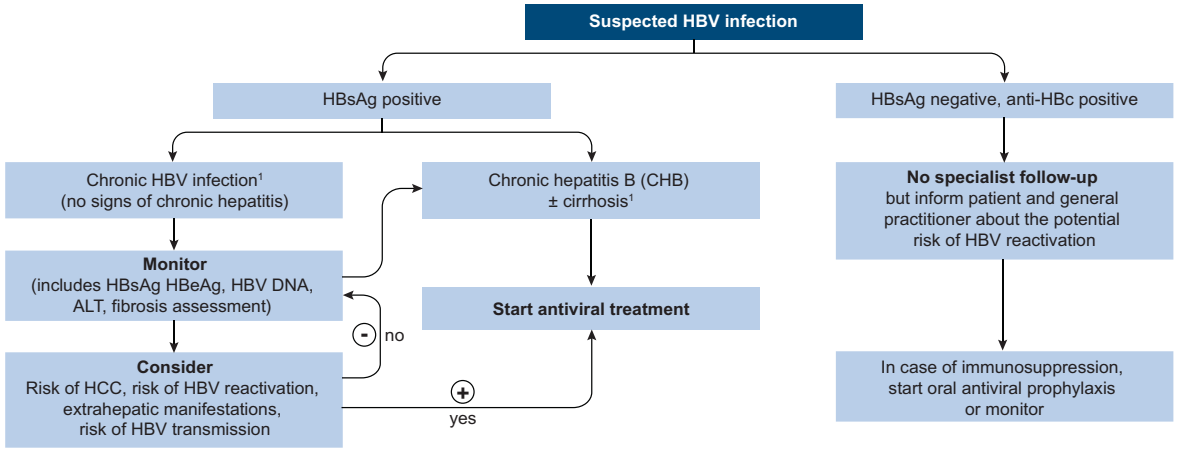


Fig. 2. Algorithm for the management of HBV infection. [1]see definitions in text and Fig. 1.

superiority of such a combined approach, however, is lacking, and there are still many unresolved issues with respect to patient selection, timing, as well as the duration of the combination strategy, which may be addressed in future studies.

Definitions of response

Responses can be divided into virological, serological, biochemical, 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.[1]

Virological responses

(1) NA therapy

- Virological response during NA is defined as undetectable HBV DNA by a sensitive polymerase chain reaction (PCR) assay with a limit of detection of 10 IU/ml. Primary non-response is defined by a less than one $\log_{10}$ decrease of serum HBV DNA after 3 months of therapy. 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 12 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. HBV resistance to NA(s) is characterised by selection of HBV variants with amino acid substitutions that confer reduced susceptibility to the administered NA(s).
- In patients who discontinue NA, sustained off-therapy virological response could be defined as serum HBV DNA levels <2,000 IU/ml for at least 12 months after the end of therapy.

(2) PegIFNα therapy

- Virological response is defined as serum HBV DNA levels <2,000 IU/ml. It is usually evaluated at 6 months and at the end of therapy.
- Sustained off-therapy virological response is defined as serum HBV DNA levels <2,000 IU/ml for at least 12 months after the end of therapy.

Serological responses for HBeAg are HBeAg loss and HBeAg seroconversion, *i.e.*, HBeAg loss and development of anti-HBe (only for HBeAg-positive patients).

Serological responses for HBsAg are HBsAg loss and HBsAg seroconversion, *i.e.*, HBsAg loss and development of anti-HBs (for all patients).

Biochemical response is defined as a normalisation of ALT levels based on the traditional ULN (~40 IU/L). 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. It should be noted that the rates of sustained off-treatment biochemical responses may sometimes be difficult to evaluate, as transient 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.

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

NAs for naïve CHB patients

Efficacy

Recommendations

- The long-term administration of a potent NA with high barrier to resistance is the treatment of choice regardless of the severity of liver disease (Evidence level I, grade of recommendation 1).
- The preferred regimens are ETV, TDF and TAF as monotherapies (Evidence level I, grade of recommendation 1).
- LAM, ADV and TBV are not recommended in the treatment of CHB (Evidence level I, grade of recommendation 1).

Table 2. Main concepts and features of current treatment strategies of chronic hepatitis B.

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)[1]
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment adverse events (psychiatric, neurological, endocrinological)	Probably not (uncertainties regarding kidney function, bone diseases for some NA)
Contraindications	Many (*i.e.*, decompensated disease, co-morbidities etc.)	None (dose adjustment according to eGFR[2])
Strategy	Induction of a long-term immune control by finite treatment	Stopping hepatitis and disease progression by inhibiting viral replication
Level of viral suppression	Moderate (variable response pattern)	Universally high
Effect on HBeAg loss	Moderate, depending on baseline characteristics	Low in the first year, increases to moderate during long-term treatment
Effect on HBsAg levels	Variable, depending on baseline characteristics (overall higher as compared to NA)	Low: slowly increases with treatment time in HBeAg-positive patients[3]; usually very low in HBeAg-negative patients
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance development	No	Minimal to none[4]

PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; NA, nucleoside/nucleotide analogues; eGFR, estimated glomerular filtration rate.

[1] See section on 'Treatment strategies'.

[2] Dose adjustments in patients with eGFR <50 ml/min are required for all NA, except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis).

[3] A plateau in serologic responses has been observed beyond treatment year 4.

[4] So far no TDF or TAF resistance development has been detected.

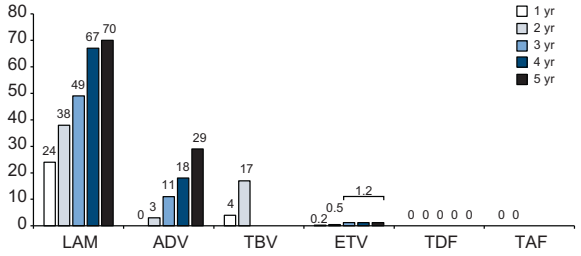


Fig. 3. Cumulative incidence of HBV resistance for lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), tenofovir (TDF) and tenofovir alafenamide (TAF) in pivotal trials in nucleos(t)ide-naïve patients with chronic hepatitis B. (Collation of currently available data – not from head-to-head studies). No evidence of resistance has been shown after 8 years of TDF treatment.[69]

The efficacy of all NAs has been assessed in randomised controlled phase III clinical trials (Table 3 and 4). The treatment strategy for non-cirrhotic and compensated cirrhotic HBV patients is identical given the efficacy and long-term safety profile in NA therapy. In HBeAg-positive CHB, 5 years of ETV achieve a 99% cumulative probability of virologic response and 53% probability of HBeAg loss.[26] After 5 years of TDF treatment in patients with HBeAg-positive CHB, 97% of those on-treatment had virologic response and 73% had normal ALT,[34] while HBeAg loss was present in 49%, HBeAg seroconversion in 40%, HBsAg loss in 10% and HBsAg seroconversion in 8%.

In patients with HBeAg-negative CHB, the 5-year cumulative probability of virological and biochemical responses on ETV was 98% and 95%, respectively, while the rate of resistance to ETV was <1%.[26,64–68] After 8 years, 99% of HBeAg-negative CHB patients treated with TDF in the registration trial achieved virological response (HBV DNA <400 copies/ml) without evidence of TDF resistance and 88% normalised ALT.[69] During 3–4 years of TDF treatment in HBeAg-negative CHB patients in real practice, the virological response rates ranged from 92% to 100% without the emergence of TDF resistance, while 75% of patients had normalised ALT.[70–73] No HBeAg-negative CHB patient cleared HBsAg wihin the first year of ETV or TDF therapy and very few (~1%) achieved this endpoint during long-term (8 years) therapy.

In patients with HBeAg-positive CHB, the rates of virologic response on TAF were 64% at week 48 and 75% at week 96[74,75] HBeAg loss and anti-HBe seroconversion were achieved in 14% and 10% of patients at week 48 and 22% and 18% at week 96, respectively. In the same study, ALT normalisation rates at week 96 by traditional values were higher in patients treated with TAF than TDF (75% *vs.* 68%), whereas only 1% of patients cleared HBsAg.[74–76] In HBeAg-negative CHB patients, TAF achieved virologic response in 94% of patients at week 48,[76] which was maintained in most cases at week 96 (90%). Only one TAF treated HBeAg-negative CHB patient (<1%) cleared HBsAg by week 96.[77] These virological and serological results are similar to those observed in the TDF arms in both studies. Only 96-week results are available for TAF to date, with the studies still ongoing (Table 3 and 4).

Monitoring of patients treated with ETV, TDF or TAF
Recommendations

- All patients treated with NA should be followed with periodical assessments including ALT and serum HBV DNA (Evidence level I, grade of recommendation 1).
- Patients at risk of renal disease treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodical renal monitoring including at least estimated glomerular filtration rate (eGFR) and serum phosphate levels (Evidence level II-2, grade of recommendation 1).
- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure (Evidence level II-2/I, grade of recommendation 1).

All patients considered for treatment with a NA with high barrier to resistance (ETV, TDF, TAF) should undergo periodical monitoring. At baseline, full blood count, liver and kidney (eGFR and serum phosphate levels) function tests, serum HBV DNA levels assessed by a sensitive PCR assay should be performed. Appropriate dosing adjustments of ETV and TDF are recommended for patients with eGFR <50 ml/min. TAF dosage remains at 25 mg until eGFR is <15 ml/min, with modeling pharmacokinetics data suggesting no dose change between <15 ml/min and formal renal support, although this is not within the label (Vemlidy® SmPC).[78] 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 (eGFR) <60 ml/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, or solid organ transplantation.

During treatment, liver function tests should be performed every 3–4 months during the first year and every six months thereafter. Serum HBV DNA should be determined every 3–4 months during the first year and every 6–12 months thereafter. HBsAg should be checked at 12-month intervals if HBV DNA remains undetectable, while patients who clear HBsAg should be tested for anti-HBs.

Minimal rates of renal function decline have been reported during long-term therapy with ETV and TDF, but the nephrotoxic potential is higher for TDF. Cases of Fanconi syndrome associated with TDF therapy and rescued after a switch to ETV have been reported. In addition, studies using sensitive markers of glomerular and tubular kidney function and of bone mineral density have also reported chronic tubular damage and decline of eGFR and bone mineral density in TDF treated patients.[70,79–87] Therefore, it seems appropriate for now to monitor all CHB patients treated with TDF therapy for adverse renal effects with serum creatinine (eGFR) and serum phosphate levels. Moreover, CHB patients at high renal risk undergoing any NA therapy should be monitored with serum creatinine (eGFR) levels. The frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, if no deterioration. Closer renal monitoring is required in patients who develop creatinine clearance <60 ml/min or serum phosphate levels <2 mg/dl.

In the two registrational TAF trials, TAF compared to TDF demonstrated superiority in the drug effects on several markers of renal (both glomerular and tubular) function and bone turnover at weeks 48 and 96.[74–77,88] In both groups of patients there was a significant difference in markers reflecting renal and bone function at week 48. A significant difference was noted in decrease of eGFR in both studies: −0.6 ml/min *vs.* −5.4 ml/min in HBeAg-positive patients (p <0.0001), −1.8 ml/min *vs.* −4.8 ml/min in HBeAg-negative patients (p = 0.004). Similar mean serum creatinine changes were demonstrated between TAF and TDF treated subjects: HBeAg-positive TAF treated patient's 0.01 mg/dl *vs.* 0.03 mg/dl in TDF (p = 0.02); HBeAg-negative 0.01 mg/dl *vs.* 0.02 mg/dl (p = 0.32). Likewise, a significantly smaller percentage decline in bone mineral density at the hip was reported in TAF patients over TDF treated patients (−0.10% *vs.* −1.72% in HBeAg-positive patients [p <0.0001], and −0.29% *vs.* −2.16% in HBeAg-negative [p <0.0001]) and spine (−0.42% *vs.* −2.29% in HBeAg- positive, −0.88% *vs.* −2.51% HBeAg-negative. Additional data with biomarkers of renal tubular function and bone turnover suggest less systemic effects in TAF compared to TDF, with less progression of chronic kidney disease and bone effects up to week 96.[75,77] Long-term clinical data are lacking, however, similar findings of superiority of TAF over TDF have also been found in recent studies in HIV infected patients at risk for or with established renal and bone impairment.[89–92]

These co-infected data also demonstrate stabilisation in renal parameters (GFR, creatinine) but improvement in proteinuria, albuminuria and tubular proteinuria, (p <0.001) as well as increases in hip and spine bone mineral densitometry from baseline to week 48 (mean percent change +1.47 and +2.29, respectively, p <0.05)[91]; with similar findings to 96 weeks.[92]

Whether these findings translate into improved long-term clinical outcomes in CHB patients remains to be defined, but an optimised safety profile of long-term NA therapy might be preferred, particularly in an ageing CHB population, with accruing co-morbidities. Thus, in CHB patients with deteriorating renal function or low eGFR and/or osteopenia/osteoporosis, particularly in older age, the minimisation of progression of the physiological decline into pathological abnormality should also be considered when choosing NA therapy (Table 5). In such subgroups of CHB patients, both ETV and TAF represent suitable choices with TAF having an advantage in patients with previous exposure to LAM.

Long-term outcome during NA
Recommendations

- Patients under effective long-term NA therapy should remain under surveillance for HCC (Evidence level II-2, grade of recommendation 1).
- HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores at the onset of NA therapy (Evidence level II-2, grade of recommendation 1).

Long-term ETV or TDF monotherapy has been shown to halt progression of liver disease, and can also result in a significant improvement of histological necroinflammation and fibrosis,

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

	PegIFN		Nucleoside analogues			Nucleotide analogues		
	PegIFNα2a	PegIFNα2b	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	180 μg	100 μg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
Anti-HBe-seroconversion	32%	29%	16–18%	22%	21%	12–18%	21%	10%
HBV DNA <60–80 IU/ml	14%	7%	36–44%	60%	67%	13–21%	76%	64%
ALT normalisation#	41%	32%	41–72%	77%	68%	48–54%	68%	72%
HBsAg loss	3%	7%	0–1%	0.5%	2%	0%	3%	1%

References: see EASL CPG 2012[1] for all drugs except for TAF.[76]
PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; TBV, telbivudine; ADV, adefovir; ALT, alanine aminotransferase.
* PegIFNα 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 (xULN) in the ETV or ⩽1.3×ULN in the TBV trial). The lower quantification limit of HBV DNA assays was different across studies: <29 IU/ml for TAF studies.

Table 4. Results of main studies for the treatment of HBeAg-negative chronic hepatitis B at 6 months following 48 weeks of pegylated interferon alfa (PegIFNα) and at 48 or 52 weeks of nucleos(t)ide analogue therapy.

	PegIFN	Nucleoside analogues			Nucleotide analogues		
	PegIFNα2a	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	180 μg	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
HBV DNA <60–80 IU/ml	19%	72–73%	88%	90%	51–63%	93%	94%
ALT normalisation#	59%	71–79%	74%	78%	72–77%	76%	83%
HBsAg loss	4%	0%	0%	0%	0%	0%	0%

References: EASL CPG 2012[1] for all drugs except for TAF.[74]
PegIFNα, pegylated interferon alfa; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; TBV, telbivudine; ADV, adefovir; ALT, alanine aminotransferase.
* PegIFNα 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 ETV or ⩽1.3-times the ULN in the TBV trial). The lower quantification limit of HBV DNA assays was different across studies: for TAF studies it was <29 IU/ml.

often with a regression of established cirrhosis.[1,34] Moreover, complications of pre-existing decompensated cirrhosis, particularly at an early stage of decompensation, improve or even disappear and the need for liver transplantation is dramatically reduced.[1]

HCC may still develop and remains the major concern for CHB patients treated with NAs.[24,25] Long-term therapy with NAs appears to favourably impact HCC incidence when data from randomised or matched controlled studies are considered.[24,25] After the first 5 years of ETV or TDF therapy in CHB patients, recent data suggest that the HCC incidence is decreasing further, with the decrease being more evident in patients with baseline cirrhosis.[93] In addition, HCC seems to be the only factor affecting long-term survival in ETV or TDF treated CHB patients with or without compensated cirrhosis.[94] Since NAs are used in the majority of CHB patients because of their favourable effects on the overall long-term outcome, the main clinical challenge is to identify the patients at risk of HCC who require close surveillance. The Asian HCC risk scores, GAG-HCC, CU-HCC and REACH-B, have been validated in treated Asian CHB patients,[25] however the PAGE-B score is the only one that offers good predictability for HCC in Caucasian treated CHB patients.[28] Based on the HCC risk scores, patients can be classified into those at low, medium and high risk of HCC. Patients in the low HCC risk group have no or negligible probability of HCC development and therefore may not require HCC surveillance.[25,28]

Despite the remaining risk of developing HCC, the overall survival improves in patients under long-term effective NA(s) therapy.[1,39,94–96] Loss of HBsAg during long-term NA therapy may occur in a minority of CHB patients who were initially HBeAg-positive (approximately 10–12% after 5–8 years of therapy) while is rare in patients with HBeAg-negative CHB (<1–2% after 5–8 years of therapy).[1,83]

NA discontinuation

Recommendations

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (⩾3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

Table 5. Indications for selecting ETV or TAF over TDF.*

1. Age >60 years
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
Osteoporosis
3. Renal alteration**
eGFR <60 ml/min/1.73 m^2
Albuminuria >30 mg/24 h or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dl)
Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ⩾15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

Since NA therapy does not usually achieve HBV eradication and rarely results even in HBsAg loss,[83] long-term therapeutic regimens are given in the majority of NA treated CHB patients. A widely accepted stopping rule exists only for a proportion of patients with HBeAg-positive CHB who can discontinue NAs if they achieve HBeAg seroconversion and HBV DNA undetectability and have completed 6 or preferentially 12 months of ensuing consolidation therapy.[1,56] According to the existing data, HBeAg seroconversion will remain in the majority (approximately 90%) and virological remission defined as HBV DNA <2,000–20,000 IU/ml will be maintained in ~50% of such patients at 3 years after NAs cessation.[41] Alternatively, clinicans may choose to continue NA therapy until HBsAg clearance, which represents the safest current treatment endpoint.[1]

Long-term, perhaps indefinite, NA therapy is usually given in HBeAg-negative CHB patients, who are considered to be able to safely stop NAs only if they achieve HBsAg loss.[1] Recent evidence, accumulating mainly from Asian countries, in which NAs can be discontinued in HBeAg-negative CHB patients who achieve serum HBV DNA undetectability on three separate occasions 6 months apart,[97] suggests that the discontinuation of NAs might be also feasible in this setting. An important factor affecting the probability of off-NA virological remission appears to be the duration of on-therapy HBV DNA undetectability.[41] According to the existing data, virological remission defined as HBV DNA <2,000–20,000 IU/ml will be maintained in approximately 50% of such patients 3 years after NAs cessation if they have remained for more than two years on virological remission during therapy.[41] Since such findings are based on studies with durations of on-therapy virological remission of >2 to 5 years,[41] the optimal duration of on NAs remission before discontinuation remains unclear. Since overt hepatitis flares and life-threatening episodes have been rarely reported in patients with pre-existing cirrhosis who discontinue NAs,[98] treatment discontinuation is currently discouraged in patients with cirrhosis. Moreover, NAs may be discontinued only in patients who can be followed closely with ALT and HBV DNA determinations at least during the first year following NAs cessation. Unfortunately, no reliable predictor of post-NAs remission has been identified to date. Retreatment criteria are also important, but have yet to be determined.[41] Based on reasonable clinical judgment, treatment indications for naïve CHB patients may be also applied in patients who discontinue NAs.

Management of patients with NA failure

Recommendations

- Prevention of resistance should rely on the use of first line therapy with high barrier to resistance NAs (Evidence level I, grade of recommendation 1).
- Compliance to NA therapy should be checked in all cases of treatment failure (Evidence level II-1, grade of recommendation 1).
- Management of treatment failure should be based on NAs cross-resistance data (Evidence level II-2, grade of recommendation 1).
- Treatment adaptation should be performed as soon as virologic failure under NAs is confirmed (Evidence level II-1, grade of recommendation 1).

Preventing the emergence of resistance is based on the use of NAs with high barrier to resistance and maximal viral suppression as a first line therapy (Fig. 3). The combination of NAs with low barrier to resistance, such as LAM or TBV with ADV, should be avoided, as this may lead to inappropriate viral suppression and the emergence of multidrug resistant strains. In addition, sequential monotherapies with agents with a low barrier to resistance should be strictly avoided because of the high risk of emerging multidrug resistance strains.[99]

Managing NA failures in CHB patients remains a crucial issue in countries in which ETV, TDF and TAF are not available or fully reimbursed for naïve patients or treatment experienced patients. By contrast, in countries where NAs with a high barrier to resistance have been routinely used for many years, the impact of treatment failures has become minimal. Treatment failure can be defined as primary non-response, partial virological response and virological breakthrough (see section 'Definitions of response').[100]

Primary non-response. In patients with primary non-response to any NA, it is important to check for compliance. Poor compliance is now the main cause of primary non-response. In a compliant patient with a primary non-response, genotyping of HBV strains for identifying possible resistance mutations may help in formulating a rescue strategy. Primary non-response is almost exclusively seen with ADV because of suboptimal antiviral potency and should lead to a rapid switch to TDF or ETV.

Partial virological response. Partial virological response may be encountered with all available NAs. It is always important to check for compliance. If patients receive NA with low barrier to resistance (LAM, ADV, TBV), it is recommended to change to a more potent drug without cross-resistance. Most of the time, partial virological response under ETV or TDF is associated with a very high pretreatment viral load and not the result of a lack of efficacy but rather of the potency limit of the antiviral drug. 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 given the rise in rates of virological response over time and the very low risk of resistance with long-term monotherapy with both agents. It can be assumed that the same applies to TAF. In those with plateauing levels of

HBV DNA a switch to the other drug or a combination of ETV + TDF/TAF can be envisaged especially in patients with advanced liver disease (see section 'Long-term outcome during NA').

Virological breakthrough. Virological breakthrough in compliant patients is mainly related to the development of HBV drug resistance. The rate of virological breakthrough depends on the barrier to resistance of the NA. Treatment adaptation should be performed as soon as viral breakthrough is identified and confirmed one month apart to prevent a further increase in viral load, subsequent ALT elevation and progression of liver disease including the risk of liver failure.[99,100]

Management of antiviral drug resistance

Although a concern, antiviral drug resistance has become a manageable issue. The risk of resistance is associated with high baseline HBV DNA levels, a slow decline in HBV DNA and a previous suboptimal NA treatment. Resistance should be identified by HBV DNA monitoring and ideally identification of the pattern of resistance mutations should be used to adapt treatment strategy.

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. Table 6 shows cross-resistance data for the most frequent resistant variants. Table 7 shows the recommendations for treatment adaptation.[99,100] In patients with multidrug resistance, genotypic resistance testing should be performed by a reference laboratory. Combination of TDF with ETV has been evaluated in several clinical studies and appears to be a safe option as a rescue therapy.[101–104]

PegIFNα monotherapy for CHB patients

Efficacy

Recommendations

- PegIFNα can be considered as an initial treatment option for patients with mild to moderate HBeAg-positive or -negative CHB (Evidence level I, grade of recommendation 2).
- The standard duration of PegIFNα therapy is 48 weeks (Evidence level I, grade of recommendation 1).
- The extension of the duration of PegIFNα therapy beyond week 48 may be beneficial in selected HBeAg-negative CHB patients (Evidence level II-1, grade of recommendation 2).

Only patients with mild to moderate CHB and perhaps selected patients with compensated cirrhosis but no portal hypertension should be considered for PegIFNα therapy (Table 2). In HBeAg-positive CHB patients, response rates at 6 months following 12 months of PegIFNα therapy are 20–30% (Table 3). Although most patients respond with HBeAg loss or seroconversion during the first 6 months of therapy, a 6 month course of PegIFNα and/or a lower dose are inferior to the recommended 12 month course. A combined endpoint of HBeAg loss with HBV DNA <2,000 IU/ml at 6 months post-treatment was achieved in 23% in a meta-analysis of three large trials[105] (Table 3). Among patients who achieved HBeAg loss at 6 months post-treatment, HBeAg negativity was sustained 3 years post-treatment in 81%. Rates of HBsAg loss following 12 months of treatment are 3–7%. HBsAg loss rates increase after the end of PegIFNα therapy in initially HBeAg-positive CHB patients with sustained virological responses (Table 3). Of the patients with an initial HBeAg loss, 30% experienced HBsAg loss after 3 years of follow-up. The sustainability of HBsAg loss and seroconversion after PegIFNα is good although HBsAg seroreversions have been described.[62,106]

In HBeAg-negative CHB patients, the 48-week PegIFNα registrational trial showed sustained biochemical and virological response rates of 60% and 44% at 6 months and of 31% and 28% at 3 years after the end of therapy[1,107] (Table 4). PegIFNα was less effective in HBeAg-negative patients with genotype D or E, who had sustained virological responses in the range of 20%. Few real life studies have addressed the efficacy of PegIFNα in HBeAg-negative CHB patients with genotype B or C. In a retrospective Korean study, approximately 30% of genotype C HBeAg-negative patients achieved virological response at 1 year after the end of PegIFNα.[1,108]

HBsAg loss rarely occurred during PegIFNα therapy in HBeAg-negative CHB patients, but the rate of HBsAg loss progressively increased after PegIFNα discontinuation, from 3% at month 6 to 9% at year 3 to 12% at year 5 in the registrational trial[1] (Table 4). Similar rates were confirmed by real life studies.[1,107] Overall, among sustained responders, approximately 30% clear HBsAg in the long-term.

Two studies assessed the safety and efficacy of extending the duration of PegIFNα therapy beyond 48 weeks in HBeAg-negative CHB patients. In a European randomised trial with predominantly genotype D patients, 96 compared to 48 weeks of PegIFNα therapy achieved higher rates of sustained virological response (29% *vs.* 12%, $p = 0.03$) and HBsAg loss (6% *vs.* 0%).[109] Similarly, a Chinese study including HBeAg-negative CHB patients with genotype B or C showed that 72 compared to 48 weeks of PegIFNα resulted in higher rates of sustained virological response (50% *vs.* 16%, $p = 0.001$) and HBsAg loss (36% *vs.* 10%, $p < 0.05$).[110]

Monitoring of patients treated with PegIFNα

Recommendations

- All CHB patients treated with PegIFNα should be followed with periodical assessments of at least full blood count, ALT, TSH, serum HBV DNA and HBsAg levels (Evidence level I/II-2, grade of recommendation 1).
- HBeAg-positive CHB patients treated with PegIFNα should be also followed with periodical assessments of HBeAg and anti-HBe (Evidence level I, grade of recommendation 1).
- CHB patients with virological response after PegIFNα therapy should remain under long-term follow-up because of the risk of relapse (Evidence level II-2, grade of recommendation 1).

In patients treated with PegIFNα, full blood counts and serum ALT levels should be monitored monthly and TSH should be monitored every 3 months.[1] All patients should be monitored for safety through 12 months of treatment. Serum HBV DNA and HBsAg levels in all CHB patients and HBeAg and anti-HBe in

HBeAg-positive CHB patients should be checked at 3, 6 and 12 months of PegIFNα treatment and at 6 and 12 months post-treatment. Sustained serum HBV DNA <2,000 IU/ml, or even better HBsAg loss, together with ALT normalisation in all CHB patients as well as with HBeAg seroconversion in HBeAg-positive CHB patients are the desired treatment endpoints. Sustained virological response after PegIFNα is usually associated with remission of the liver disease, but all such patients require long-term follow-up because of the risk of exacerbation with development of HBeAg-negative CHB or even of HBeAg seroreversion in initially HBeAg-positive patients. The risk of HBV reactivation seems to diminish over time. In patients with undetectable HBV DNA (and negative HBeAg), HBsAg should be checked at 12 month intervals, as the rate of HBsAg loss increases over time. Patients who become HBsAg-negative should be tested for anti-HBs.

Predictors of PegIFNα response and stopping rules

Recommendations

- In HBeAg-positive CHB patients, HBsAg levels >20,000 IU/ml for genotype B and C, or no decline of HBsAg levels for genotype A and D, at 12 weeks of PegIFNα therapy are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 2).
- In HBeAg-positive CHB patients with genotype A-D, HBsAg levels >20,000 IU/ml at 24 weeks of PegIFNα therapy are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 2).
- In HBeAg-negative CHB patients with genotype D, a combination of no decrease in HBsAg levels and <2 $\log_{10}$ IU/ml reduction in serum HBV DNA levels at 12 weeks of PegIFNα therapy predicts no response and should be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 1).

Pretreatment. In HBeAg-positive CHB patients, pretreatment predictors of response are low viral load, high serum ALT levels (above 2–5 times ULN), HBV genotype and high activity scores on liver biopsy. HBV genotypes A and B have been shown to be associated with higher rates of HBeAg seroconversion and HBsAg loss than genotypes C and D.

In HBeAg-negative CHB patients, high baseline ALT, low baseline HBV DNA, younger age, female gender and HBV genotype were independent predictors of response to PegIFNα therapy but the negative and positive values of these variables are low. Patients with genotypes B or C had a better chance of response than genotype D patients.[1] Using pooled data from several studies of PegIFNα therapy in HBeAg-negative CHB patients, a baseline score system (ranging from 0–7) that combined five variables (HBV genotype, HBV DNA, ALT, HBsAg levels and age) identified patients with high and low likelihood of response, but this score has not been validated yet.[111,112] Baseline host genetic testing to prioritize CHB patients for PegIFNα therapy is not currently recommended in clinical practice, as the initial promising results were not confirmed in subsequent studies.[113,114]

During treatment. The most important on-treatment predictor of response to PegIFNα is serum HBsAg levels,[105] although they are influenced by HBV genotype.[115] In HBeAg-positive CHB patients, a decline of HBsAg levels below 1,500 IU/ml at 12 weeks is a reasonable predictor of HBeAg seroconversion (positive predictive value: 50%), while HBsAg levels >20,000 IU/ml for HBV genotype B and C or no decline of HBsAg levels for HBV genotype A and D are associated with a very low probability of subsequent HBeAg seroconversion[105] (Fig. 4). At week 24 HBsAg levels >20,000 IU/ml predict no response regardless of genotype (Fig. 4). A substantial HBV DNA decrease at 12 weeks has been associated with a 50% chance of HBeAg seroconversion. Also, HBeAg levels and immunologically induced ALT flares followed by a HBV DNA decrease are associated with more frequent HBeAg seroconversion. However, clinically meaningful cut-offs for HBV DNA and HBeAg levels as a tool for on-treatment response prediction have not been reported, these are based on validated studies using adequate outcomes.[116]

In HBeAg-negative CHB patients, a combination of a lack of decrease in HBsAg levels and <2 $\log_{10}$ IU/ml decline in HBV DNA at 12 weeks of PegIFNα predicts a no response in genotype D patients (negative predictive value: 100%) (Fig. 4). This stopping rule would allow approximately 20% of patients to discontinue PegIFNα.[1,117,118] No robust on-treatment stopping rules have been developed for HBeAg-negative CHB patients with genotype B or C and very few data are available for those with genotype A and E.[118] Some studies have also looked for

Table 6. Cross-resistance data for the most frequent resistant HBV variants.

HBV variant	LAM	LDT	ETV	ADV	TDF/TAF*
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	I	S	R	I
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

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).

ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; ADV, adefovir.

* *In vitro* data for tenofovir, *in vivo* data for TDF, no clinical data for TAF.

Table 7. Management of patients who develop NA resistance.

Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistance: switch to TDF or TAF If HBV DNA plateaus: add ETV*** or switch to ETV
TDF or TAF resistance**	If LAM-naïve: switch to ETV If LAM-R: add ETV*
Multidrug resistance	Switch to ETV plus TDF or TAF combination

ETV, entecavir; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; LAM, lamivudine; ADV, adefovir; TBV, telbivudine.
* The long-term safety of these combinations is unknown.
** Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile.
*** Especially in patients with ADV resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted.

on-treatment positive predictors of sustained response. For HBeAg-negative CHB patients with non-D genotype, a $\geqslant$10% decline in serum HBsAg from baseline to week 12 of PegIFNα treatment had a higher probability of achieving a sustained response than those with a <10% decline (47% *vs.* 16%, p <0.01) but the positive predictive value was low (~50%).[107]

Safety of PegIFNα

PegIFNα therapy is associated with considerable side effects although patients with HBV infection seem to tolerate it reasonably well because they are often younger and have less comorbidity than patients who were treated with this agent in the setting of HCV infection.[1] The most frequently reported side effects are flu-like syndrome, myalgia, headache, fatigue, weight loss, depression, hair loss and local reactions at the site of injection. Hepatitis flares may occur which can result in decompensation of liver disease, therefore PegIFNα is contraindicated in patients with decompensated cirrhosis. PegIFNα treatment is also associated with mild myelosuppression, but neutropenia and thrombocytopenia are usually well managed with dose-reduction and only rarely result in clinically significant infection or bleeding. The combination of PegIFNα with telbivudine is contraindicated due to a high risk of neuropathy.

Long-term outcome after PegIFNα

Recommendation

- Patients with sustained responses after PegIFNα therapy and high baseline HCC risk should remain under surveillance for HCC even if they achieve HBsAg loss (Evidence level III, grade of recommendation 1).

The majority of patients who achieve sustained off-treatment responses after IFNα or PegIFNα therapy maintains such responses during long-term follow-up of at least 5 years.[119] In sustained responders, there is no progression of liver disease and baseline liver histological lesions improve.[1] HCC may still develop after PegIFNα therapy, even in patients with sustained off-treatment responses, particularly in those with pre-existing cirrhosis.[120] The benefit from PegIFNα therapy on the HCC incidence seems to be more clear in Asian patients[120] and perhaps superior than that of NA therapy.[121] In addition, old cohort studies with standard IFNα and systematic reviews show that the incidence of HCC is decreased in IFNα treated compared to untreated CHB patients, with such an effect being clearer in Asian patients and those with sustained off-treatment responses and/or compensated cirrhosis.[1,24] Cohort studies in both HBeAg-positive and HBeAg-negative CHB have shown that courses of standard IFNα treatment result in improved overall long-term outcomes including survival in patients with sustained off-treatment responses.[1] Survival data are not available for PegIFNα therapy, but the same favourable outcomes are expected if sustained off-treatment responses are achieved. Rates of HBsAg loss in sustained responders are gradually increasing approaching 50% at 5 years after the end of therapy.[119]

Combination therapy for CHB

NA plus NA

Recommendations

- *De novo* combination therapy with two NAs with high barrier to resistance (ETV, TDF, TAF) is not recommended (Evidence level I, grade of recommendation 1).
- In treatment-adherent patients with incomplete suppression of HBV replication reaching a plateau during either ETV or TDF/TAF long-term therapy, a switch to the other drug or combining both drugs may be considered (Evidence level III, grade of recommendation 2).

There have been only a few studies evaluating the role of *de novo* combination therapy with potent NAs in treatment naïve chronic HBV infection. In a large prospective multicentre study, HBeAg-positive and –negative CHB patients were randomised to either ETV or ETV plus TDF.[122] The primary endpoint (HBV DNA <50 IU/ml at week 96) was reached in 76% and 83% of patients treated with mono- or combination therapy, respectively (p = 0.088). In the subgroup of HBeAg-positive patients, ETV/TDF combination achieved significantly higher rates of HBV DNA <50 IU/ml (80% *vs.* 70%, p = 0.046), which was entirely attributable to the HBeAg-positive subgroup with baseline HBV DNA levels $\geqslant 10^8$ IU/ml (79% *vs.* 62%). However, no difference was found in the rate of HBeAg seroconversions. None of the patients developed resistance, whereas ALT normalisation was observed more frequently in the ETV monotherapy group (82% *vs.* 69%). This combination did not provide added value in terms of HBsAg kinetics.[123]

In a second double-blind study, HBeAg-positive treatment naïve patients with high HBV DNA and normal ALT levels were randomly assigned to either TDF plus placebo or a combination of TDF plus emtricitabine for 192 weeks.[124] At week 192, 55% and 76% of patients in the TDF monotherapy and the combination group respectively reached the primary endpoint, which was HBV DNA <69 IU/ml (p = 0.016). Of those who did not meet the primary endpoint, the majority had low levels of ongoing HBV replication, with serum HBV DNA <500 IU/ml. However, HBeAg seroconversion occurred in only 5% of patients (all in the monotherapy group), while no patient developed HBV resistance.

Although both of the above studies showed a higher percentage of complete HBV DNA suppression with NA combination therapy in HBeAg-positive patients with high baseline viral load (HBV DNA $>10^8$ IU/ml), the differences in terms of on-treatment HBV DNA levels and clinical/serological endpoints observed with both strategies are not strong enough to recommend *de novo* combination for this group of patients.

The optimal management of patients with incomplete suppression of HBV replication during long-term treatment with potent NAs (ETV, TDF or TAF) is still a matter of debate. In most of these patients a continuous decline in HBV DNA levels can be observed when continuing the same agent. This approach has been shown to be safe, effective and has not been associated with the development of drug resistance in large prospective long-term studies.[1,125] So far, there are also no convincing data demonstrating that the presence of a minimal residual viremia with HBV DNA levels <69 IU/ml may have any unfavourable effects with respect to on-treatment disease progression or HCC risk in patients without cirrhosis.[126] We therefore do not recommend changing the initial treatment strategy in patients with low level and or declining HBV DNA concentrations on a potent NA monotherapy.

However, in patients with decompensated cirrhosis, not achieving a virologic response defined as HBV DNA <20 IU/ml has been shown to be a significant risk factor for developing HCC (HR = 7.74; 95% CI 1.34–44.78; $p = 0.022$) but not in those with compensated cirrhosis ($p = 0.749$).[127]

The long-term consequences of on-treatment HBV DNA levels plateauing above 69 IU/ml but being below 2,000 IU/ml are unclear. As the above mentioned studies showed some advantages of combining NAs in terms of HBV DNA suppression this approach can be considered, and is especially recommended for those with established cirrhosis. A recent retrospective study in ETV (0.5 mg daily dose) treated patients with incomplete HBV DNA response also showed that adding TDF is superior with respect to viral suppression and ALT normalisation as compared with continuing ETV monotherapy with either 0.5 mg or the higher 1.0 mg daily dose.[128,129] Switching to another potent NA (*i.e.*, from ETV to TDF/TAF or vice versa) may also sometimes lead to an improved response.

NA plus PegIFNα

Recommendations

- *De novo* combination of NA and PegIFNα is not recommended (Evidence level I, grade of recommendation 1).
- In treatment naïve HBeAg-positive patients, short-term pretreatment with a NA before PegIFNα is not recommended (Evidence level II, grade of recommendation 1).
- In long-term NA suppressed CHB patients, adding PegIFNα or switching to PegIFNα is not recommended (Evidence level II, grade of recommendation 1).

The combination of NA and PegIFNα has been used in treatment naïve and NA suppressed CHB patients. For treatment naïve patients, there is no robust evidence that a *de novo* combination of PegIFNα and NA is superior compared to PegIFNα or NA alone. Previous studies with LAM and or ADV combined with PegIFNα failed to show an advantage of the combination therapy.[1,130] In a recent randomised controlled trial, the 72-week HBsAg loss rates were superior in the PegIFNα and TDF treated patients compared to those observed in patients receiving PegIFNα alone or TDF alone (9% *vs.* 3% *vs.* 0%) but the overall rates were low and mainly confined to genotype A patients.[62,131] For treatment naïve patients, there is also no robust evidence that short-term

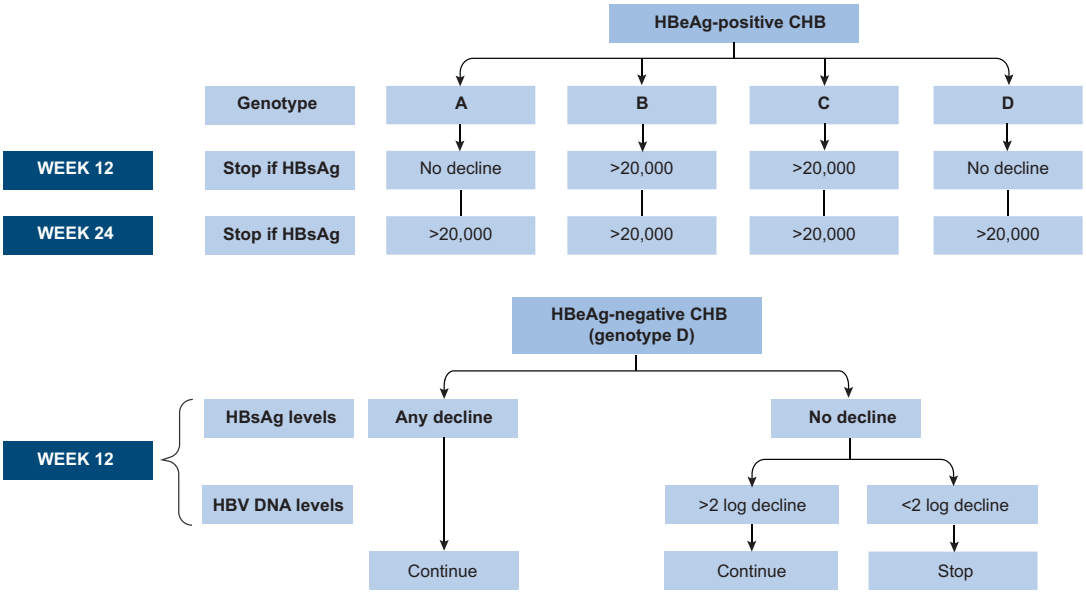


Fig. 4. Week 12 and 24 stopping rules for HBeAg-positive and -negative patients treated with PegIFNα. These rules are based upon viral genotype, HBsAg and HBV levels.

pretreatment with NA improves the rates of sustained response to PegIFNα.[130,132,133] The multicentre ARES study demonstrated that a 24-week course of PegIFNα, given to a small group of HBeAg-positive patients who were on ETV therapy for only 24 weeks, can improve the kinetics of HBeAg, HBV DNA and HBsAg, compared to those on ETV monotherapy, but a PegIFNα monotherapy arm was missing.[134]

In CHB patients under long-term effective virological remission by NA treatment, PegIFNα can be used as a 'switch to' or 'add-on' strategy. In HBeAg-positive CHB, two recent Chinese studies assessed the efficacy and safety of switching to PegIFNα for patients on long-term effective NA therapy. Following a 48-week course of PegIFNα, 6–20% of patients cleared HBsAg. Baseline HBsAg <1,500 IU/ml predicted the serological responses.[135,136] Two additional Asian studies assessed whether a 48-week course of add-on PegIFNα was superior to long-term NA therapy in HBeAg-positive patients.[137,138] While the HBsAg decline was superior in the combination group, the HBsAg loss rates did not increase significantly.

In HBeAg-negative CHB patients under NA treatment, two multicentre European studies have assessed the safety and efficacy of a 48-week add-on course of PegIFNα.[139,140] These two studies demonstrated that HBsAg kinetics were fostered by the addition of PegIFNα, but only a few patients cleared HBsAg. HBsAg levels at baseline and week 12 may predict HBsAg decline and/or HBsAg loss. There are no studies assessing the safety and efficacy of switching to PegIFNα monotherapy in HBeAg-negative CHB patients under long-term NA therapy.

As all these studies of PegIFNα therapy in patients under long-term NA therapy increase cost and side effects, this strategy should be carefully assessed in each individual patient weighing up all potential advantages and disadvantages.

Treatment of patients with decompensated cirrhosis

Recommendations

- Patients with decompensated cirrhosis should be immediately treated with a NA with high barrier to resistance, irrespective of the level of HBV replication, and should be assessed for liver transplantation (Evidence level II-1, grade of recommendation 1).
- PegIFNα is contraindicated in patients with decompensated cirrhosis (Evidence level II-1, grade of recommendation 1).
- Patients should be closely monitored for tolerability of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction (Evidence level II-2, grade of recommendation 1).

Patients with decompensated cirrhosis should be referred for liver transplantation and treated with NAs as early as possible, with the goal of achieving complete viral suppression in the shortest time possible. ETV or TDF are the preferred treatment options and both drugs have been shown to be effective but also generally safe in patients with decompensated disease.[1,141–145] The licensed ETV dose for patients with HBV decompensated cirrhosis is 1 mg (instead of 0.5 mg for patients with compensated liver disease) once daily. Less potent NAs are not recommended as they have been demonstrated to have inferior outcomes as compared to potent ones.[141,146] Despite an overall high safety profile, concerns remain that development of lactic acidosis in patients with decompensated cirrhosis may be a class effect of NAs, and close monitoring for adverse events is especially recommended for patients with a MELD score >22 and impaired kidney function.[1,147] All NAs must be adjusted to renal function. Because of its favourable safety profile, TAF might be also an interesting treatment option in patients with decompensated disease, especially in those with kidney dysfunction. However, studies concerning the safety and efficacy of TAF in these patient populations are lacking. PegIFNα is contraindicated in patients with decompensated liver disease.

The main goal of NA treatment in patients with decompensated liver disease is to achieve clinical recompensation and to avoid liver transplantation.[1,57] There is strong evidence that antiviral therapy significantly modifies the natural history of decompensated cirrhosis, improving liver function and increasing survival.[57,58,148] Meta-analyses demonstrated an overall and transplant-free survival in NA treated patients of more than 80%, respectively.[58,59] Approximately 35% of treated patients can be delisted for liver transplantation, and an improvement of Child-Pugh Score ⩾2 observed in at least 40–50%. Patients with early treatment initiation had better clinical outcomes than those with delayed treatment.[148] High baseline Child-Pugh or MELD scores are predictors of poor survival meaning that the disease may have progressed beyond the point of no return.[58,148–150] In contrast, an improvement in MELD or Child-Pugh score early on-treatment is highly predictive of transplant-free survival.[1,148,149] Undetectable HBV DNA levels can be achieved in >80% after 1 year of treatment, and are associated with a lower risk of HCC development.[58,127,148] Lifelong treatment is recommended for all patients with decompensated disease. Even under effective NA therapy, the risk of developing HCC is high in these patients, and therefore careful long-term HCC surveillance is mandatory.[1]

Prevention of HBV recurrence after liver transplantation

Recommendations

- All patients on the transplant waiting list with HBV related liver disease should be treated with NA (Evidence level II, grade of recommendation 1).
- Combination of hepatitis B immunoglobulin (HBIG) and a potent NA is recommended after liver transplantation for the prevention of HBV recurrence (Evidence level II-1, grade of recommendation 1).
- Patients with a low risk of recurrence can discontinue HBIG but need continued monoprophylaxis with a potent NA (Evidence level II-1, grade of recommendation 2).
- HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA (Evidence level II-2, grade of recommendation 1).

Before the advent of NA therapy, recurrent HBV infection in liver transplantation was a major problem.[151] All putative patients for liver transplantation should therefore be treated with NA therapy with the aim of achieving an undetectable HBV DNA level.[1] NA therapy in combination with HBIG reduces the risk of graft infection to <5%.[1,151] Potent NA therapy allows a more efficient combination treatment with synergistic effects and better tolerability with the aim of achieving anti-HBs levels of ⩾50–100 IU/L. In selected patients (*i.e.*, HBV DNA negative at liver transplantation), a short course or HBIG free regimens can be considered.[151] In selected patients, ETV prophylaxis without HBIG has been shown to be safe and effective in preventing HBV recurrence.[152] Conversely, lifelong combination therapy should be given to patients who are at a high risk for HBV recurrence, namely those who are HBV DNA positive at the time of liver transplantation, who are HBeAg-positive, have HCC, and HDV or HIV co-infection.[153–155] In the setting of liver transplantation, nephrotoxicity should always be considered and renal function should be carefully monitored because of the concomitant use of calcineurin inhibitors.

When the immune system is therapeutically suppressed in the context of liver transplantation, there is potential for HBV reactivation in HBsAg-negative patients receiving donor organs with evidence of past HBV infection (anti-HBc positive). These patients usually receive receive lifelong LAM prophylaxis.[156]

Treatment in special patient groups with HBV infection

HIV co-infected patients
Recommendations

- All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count (Evidence level II-2, grade of recommendation 1).
- HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen (Evidence level I for TDF, II-1 for TAF, grade of recommendation 1).

European and American guidelines on the management of HIV infected patients recommend the initiation of ART in HIV/HBV co-infected patients irrespective of CD4 cell count due to the increased risk of fibrosis progression, cirrhosis and HCC.[157,158] All persons with HIV/HBV co-infection should receive ART including either TDF or TAF, which have antiviral activity against HIV and HBV. Stopping TDF- or TAF-containing ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis. Drug toxicity (renal, bone density, liver) should be closely monitored during ART. ETV represents an alternative anti-HBV treatment without a strong activity against HIV.[157] At present, limited data exists on the use of TAF in HIV/HBV co-infected patients. In 72 HIV/HBV co-infected patients with a stable suppression of HIV and HBV DNA, switching ART from a TDF- to a TAF-containing regimen maintained HIV and HBV suppression in >90% of patients, with improved eGFR and bone density parameters.[159] Persons with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes.[158] Because TDF, TAF and possibly also ETV monotherapy can cause HIV resistance mutations, all HBsAg-positive patients should be screened for HIV before these drugs are used in the treatment of HBV infection.

HDV co-infected patients
Recommendations

- PegIFNα for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease (Evidence level I, grade of recommendation 1).
- In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1).
- PegIFNα treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated (Evidence level II-2, grade of recommendation 2).

At present, PegIFNα is the only available drug that has been proven to have some antiviral efficacy against chronic HDV infection.[1,160] Studies applying PegIFNα showed on-treatment virologic response rates of about 17–47%.[1] The rate of HDV RNA negativity 24 weeks after treatment cessation was, however, rather low (approximately 25%), and late relapses of HDV replication beyond week 24 after stopping therapy occurred in more than 50% of the responder patients, thus challenging the concept of sustained virologic response in HDV-HBV co-infection.[161] Hence, long-term follow-up HDV RNA monitoring is recommended for all treated patients as long as HBsAg is present in serum. HBsAg loss may develop in the long-term follow-up in approximately 10% of PegIFNα patients and can be taken as a marker of cure from HDV infection.[161,162]

Several studies tried to increase efficacy by increasing treatment duration.[163,164] However, clear evidence is lacking to confirm that this approach is beneficial for most chronically HDV infected patients. Even after 96 weeks of PegIFNα therapy, alone or in combination with TDF, 24-week post-therapy relapses occurred in 36–39% of the patients with on-treatment response.[165]

The likelihood of the long-term response to PegIFNα can be estimated to some extent by HDV RNA and HBsAg kinetics at weeks 12 and 24.[164,166–169] However, stopping PegIFNα prematurely at this stage is not recommended, if treatment is well tolerated, as the negative predictive values of these markers are not very strong, and late responses may occur in patients with early non-response. Furthermore, long-term follow-up studies suggest that an IFNα based therapy *per se* can be taken as an independent factor associated with a lower likelihood of disease progression, and to develop clinical endpoints.[162,170]

Neither NAs nor ribavirin showed significant effects on HDV RNA levels in patients with HDV infection.[1] Although HDV is

often the predominant virus in this co-infection, considerable fluctuating activity of HDV and HBV or both viruses, including alternating predominance can be seen during the natural history of this chronic co-infection.[1] NA treatment is recommended for those patients with HBV DNA levels being persistently above 2,000 IU/ml, and might be considered in order to block residual HBV replication in those with advanced liver disease. In patients with decompensated liver disease, PegIFNα should not be used and these patients should be evaluated for liver transplantation. NA should be considerd in all patients with decompensated disease if HBV DNA is detectable.

HCV co-infected patients
Recommendations

- Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment (Evidence level II, grade of recommendation 1).
- HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely (Evidence level II-2, grade of recommendation 2).
- HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation (Evidence level II, grade of recommendation 1).

In patients with chronic HBV infection, HCV co-infection accelerates liver disease progression and increases the risk of HCC.[1,171,172] Therefore, all chronic HBV patients should be screened for HCV as well as for other blood bourne viruses.[1,171,173]

With the advent of effective DAA therapy, uptake of antiviral therapy for HCV is increasing rapidly. Sustained virological response rates for HCV in HBV and HCV co-infected patients are comparable with those in HCV mono-infected patients.[173] There is a potential risk of HBV reactivation during DAAs therapy or after clearance of HCV. It must be noted that most patients with HCV/HBV co-infection, and advanced disease should be on effective NA therapy. Following a series of case reports, the US Food and Drug Administration has now issued a warning about the risk of HBV reactivating in some patients treated with DAAs for HCV. They identified 24 cases of HBV reactivation in HCV/HBV co-infected patients treated with DAAs during a 31-month period from November 2013 to July 2016.[174–177] More recent data confirms the risk of HBV reactivation associated with DAA therapy. In one publication, out of 103 patients with evidence of previous HBV exposure (HBsAg-negative, anti-HBc positive) undergoing DAA therapy, none experienced reactivation.[178] In another publication, 3 out of 10 patients with HBsAg-positive status demonstrated significant reactivation with two significant clinical events.

Out of the 327 patients treated with DAA therapy, 124 had evidence of anti-HBc with none experiencing any clinical or virological sequelae.[179]

Acute hepatitis B
Recommendations

- More than 95% of adults with acute HBV hepatitis do not require specific treatment, because they will fully recover spontaneously (Evidence level II-2, grade of recommendation 1).
- Only patients with severe acute hepatitis B, characterised by coagulopathy or protracted course, should be treated with NA and considered for liver transplantation (Evidence level II-2, grade of recommendation 1).

In patients with acute hepatitis B, preventing the risk of acute or subacute liver failure is the main treatment goal. Improving quality of life by shortening the disease associated symptoms as well as lowering the risk of chronicity can be also regarded as relevant goals of treatment. As outlined in the natural course of disease, acute HBV infection will recover clinically and virologically including seroconversion to anti-HBs without antiviral therapy in more than 95% of adults. A potentially life-threatening disease manifestation is severe or fulminant acute hepatitis B. Characteristics of severe acute hepatitis B are coagulopathy (most studies defined this as international normalised ratio [INR] >1.5), or a protracted course (*i.e.*, persistent symptoms or marked jaundice for >4 weeks), or signs of acute liver failure.[107,180] Although randomised controlled trials are lacking, several cohort studies indicate that the early antiviral therapy with highly potent NAs can prevent progression to acute liver failure and subsequently liver transplantation or mortality.[107,181] This effect, however, is not seen if antiviral therapy is initiated late in the course of severe acute hepatitis B in patients with already manifested acute liver failure and advanced hepatic encephalopathy.[182] Data supports the use of TDF, ETV or even LAM. One single-center retrospective analysis from Hong Kong reported a higher short-term mortality in patients with acute exacerbation of chronic hepatitis B (not primary hepatitis B infection) upon treatment with ETV compared to historic controls treated with LAM.[183] Large case series, however, support that TDF, ETV or LAM can be safely used in acute severe hepatitis B.[181,184] In principle, TAF should be also effective in this setting, but no data are currently available on the use of TAF in severe acute hepatitis B. The use of glucocorticoids in acute severe hepatitis B is supported by older studies, but these studies in most cases did not include current antiviral drugs.[185] The management of acute liver failure and the indication for liver transplantation are discussed in detail in separate EASL CPGs.[151,180] Early NA treatment does not increase the risk of chronicity[181,186]; in fact, observational data from a multicentre cohort even indicated reduced rates of chronicity, if NA treatment was initiated within 8 weeks of acute hepatitis B presentation in genotype A infected individuals.[187]

Children
Recommendations

- In children, the course of the disease is generally mild, and most of the children do not meet standard treatment indications. Thus, treatment should be considered with caution (Evidence level II-3, grade of recommendation 1).
- In children or adolescents who meet treatment criteria, ETV, TDF, TAF, and PegIFNα can be used in this population (Evidence level II-2, grade of recommendation 2).

Chronic HBV infection runs an asymptomatic course in most children, but the lifetime risk of significant clinical complications is not negligible. Since the World Health Organization recommended global HBV vaccination, the incidence of HBV in children has declined worldwide.[188] Issues around the characterisation of the phase of chronic HBV infection, and the indications for treatment, exist in the paediatric population as well, compounded by an enhanced requirement for safety, and thus extrapolation from adult strategies may be unhelpful. Treatment indications should be carefully evaluated,[1] and other co-morbidities, such as non-alcoholic fatty liver disease considered. Overall, a conservative approach is warranted. A joint EASL-ESPHAGN review provides a detailed relevant review.[189,190]

Conventional IFNα, LAM, ADV, ETV and TDF have been evaluated for safety and efficacy in children, which were comparable to adults.[1,190] In a study including adolescents 12 to <18 years old with HBeAg-positive and negative chronic HBV hepatitis, 72 weeks of TDF compared to placebo achieved significantly higher rates of virological response (HBV DNA <400 copies/ml: 89% *vs.* 0%, p <0.001) and ALT normalisation (74% *vs.* 31%, p <0.001), but similarly low HBeAg clearance rates. TDF proved safe and no patient developed resistance. Another recent study with ETV in adolescents confirmed no improvement in HBeAg seroconversion rates in cases with normal ALT (<30 IU/L).[188,189,191] ETV has also been studied in children between the ages of 2–12.[192]

Healthcare workers
Recommendations

- HBV infection alone should not disqualify infected persons from the practice or study of surgery, dentistry, medicine, or allied health fields (Evidence level III, grade of recommendation 1).
- Healthcare workers performing exposure prone procedures with serum HBV DNA >200 IU/ml may be treated with NA to reduce transmission risk (Evidence level II-2, grade of recommendation 2).

According to the recommendations of Center for Disease Control (CDC), HBV infection alone should not disqualify infected persons from the practice or study of surgery, dentistry, medicine, or allied health fields.[193] However, percutaneous injuries sustained by healthcare personnel during certain surgical, obstetrical, and dental procedures provide a potential route of HBV transmission to patients as well as providers.[194] Thus, healthcare workers may require antiviral therapy, even if they do not fulfill the typical indications for treatment, to reduce direct transmission during exposure prone procedures to patients. Policies for HBsAg-positive healthcare workers vary among countries. No prospective clinical trials are available to demonstrate the efficacy of antiviral treatment for preventing transmission by healthcare workers, but no HBV transmissions from healthcare workers to patients have been reported, if the healthcare worker has serum HBV DNA levels below 200 IU/ml. Thus, healthcare workers, including surgeons, gynaecologists and dentists, who are HBsAg-positive with HBV DNA >200 IU/ml may be treated with a potent NA (*i.e.*, ETV, TDF, TAF) to reduce levels of HBV DNA ideally to undetectable or at least to <200 IU/ml (CDC recommendation: <1,000 IU/ml; recommendation in many countries: <2,000 IU/ml) before resuming exposure prone procedures.[194] Monitoring for compliance and efficacy in practicing surgeons is required. Healthcare workers performing exposure prone procedures that are not on antiviral treatment might be more frequently retested, especially if they are tested around the HBV DNA threshold, due to fluctuations in viremia.[195] The long-term safety, efficacy, complications and economic implications of such a policy are unknown.

Pregnancy
Recommendations

- Screening for HBsAg in the first trimester of pregnancy is strongly recommended (Evidence level 1, grade of recommendation 1).
- 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 (Evidence level II-2, grade of recommendation 2).
- Pregnant women with CHB and advanced fibrosis or cirrhosis, therapy with TDF is recommended (Evidence level II-2, grade of recommendation 1).
- In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF (Evidence level II-2, grade of recommendation 1).
- In all pregnant women with high HBV DNA levels (>200,000 IU/ml) or HBsAg levels >4 $\log_{10}$ IU/ml, antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery (Evidence level 1, grade of recommendation 1).
- Breast feeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis (Evidence level III, grade of recommendation 2).

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

PegIFNα is contraindicated during pregnancy. There are no adequate and well-controlled studies of LAM, ADV and ETV in pregnant women. Reproduction studies have been performed in animal and in humans with TDF and TBV and revealed no evidence of harm to the fetus due to these drugs.[1] Among the last two agents, TDF should be preferred, because it has a better resistance profile and more extensive safety data in pregnant HBV positive women.[1,196–198]

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. In a woman of childbearing age with advanced fibrosis or cirrhosis who agrees for a "planned pregnancy" in the future, PegIFNα therapy may be tried as it is given for a finite duration. It should be noted that effective contraception is required during PegIFNα therapy. If PegIFNα is not possible or has failed, treatment with TDF has to be initiated and maintained even during a future pregnancy.

If female patients become unexpectedly pregnant during HBV therapy, treatment indications should be re-evaluated. The same treatment indications apply to women who are first diagnosed to have CHB during pregnancy. Patients with advanced fibrosis or cirrhosis should definitely continue to be treated, but the treating agent should be TDF.

The prevention of HBV perinatal transmission, which is considered to occur mainly at delivery, and causes the majority of chronic HBV infection is based on the combination of HBIG and vaccination given within 12 h of birth. This prophylaxis reduces the rate of perinatal transmission from >90% to <10%.[1] HBIG and vaccine failures occur almost exclusively in HBeAg-positive women with high HBV DNA levels (>200,000 IU/ml) and/or HBsAg level above 4–4.5 $\log_{10}$ IU/ml.[198–201] NA prophylaxis could be also useful in the few HBeAg-negative women with high levels of viremia but normal ALT levels.[198–201] These mothers should be informed that utilising a NA to reduce their viremia levels increase the effectiveness to HBIG and vaccination. LAM, TBV or TDF prophylaxis has been used in this setting during the last trimester of pregnancy. Of them, TDF is the preferred agent due to its characteristics mentioned previously. In a randomised study in pregnant HBsAg-positive women with high HBV DNA levels (>200,000 IU/ml), the rate of mother to child HBV transmission at post-partum week 28 was 0% in those treated with TDF compared to 7% in the placebo control group per protocol analysis having a similar safety profile.[198] If NA therapy is given as prophylaxis, *i.e.*, only for the prevention of perinatal transmission, its duration is not well defined (stopping at delivery or within the first 3 months after delivery). The potential advantage of stopping at delivery is no interference in breast feeding. In addition, TDF ameliorated maternal ALT elevations which can occur during pregnancy or early after delivery in untreated mothers.[202]

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. In women treated with TDF, tenofovir concentrations in breast milk have been reported but its oral bioavailability is limited and thus infants are exposed to only small concentrations.

Patients undergoing immunosuppressive therapy or chemotherapy

Recommendations

- All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level I, grade of recommendation 1).
- All HBsAg-positive patients should receive ETV or TDF or TAF as treatment or prophylaxis (Evidence level II-2, grade of recommendation 1).
- HBsAg-negative, anti-HBc positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation (Evidence level II-2, grade of recommendation 1).

In HBsAg-positive and HBsAg-negative, anti-HBc positive patients receiving chemotherapy or immunosuppressive therapy, including the established and emerging new biological response modifiers, the risk of HBV reactivation can be high, particularly if rituximab is given alone or in combination with steroids.[1] The risk of HBV reactivation can be classified as high (>10%), moderate (1–10%) or low (<1%).[52,203] Therefore, all candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg, anti-HBs and anti-HBc prior to immunosuppression treatment.

Vaccination of HBV seronegative patients is recommended. Higher doses or reinforced vaccine may be required to achieve anti-HBs response in immunocompromised patients.[1,107]

HBsAg-positive patients. All HBsAg-positive candidates for chemotherapy and immunosuppressive therapy should be urgently referred to a specialist for further assessment and diagnosis of the phase of HBV infection. All these patients should start potent NA as a treatment or as prophylaxis.

Patients with chronic hepatits B should be treated with ETV, TDF or TAF, similarly to the immunocompetent patients. Monitoring and stopping rules for NAs are the same with the immunocompetent patients.

In contrast, the optimal management of patients with chronic HBV infection, but without chronic hepatitis, remains controversial. Prophylactic administration of LAM has been shown to reduce the risk of HBV reactivation and the associated morbidity and mortality,[1] but a residual risk of HBV reactivation remains approximately in 10% of chronic HBV patients with low viremia (HBV DNA <2,000 IU/ml) and in a higher proportion of those with higher viremia levels. As recent studies suggest that ETV or TDF can be successfully used in such patients,[204] prophylaxis with ETV, TDF, TAF is recommended in this setting. Prophylaxis should continue for at least 12 months (18 months for rituximab-based regimens) after cessation of the immunosuppressive treatment and discontinued only if the underlying disease is under remission. Liver function tests and HBV DNA should be tested every 3 to 6 months during prophylaxis and for at least 12 months after NA withdrawal as a large proportion of HBV reactivations develops after NA discontinuation.[205–209]

HBsAg-negative, anti-HBc positive subjects. The risk of HBV reactivation in this group varies widely according to the virological profile, underlying disease and the type and duration of immunosuppressive regimen. These subjects can be tested for serum HBV DNA before immunosuppression. If viremic, they should be treated similarly to HBsAg-positive patients.

In the high risk group (>10%), including anti-HBc positive subjects who need to be treated with rituximab in the onco-hematological setting or those undergoing stem cell transplantation, antiviral prophylaxis is recommended. Prophylaxis should continue for at least 18 months after stopping immunosuppression and monitoring should continue for at least 12 months after prophylaxis withdrawal. LAM may be used safely in this setting although few cases of HBV exacerbation due to LAM resistance have been reported.[210–212] Prophylaxis with ETV or TDF or TAF can be also considered in HBsAg-negative, anti-HBc positive patients receiving highly immunosuppressive regimens of extended duration.[213,214]

In HBsAg-negative, anti-HBc positive subjects with moderate (<10%) or low (<1%) risk of HBV reactivation, pre-emptive therapy, not prophylaxis, is generally recommended.[205,206] The main virological event in these anti-HBc positive patients is HBsAg reappearance (seroreversion), constantly associated with hepatitis flare; by converse HBV DNA detection leads to seroreversion and hepatitis in only 50% of cases.[212] Pre-emptive therapy is based upon monitoring HBsAg and/or HBV DNA every 1–3 months during and after immunosuppression, and starting ETV, TDF or TAF treatment in case of detectable HBV DNA or HBsAg seroreversion. As HBsAg seroreversion can lead to a severe, even fatal, acute hepatitis, NA should be started as early as possible, independently of ALT levels. For selected clinical settings, characterised by long duration of immunosuppression, limited compliance to monitoring or unknown risk of viral reactivation for new biologicals, universal prophylaxis, rather than pre-emptive therapy, is recommended.

Dialysis and renal transplant patients

Recommendations

- All dialysis and renal transplant recipients should be screened for HBV markers (Evidence level II-2, grade of recommendation 1).
- HBsAg-positive dialysis patients who require treatment should receive ETV or TAF (Evidence level II-2, grade of recommendation 1).
- All HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment (Evidence level II-2, grade of recommendation 1).
- HBsAg-negative, anti-HBc positive subjects should be monitored for HBV infection after renal transplantation (Evidence level III, grade of recommendation 1).

HBV is still prevalent in dialysis and renal transplant patients and may cause significant morbidity and mortality.[1] All dialysis and renal transplant patients should be screened for HBV markers. Though vaccine responsiveness is impaired, HBV seronegative patients should be vaccinated, preferentially with a reinforced vaccine.[215,216]

All HBsAg-positive patients should be referred to a specialist for further assessment and diagnosis of the phase of HBV infection.

Dialysis patients. Patients with chronic HBV infection but not chronic hepatitis B should be monitored, as there is no strong evidence to suggest they have increased mordibity and mortality.[1] In contrast, all patients with HBeAg-positive or -negative chronic hepatitis B should receive a NA, as the preferred treatment strategy, independently of the transplantation program.[205,217,218] ETV is recommended for NA naïve patients,[219] TAF could be used for both NA naïve and NA experienced/resistant patients but studies are still ongoing.[74,76] All doses of NAs should be adjusted according to eGFR values in patients with eGFR <50 ml/min (see insert packages), except for TAF which does not require dose adjustment if eGFR is >15 ml/min. PegIFNα could be also used in selected patients. Given that dialysis may reduce ALT levels, caution must be taken to use this marker to assess treatment indications.

HBsAg-negative, anti-HBc positive subjects do not require treatment nor prophylaxis but must be monitored for HBV markers.

Renal transplant recipients. All HBsAg-positive patients should receive anti-HBV prophylaxis or treatment with a NA.[1,205,217,218] ETV is the preferred option for NA naïve patients. TDF should be avoided because of renal safety issues and may be considered only for patients with NA resistance if TAF is not available.[74,76,79] TAF could be a good treatment option for both NA naïve and resistant patients, although its efficacy and safety in this setting are currently unknown. Though several studies have used LAM in the past, this drug is not recommended because of the high risk of resistance. NA prophylaxis and treatment should be continued long-term. Long-term NA therapy has been shown to reduce liver complications and improve survival. PegIFNα is contraindicated because of the risk of rejection.

Renal function should be carefully monitored during treatment with a NAs.[79] Unexpected deterioration of renal function during NA therapy may necessitate a change of treatment or dose adaptation. Arterial hypertension and diabetes mellitus should be optimally controlled in renal transplant recipients.

HBsAg-negative, anti-HBc positive renal transplant recipients do not require prophylaxis or treatment. Monitoring of HBsAg is recommended to identify the few cases of HBsAg seroreversion in which ETV or TAF should be started immediately, irrespectively of ALT levels.

Extrahepatic manifestations

Recommendations

- Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NA (Evidence level II-2, grade of recommendation 1).
- PegIFNα should not be administered in patients with immune-related extrahepatic manifestations (Evidence level III, grade of recommendation 1).

HBV related extrahepatic manifestations include vasculitis, skin manifestations (purpura), polyarteritis nodosa, arthralgias, peripheral neuropathy and glomerulonephritis. Mixed cryoglobulinemias, positive rheumatoid factor or inflammatory markers (complement factors C3/C4, C-reactive protein, blood sedimentation rate) may be found in these patients. HBsAg-positive patients with extrahepatic manifestations and active HBV replication may respond to antiviral therapy. PegIFNα can worsen some immune mediated extrahepatic manifestations and should not be administered in HBV infected patients with immune-related extrahepatic manifestations. Although controlled studies of antiviral therapy in this setting are lacking, case reports suggest that the use of NA is safe and effective.[61,220] Plasmapheresis, corticosteroids and potentially other immune-suppressive drugs during the initial phase can be useful in addition to NA therapy in special cases.

New biomarkers of HBV infection

Viral cccDNA is the key genomic form that is responsible for the persistence of infection and was shown to persist in the liver of infected patients even after long-term NA therapy and even after HBsAg loss and seroconversion.[221,222] The regulation of the intrahepatic pool of cccDNA involves several factors including the dynamics of infection in the liver and the intrahepatic antiviral immune response.[223] Furthermore, cccDNA transcriptional activity is controlled by fine epigenetic regulation which can involve viral and host factors.[13,224] Besides the need for standardized assays, the main limitation of cccDNA studies is the requirement of liver biopsy; thus surrogate biomarkers are being evaluated (see below). It is noteworthy that not all transcripts are expressed from cccDNA, but can also be expressed from viral sequences integrated in the host genome. Viral genome replication cannot occur from these integrants, but HBsAg expression can occur either from the envelope gene in cccDNA and/or in viral integrants, explaining at least in part why quantification of HBsAg is not a perfect biomarker for intrahepatic cccDNA.[225] Quantification of cccDNA levels and its transcriptional activity will be important in clinical trials evaluating novel treatment concepts to cure HBV infection.

Hepatitis B core-related antigen (HBcrAg) is a composite biomarker comprising several antigens expressed from the precore/-core gene: HBcAg, HBeAg, and prec22 precursor protein.[226] The HBcrAg associated proteins can also be detected in circulating hepatitis B virions (Dane particles) as well as in HBV DNA negative Dane particles containing the 22 kDa precore protein and exceeding Dane particles by ~100-fold, and probably also in pregenomic RNA containing virions.[227] The marker does not overlap with HBsAg quantification, and in contrast to HBsAg, HBcrAg quantification might not be influenced by translation from integrated viral sequences. Hence, HBcrAg quantification may provide additional information concerning the translational activity of the HBV infection beyond HBsAg quantification. How to best use this new assay in the management of patients with chronic HBV infection is still a matter of debate. It has been demonstrated that the serum HBcrAg levels may partly reflect the amount of intrahepatic DNA and cccDNA in hepatocytes especially in HBeAg-positive patients.[228,229] It might also be helpful in defining the phase of chronic HBV infection, especially in HBe-negative patients, as well as predicting the long-term HCC risk.[228,230–232] Some studies suggest that this biomarker can be also used to monitor NA or PegIFNα based treatments and predicting therapeutic efficacy including the risk of relapse after stopping NAs.[233–235] Most of these studies were performed in Japan, and large correlation studies derived from Caucasian patients are lacking. Therefore, further studies are awaited providing clear evidence for a superiority of this marker for clinical decision making over established HBV biomarkers like HBsAg and HBV DNA quantification.

Circulating HBV RNA was first described in 1996 in the serum of HBV infected patients and later as a potential new marker for monitoring NA therapy. HBV RNA can be released into the serum in the form of enveloped pregenomic RNA containing virions,[236] but the full characterisation of these circulating RNAs is ongoing. Because of its strong correlation with intrahepatic cccDNA, serum HBV RNA is an interesting marker to study cccDNA transcriptional activity.[236–238] A strong correlation between quantitative serum HBV RNA dynamics and HBeAg loss in both NA and PegIFNα treated patients[239] was recently demonstrated by using a new rapid amplification of cDNA-ends with polymerase chain reaction (RACE-PCR).[240] HBV RNA quantification might be also helpful in predicting viral rebound after discontinuation of NAs.[236] It should be further explored whether the simultaneous testing of different replicative, transcriptional and translational HBV biomarkers will allow for a better definition of the individual "activity" of the chronic HBV infection helping to better predict long-term treatment outcomes.

Future treatment options

Future treatment options for HBV

Many research programs are ongoing to develop new treatment concepts that focus on the clearance of HBsAg in a significant proportion of patients, with the principle aims of: i) stopping treatment with no risk of virological relapse and no risk of liver disease progression and, ii) to further decrease the risk of HCC.

Several definitions of cure have been proposed following several international workshops.[241,242] A true cure may not be feasible because HBV DNA is integrated into the host genome. Furthermore, among persons who recovered from acute hepatitis B, viral cccDNA can still be detected in the liver explaining the reactivation of HBV replication when these 'recovered' persons are profoundly immunosuppressed. The ability to 'cure' HBV at earlier stages of liver disease would theoretically have a greater impact on reducing the risk of HCC.

The novel treatment options under pre-clinical and early clinical evaluation can be categorized into direct antivirals and immunotherapeutic agents.

Direct-acting antivirals include HBV entry inhibitors, drugs aiming at cccDNA destruction or silencing, approaches targeting viral transcripts by siRNA or anti-sense oligonucleotides, nucleocapsid assembly modulators, approaches to decrease HBsAg release in serum. This list is not meant to be comprehensive as many viral targets are currently being screened for drug discovery. First phase clinical trials are ongoing for several of these agents.[241,243]

Several potential target mechanisms for immune modulation to engender or restore HBV specific immune responses in conjunction with profound inhibition of HBV replication and HBsAg production to attain immunological control have been suggested.[241,243] Several approaches are currently being evaluated

in clinical trials to restore innate immunity in CHB patients. Among them, Toll-like receptors 7 (TLR7) agonists have been the most explored, but other strategies that restore IFNα responsiveness or other antiviral innate pathways are under investigation. The lack of a T cell mediated response in chronic HBV is partly due to the expression of co-inhibitory receptors and by the expression of immunosuppressive cytokines. Recent cancer therapies have indicated the potential of check-point inhibitors to restore anti-tumor adaptive immunity. Interesting results have been obtained for HBV in animal models and in *ex vivo* studies in humans. The main concerns of this approach are the potential induction of uncontrolled hepatitis flares and autoimmunity. Several therapeutic vaccines have been evaluated with limited success, but new vaccine formulations are under clinical evaluation.[241,243]

Combinations of antiviral therapy targeting multiple steps in the HBV lifecycle that suppress viral replication and viral antigen production and immune modulatory therapy to restore immune response to HBV will likely be needed to achieve the goal of a HBV 'cure'.

Given the focused drug discovery effort and the potential of a future 'cure' strategy, it is important to be cognisant, when considering the current clinical management of CHB patients, of the potential evolution of therapy in HBV. Patients who are willing to participate and/or are in phases of the disease that are not eligible for therapy within the current guidelines may be considered for clinical trial participation.

Future treatment options for HDV

At present, patients co-infected by HBV and HDV have to be treated with PegIFNα. The success rate of these treatments is low. Several candidates are being evaluated in clinical trials mainly in combination with PegIFNα and/or NA including HBV/HDV entry inhibitors (Myrcludex-B),[244,245] drugs inhibiting the release of HBsAg (nucleic acid polymers),[246] and inhibitors of the prenylation of the large HDV antigen.[243,247] Whenever possible, enrollment in these new clinical trials should be considered, either as a rescue of PegIFNα failure or to improve treatment success rate in naïve patients.

Unresolved issues and unmet needs

- When to start antiviral therapy in patients with HBeAg-positive chronic HBV infection
- Stopping rules for HBeAg-negative patients treated with NA
- Retreatment criteria after NA discontinuation
- How to accelerate HBsAg decline in long-term NA treated patients?
- Better baseline or on-treatment predictors of sustained treatment in patients treated with PegIFNα
- Definition of the residual risk of HCC in patients on long-term NA therapy and impact on surveillance
- Unmet need: new treatments with finite duration and high cure rates
- How to define a cure of HBV infection? Definition of novel endpoints
- Biomarkers for the cure of infection and for the cure of the liver disease

Conflict of interest

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References

[1] European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–185.
[2] Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet 2015;386:1546–1555.
[3] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–2128.
[4] Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212–2219.
[5] Chen C-L, Yang J-Y, Lin S-F, Sun C-A, Bai C-H, You S-L, et al. Slow decline of hepatitis B burden in general population: Results from a population-based survey and longitudinal follow-up study in Taiwan. J Hepatol 2015;63:354–363.
[6] Coppola N, Alessio L, Gualdieri L, Pisaturo M, Sagnelli C, Caprio N, et al. Hepatitis B virus, hepatitis C virus and human immunodeficiency virus

infection in undocumented migrants and refugees in southern Italy, January 2012 to June 2013. Euro Surveill 2015;20:30009.
[7] Hampel A, Solbach P, Cornberg M, Schmidt RE, Behrens GM, Jablonka A. Current seroprevalence, vaccination and predictive value of liver enzymes for hepatitis B among refugees in Germany. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59:578–583.
[8] Iqbal K, Klevens RM, Kainer MA, Baumgartner J, Gerard K, Poissant T, et al. Epidemiology of acute hepatitis B in the united states from population-based surveillance, 2006–2011. Clin Infect Dis 2015;61:584–592.
[9] Ott JJ, Horn J, Krause G, Mikolajczyk RT. Time trends of chronic HBV infection over prior decades – A global analysis. J Hepatol 2017;66:48–54.
[10] Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the global burden disease study 2013. Lancet 2016;388:1081–1088.
[11] Seeger C, Mason WS. Molecular biology of hepatitis B virus infection. Virology 2015;479–480:672–686.
[12] Tong S, Revill P. Overview of hepatitis B viral replication and genetic variability. J Hepatol 2016;64:S4–S16.
[13] Lucifora J, Protzer U. Attacking hepatitis B virus cccDNA–The holy grail to hepatitis B cure. J Hepatol 2016;64:S41–S48.
[14] Levrero M, Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. J Hepatol 2016;64:S84–S101.
[15] Kramvis A. Genotypes and genetic variability of hepatitis B virus. Intervirology 2014;57:141–150.
[16] Bertoletti A, Ferrari C. Adaptive immunity in HBV infection. J Hepatol 2016;64:S71–S83.
[17] Maini MK, Gehring AJ. The role of innate immunity in the immunopathology and treatment of HBV infection. J Hepatol 2016;64:S60–S70.
[18] Li Y, Si L, Zhai Y, Hu Y, Hu Z, Bei J-X, et al. Genome-wide association study identifies 8p21.3 associated with persistent hepatitis B virus infection among Chinese. Nat Commun 2016;7:11664.
[19] Mason WS, Gill US, Litwin S, Zhou Y, Peri S, Pop O, et al. HBV DNA integration and clonal hepatocyte expansion in chronic hepatitis B patients considered immune tolerant. Gastroenterology 2016;151:986–998.
[20] Kennedy PT, Sandalova E, Jo J, Gill U, Ushirolumb I, Tan AT, et al. Preserved T-cell function in children and young adults with immune-tolerant chronic hepatitis B. Gastroenterology 2012;143:637–645.
[21] Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HL, Chan HL. The role of quantitative hepatitis B surface antigen revisited. J Hepatol 2017;66:398–411. http://dx.doi.org/10.1016/j.jhep.2016.08.009.
[22] Yang R, Song G, Guan W, Wang Q, Liu Y, Wei L. The Lumipulse G HBsAg-Quant assay for screening and quantification of the hepatitis B surface antigen. J Virol Methods 2016;228:39–47.
[23] Raffetti E, Fattovich G, Donato F. Incidence of hepatocellular carcinoma in untreated subjects with chronic hepatitis B: a systematic review and meta-analysis. Liver Int 2016;36:1239–1251.
[24] Varbobitis I, Papatheodoridis GV. The assessment of hepatocellular carcinoma risk in patients with chronic hepatitis B under antiviral therapy. Clin Mol Hepatol 2016;22:319–326.
[25] Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: Assessment and modification with current antiviral therapy. J Hepatol 2015;62:956–967.
[26] Arends P, Sonneveld MJ, Zoutendijk R, Carey I, Brown A, Fasano M, et al. Entecavir treatment does not eliminate the risk of hepatocellular carcinoma in chronic hepatitis B: Limited role for risk scores in Caucasians. Gut 2015;64:1289–1295.
[27] Papatheodoridis GV, Dalekos GN, Yurdaydin C, Buti M, Goulis J, Arends P, et al. Incidence and predictors of hepatocellular carcinoma in Caucasian chronic hepatitis B patients receiving entecavir or tenofovir. J Hepatol 2015;62:363–370.
[28] Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800–806.
[29] Brouwer W, Hansen B, Raffetti E, Donato F, Fattovich G. The PAGE-B score stratifies chronic hepatitis B patients with compensated cirrhosis at high risk of hepatocellular carcinoma development with good accuracy. Hepatology 2015;62 (Suppl.):93A–207A.
[30] Brouwer W, van der Meer A, Boonstra A, Plompen E, Pas S, de Knegt R, et al. The PAGE-B score accurately predicts clinical outcome and outperforms other biomarkers over 15 years of follow-up in a diverse cohort of chronic hepatitis B patients. Hepatology 2015;62 (Suppl.):93A–207A.
[31] Li Y, Huang YS, Wang ZZ, Yang ZR, Sun F, Zhan SY, et al. Systematic review with meta-analysis: The diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. Aliment Pharmacol Ther 2016;43:458–469.
[32] European Association for Study of LiverAsociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–264.
[33] 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. Chinese J Evidence-Based Med 2009;9:8–11.
[34] Su T-H, Hu T-H, Chen C-YC-L, Huang Y-HY-W, Chuang W-L, Lin C-LC-C, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755–1764. http://dx.doi.org/10.1111/liv.13253.
[35] Lampertico P, Invernizzi F, Viganò M, Loglio A, Mangia G, Facchetti F, et al. The long-term benefits of nucleos(t)ide analogs in compensated HBV cirrhotic patients with no or small esophageal varices: A 12-year prospective cohort study. J Hepatol 2015;63:1118–1125.
[36] Kim WR, Loomba R, Berg T, Aguilar Schall RE, Yee LJ, Dinh PV, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. Cancer 2015;121:3631–3638.
[37] Coffin CS, Rezaeeaval M, Pang JX, Alcantara L, Klein P, Burak KW, et al. The incidence of hepatocellular carcinoma is reduced in patients with chronic hepatitis B on long-term nucleos(t)ide analogue therapy. Aliment Pharmacol Ther 2014;40:1262–1269.
[38] Hosaka T, Suzuki F, Kobayashi MM, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98–107.
[39] Su T-H, Hu T-H, Chen C-Y, Huang Y-H, Chuang W-L, Lin C-L, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755–1764.
[40] Wu C-Y, Lin J-T, Ho HJ, Su C-W, Lee T-Y, Wang S-Y, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. Gastroenterology 2014;147:143–151.
[41] Papatheodoridis G, Vlachogiannakos I, Cholongitas E, Wursthorn K, Thomadakis C, Touloumi G, et al. Discontinuation of oral antivirals in chronic hepatitis B: A systematic review. Hepatology 2016;63:1481–1492.
[42] Marcellin P, Xie Q, Paik SW, Flisiak R, Piratvisuth T, Petersen J, et al. Effectiveness of peginterferon Alfa-2a therapy in HBeAg-positive and HBeAg-negative patients with chronic hepatitis B: final results 3 years post-treatment of the prospective, global, observational S-collate study. J Hepatol 2017;64:S598–S599.
[43] Jacobson IM, Marcellin P, Buti M, Gane EJ, Sievert W, Tsai N, et al. Factors associated with the lack of achievement of nor-mal ALT in chronic hepatitis B (CHB) patients treated with tenofovir DF (TDF) for up to 5 years. Hepatology 2012;56:394A.
[44] Spradling PR, Bulkow L, Teshale EH, Negus S, Homan C, Simons B, et al. Prevalence and causes of elevated serum aminotransferase levels in a population-based cohort of persons with chronic hepatitis B virus infection. J Hepatol 2014;61:785–791.
[45] Chi H, Arends P, Reijnders JG, Carey I, Brown A, Fasano M, et al. Flares during long-term entecavir therapy in chronic hepatitis B. J Gastroenterol Hepatol 2016;31:1882–1887.
[46] Sonneveld MJ, Zoutendijk R, Flink HJ, Zwang L, Hansen BE, Janssen HL. Close monitoring of hepatitis B surface antigen levels helps classify flares during peginterferon therapy and predicts treatment response. Clin Infect Dis 2013;56:100–105.
[47] Kim G-A, Lim Y-S, An J, Lee D, Shim JH, Kim KM, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. Gut 2014;63:1325–1332.
[48] Seto W-K, Cheung K-S, Wong DK-H, Huang F-Y, Fung J, Liu KS-H, et al. Hepatitis B surface antigen seroclearance during nucleoside analogue therapy: surface antigen kinetics, outcomes, and durability. J Gastroenterol 2016;51:487–495.
[49] Perrillo RP, Martin P, Lok AS. Preventing hepatitis B reactivation due to immunosuppressive drug treatments. JAMA 2015;313:1617.
[50] Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology 2015;61:703–711.
[51] Mallet V, van Bömmel F, Doerig C, Pischke S, Hermine O, Locasciulli A, et al. Management of viral hepatitis in patients with haematological malignancy and in patients undergoing haemopoietic stem cell transplantation:

recommendations of the 5th European Conference on Infections in Leukaemia (ECIL-5). Lancet Infect Dis 2016;16:606–617.
[52] Perrillo RP, Gish R, Falck-Ytter YT. American gastroenterological association institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:221–244.
[53] Liu J, Yang H-I, Lee M-H, Lu S-N, Jen C-L, Batrla-Utermann R, et al. Spontaneous seroclearance of hepatitis B seromarkers and subsequent risk of hepatocellular carcinoma. Gut 2014;63:1648–1657.
[54] Kim G-A, Lee HC, Kim M-J, Ha Y, Park EJ, An J, et al. Incidence of hepatocellular carcinoma after HBsAg seroclearance in chronic hepatitis B patients: a need for surveillance. J Hepatol 2015;62:1092–1099.
[55] Papatheodoridis GV, Manolakopoulos S, Liaw YF, 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;57:196–202.
[56] Terrault NA, Bzowej NH, Chang K-M, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283.
[57] Lok AS, McMahon BJ, Brown RS, Wong JB, Ahmed AT, Farah W, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 2016;63:284–306.
[58] Peng C-Y, Chien R-N, Liaw Y-F. Hepatitis B virus-related decompensated liver cirrhosis: Benefits of antiviral therapy. J Hepatol 2012;57:442–450.
[59] Singal AK, Fontana RJ. Meta-analysis: Oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. Aliment Pharmacol Ther 2012;35:674–689.
[60] Boglione L, D'Avolio A, Cariti G, Di Perri G. Telbivudine in the treatment of hepatitis B-associated cryoglobulinemia. J Clin Virol 2013;56:167–169.
[61] Mazzaro C, Dal Maso L, Urraro T, Mauro E, Castelnovo L, Casarin P, et al. Hepatitis B virus related cryoglobulinemic vasculitis: A multicentre open label study from the Gruppo Italiano di Studio delle Crioglobulinemie – GISC. Dig Liver Dis 2016;48:780–784.
[62] Marcellin P, Ahn SH, Ma X, Caruntu FA, Tak WY, Elkashab M, et al. Combination of tenofovir disoproxil fumarate and peginterferon α-2a increases loss of hepatitis B surface antigen in patients with chronic hepatitis B. Gastroenterology 2016;150:134–144.
[63] Marcellin P, Ahn SH, Chuang W-L, Hui AJ, Tabak F, Mehta R, et al. Predictors of response to tenofovir disoproxil fumarate plus peginterferon alfa-2a combination therapy for chronic hepatitis B. Aliment Pharmacol Ther 2016;44:1–10.
[64] Lampertico P, Soffredini R, Viganò M, Minola E, Cologni G, Rizzi M, et al. 755 5-Year entecavir treatment in nuc-naïve, field-practice patients with chronic hepatitis B showed excellent viral suppression and safety profile but no prevention of HCC in cirrhotics. J Hepatol 2013;58:S306–S307.
[65] Seto WK, Lam YF, Fung J, Wong DK, Huang FY, Hung IF, et al. Changes of HBsAg and HBV DNA levels in Chinese chronic hepatitis B patients after 5 years of entecavir treatment. J Gastroenterol Hepatol 2014;29:1028–1034.
[66] Ono A, Suzuki F, Kawamura Y, Sezaki H, Hosaka T, Akuta N, et al. Long-term continuous entecavir therapy in nucleos(t)ide-naive chronic hepatitis B patients. J Hepatol 2012;57:508–514.
[67] Luo J, Li X, Wu Y, Lin G, Pang Y, Zhang X, et al. Efficacy of entecavir treatment for up to 5 years in nucleos(t)ide-naïve chronic hepatitis B patients in real life. Int J Med Sci 2013;10:427–433.
[68] Tanwandee T, Charatcharoenwitthaya P, Chainuvati S, Chotiyaputta W, Nimanong S. Efficacy and safety of entecavir treatment of chronic hepatitis B patients in real-world clinical practice. Hepatology 2013;20:672A.
[69] Marcellin P, Gane EJ, Flisiak R, Trinh HN, Petersen J, Gure S, et al. Long term treatment with tenofovir disoproxil fumarate for chronic hepatitis B infection is safe and well tolerated and associated with durable virologic response with no detectable resistance: 8 year results from two phase 3 trials. Hepatology 2014;60:313A–317A.
[70] Petersen J, Heyne R, Mauss S, Schlaak J, Schiffelholz W, Eisenbach C, et al. Effectiveness and safety of tenofovir disoproxil fumarate in chronic hepatitis B: A 3-year prospective field practice study in Germany. Dig Dis Sci 2016;61:3061–3071.
[71] Tabernero D, Sánchez-Tapias JM, Calleja JL, Moreira V, Manzano ML, Crespo J, et al. P1058 long-term efficacy of tenofovir in previously treated and naive patients. results from the spanish chronic hepatitis B registry (Ciberhep). J Hepatol 2014;60:S429.
[72] Marcellin P, Zoulim F, Hézode C, Causse X, Roche B, Truchi R, et al. Effectiveness and safety of tenofovir disoproxil fumarate in chronic hepatitis B: A 3-year, prospective, real-world study in France. Dig Dis Sci 2016;61:3072–3083.
[73] Lampertico P, Soffredini R, Yurdaydin C, Idilman R, Papatheodoridis GV, Mar-gariti E, et al. Four years of tenofovir monotherapy for NUC naïve field practice European patients suppresses HBV replication in most patients with a favorable renal safety profile but does not prevent HCC in patients with or without cirrhosis. Hepatology 2013;58:647A–705A.
[74] Buti M, Gane E, Seto WK, Chan HL, Chuang W-L, Stepanova T, et al. Tenofovir alafenamide *vs.* tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1:196–206.
[75] Agarwal K, Fung S, Seto WK, Lim YS, Gane E, Janssen HL, et al. A phase 3 study comparing tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) in patients with HBeAg-positive, chronic hepatitis B (CHB): efficacy and safety results at week 96. J Hepatol 2017;66:S478.
[76] Chan HL, Fung S, Seto WK, Chuang W-L, Chen C-Y, Kim HJ, et al. Tenofovir alafenamide *vs.* tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1:185–195.
[77] Brunetto M, Lim YS, Gane E, Seto WK, Osipenko M, Ahn SH, et al. A phase 3 study comparing tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) in patients with HBeAg-negative, chronic hepatitis B (CHB): efficacy and safety results at week 96. J Hepatol 2017;66:S25–S26.
[78] Custodio JM, Fordyce M, Garner W, Vimal M, Ling KH, Kearney BP, et al. Pharmacokinetics and safety of tenofovir alafenamide in HIV-uninfected subjects with severe renal impairment. Antimicrob Agents Chemother 2016;60:5135–5140.
[79] Lampertico P, Chan HL, Janssen HL, Strasser SI, Schindler R, Berg T. Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients. Aliment Pharmacol Ther 2016;44:16–34.
[80] Gill US, Zissimopoulos A, Al-Shamma S, Burke K, McPhail MJ, Barr DA, et al. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: can the fracture risk assessment tool identify those at greatest risk? J Infect Dis 2014;211:1–9.
[81] Maggi P, Montinaro V, Leone A, Fasano M, Volpe A, Bellacosa C, et al. Bone and kidney toxicity induced by nucleotide analogues in patients affected by HBV-related chronic hepatitis: A longitudinal study. J Antimicrob Chemother 2014;70:1150–1154.
[82] Fung S, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, et al. Tenofovir disoproxil fumarate (TDF) *vs.* emtricitabine (FTC)/TDF in lamivudine resistant hepatitis B: A 5-year randomised study. J Hepatol 2016;66:11–18.
[83] Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci 2015;60:1457–1464.
[84] Han Y, Zeng A, Liao H, Liu Y, Chen Y, Ding H. The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: A systematic review and Meta-analysis. Int Immunopharmacol 2017;42:168–175.
[85] Ahn J, Lee HM, Lim JK, Pan CQ, Nguyen MH, Ray Kim W, et al. Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. Aliment Pharmacol Ther 2016;43:134–144.
[86] Law S-T, Lee MK, Li KK, Mok CK. Comparison of efficacy and renal safety of telbivudine and entecavir in treatment-naive elderly patients with chronic hepatitis B. Eur J Gastroenterol Hepatol 2016;28:193–198.
[87] Coppolino G, Simeoni M, Summaria C, Postorino MC, Rivoli L, Strazzulla A, et al. The case of chronic hepatitis B treatment with tenofovir: an update for nephrologists. J Nephrol 2015;28:393–402.
[88] Chuang WL, Agarwal K, Hwang JS, Caruntu F, Wong F, Hann HW, et al. Continued improvement in renal laboratory parameters in CHB patients treated with tenofovir alfenamide (TAF) compared with tenofovir disoproxil fumarate (TDF) over 96 weeks. J Hepatol 2017;66:S695.
[89] Huhn GD, Tebas P, Gallant J, Wilkin T, Cheng A, Yan M, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. J Acquir Immune Defic Syndr 2017;74:193–200.
[90] Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 2016;16:43–52.
[91] Pozniak A, Arribas JR, Gathe J, Gupta SK, Post FA, Bloch M, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week

results from a single-arm, multicenter, open-label phase 3 study. J Acquir Immune Defic Syndr 2016;71:530–537.
[92] Post FA, Tebas P, Clarke A, Cotte L, Short W, Abram ME, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected adults with renal impairment: 96-week results from a single arm, multicenter, open label phase 3 study. J AIDS 2017;74:180–184.
[93] Papatheodoridis G, Yurdaydin C, Dalekos G, Buti M, Chi H, Van Boemmel F. The risk of hepatocellular carcinoma (HCC) is decreasing after the first 5 years of entecavir (ETV) or tenofovir (TDF) therapy in Caucasian chronic hepatitis B (CHB) patients. Hepatology 2016;64 (Suppl.):923A.
[94] Papatheodoridis G, Dalekos G, Yurdaydin C, Van Boemmel F, Buti M, Sypsa V, et al. Hepatocellular carcinoma (HCC) is the only factor affecting the excellent survival of Caucasian chronic hepatitis B (CHB) patients with or without cirrhosis under long-term entecavir (ETV) or tenofovir (TDF) therapy. Hepatology 2016;64 (Suppl.):35A–36A.
[95] Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients With liver cirrhosis. Hepatology 2013;58:1537–1547.
[96] Lim Y-S, Han S, Heo N-Y, Shim JH, Lee HC, Suh DJ. Mortality, liver transplantation, and hepatocellular carcinoma among patients with chronic hepatitis B treated with entecavir *vs.* lamivudine. Gastroenterology 2014;147:152–161.
[97] Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1–98.
[98] Jeng WJ, Sheen IS, Chen YC, Hsu CW, Chien RN, Chu CM, et al. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. Hepatology 2013;58:1888–1896.
[99] Zoulim F, Locarnini S. Optimal management of chronic hepatitis B patients with treatment failure and antiviral drug resistance. Liver Int 2013;33:116–124.
[100] Zoulim F, Locarnini S. Management of treatment failure in chronic hepatitis B. J Hepatol 2012;56:S112–S122.
[101] Park JY, Kim CW, Bae SH, Jung KS, Kim HY, Yoon SK, et al. Entecavir plus tenofovir combination therapy in patients with multidrug-resistant chronic hepatitis B: results of a multicentre, prospective study. Liver Int 2016;36:1108–1115.
[102] Lim Y-S, Yoo BC, Byun KS, Kwon SY, Kim YJ, An J, et al. Tenofovir monotherapy *vs.* tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: results of a randomised trial. Gut 2016;65:1042–1051.
[103] Zoulim F, Białkowska-Warzecha J, Diculescu MM, Goldis AE, Heyne R, Mach T, et al. Entecavir plus tenofovir combination therapy for chronic hepatitis B in patients with previous nucleos(t)ide treatment failure. Hepatol Int 2016;10:779–788.
[104] Petersen J, Ratziu V, Buti M, Janssen HL, Brown A, Lampertico P, et al. Entecavir plus tenofovir combination as rescue therapy in pre-treated chronic hepatitis B patients: an international multicenter cohort study. J Hepatol 2012;56:520–526.
[105] Sonneveld MJ, Hansen BE, Piratvisuth T, Jia J, Zeuzem S, Gane E, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. Hepatology 2013;58:872–880.
[106] Sonneveld MJ, Brouwer WP, van der Meer AJ. Posttreatment hepatitis B surface antigen seroreversion: the bane of combination therapy in chronic hepatitis B? Gastroenterology 2016;150:1254–1255.
[107] Lampertico P, Maini M, Papatheodoridis G. Optimal management of hepatitis B virus infection – EASL Special Conference. J Hepatol 2015;63:1238–1253.
[108] Chon YE, Kim DJ, Kim SG, Kim IH, Bae SH, Hwang SG, et al. An observational, multicenter, cohort study evaluating the antiviral efficacy and safety in korean patients with chronic hepatitis B receiving pegylated interferon-alpha 2a (Pegasys). Medicine 2016;95:e3026.
[109] Lampertico P, Viganò M, Di Costanzo GG, Sagnelli E, Fasano M, Di Marco V, et al. Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B. Gut 2013;62:290–298.
[110] Chen X, Chen X, Chen W, Ma X, Huang J, Chen R. Extended peginterferon alfa-2a (Pegasys) therapy in Chinese patients with HBeAg-negative chronic hepatitis B. J Med Virol 2014;86:1705–1713.
[111] Lampertico P, Rothe V, Caputo A, Papatheodoridis GV. A baseline predictive tool for selecting HBeAg-negative chronic hepatitis B patients who have a high probability of achieving sustained immune control with peginterferon alfa-2a. Hepatology 2014;60:1107A.
[112] Lampertico P, Messinger D, Cornberg M, Brunetto M, Petersen J, Kennedy P, et al. A genotype-specific baseline score to predict response at 48 weeks post-treatment to peginterferon alfa-2a in patients with HBeAg-negative chronic hepatitis B. J Hepatol 2016;64:S599–S600.
[113] Sonneveld MJ, Wong VW-S, Woltman AM, Wong GL, Cakaloglu Y, Zeuzem S, et al. Polymorphisms near IL28B and serologic response to peginterferon in HBeAg-positive patients with chronic hepatitis B. Gastroenterology 2012;142:513–520.
[114] Lampertico P, Viganò M, Cheroni C, Facchetti F, Invernizzi F, Valveri V, et al. IL28B polymorphisms predict interferon-related hepatitis B surface antigen seroclearance in genotype D hepatitis B e antigen-negative patients with chronic hepatitis B. Hepatology 2013;57:890–896.
[115] Brunetto MR, Marcellin P, Cherubini B, Yurdaydin C, Farci P, Hadziyannis SJ, et al. Response to peginterferon alfa-2a (40KD) in HBeAg-negative CHB: on-treatment kinetics of HBsAg serum levels vary by HBV genotype. J Hepatol 2013;59:1153–1159.
[116] Sonneveld MJ, Rijckborst V, Zwang L, Zeuzem S, Jenny Heathcote E, Simon K, et al. Hepatitis B e antigen levels and response to peginterferon: influence of precore and basal core promoter mutants. Antiviral Res 2013;97:312–317.
[117] 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.
[118] Goulis I, Karatapanis S, Akriviadis E, Deutsch M, Dalekos GN, Raptopoulou-Gigi M, et al. On-treatment prediction of sustained response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B patients. Liver Int 2015;35:1540–1548.
[119] Marcellin P, Bonino F, Yurdaydin C, Hadziyannis S, Moucari R, Kapprell HP, et al. Hepatitis B surface antigen levels: Association with 5-year response to peginterferon alfa-2a in hepatitis B e-antigen-negative patients. Hepatol Int 2013;7:88–97.
[120] Papatheodoridis GV, Cornberg M, Xie Q, Lampertico P, Burghaus I, Bakalos G, et al. Incidence and risk prediction of hepatocellular carcinoma: retrospective analysis of the S-collate study. Hepatol Int 2017;11:S4–S5.
[121] Liang K-H, Hsu C-W, Chang M-L, Chen Y-C, Lai M-W, Yeh C-T. Peginterferon is superior to nucleos(t)ide analogues for prevention of hepatocellular carcinoma in chronic hepatitis B. J Infect Dis 2016;213:966–974.
[122] Lok AS, Trinh H, Carosi G, Akarca US, Gadano A, Habersetzer F, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. Gastroenterology 2012;143:619–628.
[123] Zoulim F, Carosi G, Greenbloom S, Mazur W, Nguyen T, Jeffers L, et al. Quantification of HBsAg in nucleos(t)ide-naïve patients treated for chronic hepatitis B with entecavir with or without tenofovir in the BE-LOW study. J Hepatol 2015;62:56–63.
[124] Chan HL, Chan CK, Hui AJ, Chan S, Poordad F, Chang T-T, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 2014;146:1240–1248.
[125] Choi HN, Song JE, Lee HC, Jo HH, Lee CH, Kim BS. Efficacy of prolonged entecavir monotherapy in treatment-naïve chronic hepatitis B patients exhibiting a partial virologic response to entecavir. Clin Mol Hepatol 2015;21:24–31.
[126] Maier M, Liebert UG, Wittekind C, Kaiser T, Berg T, Wiegand J. Clinical relevance of minimal residual viremia during long-term therapy with nucleos(t)ide analogues in patients with chronic hepatitis B. PLoS One 2013;8 e67481.
[127] Kim SS, Hwang JC, Lim SG, Ahn SJ, Cheong JY, Cho SW. Effect of virological response to entecavir on the development of hepatocellular carcinoma in hepatitis B viral cirrhotic patients: comparison between compensated and decompensated cirrhosis. Am J Gastroenterol 2014;109:1223–1233.
[128] Ha NB, Ha NB, Trinh HN, Nguyen HA, Nguyen KK, Nguyen MH. Response to higher dose of entecavir 1.0 mg daily in patients with partial response to entecavir 0.5 mg daily. J Clin Gastroenterol 2013;47:461–465.
[129] Chaung KT, O'Brien C, Ha NB, Nguyen NH, Trinh HN, Nguyen MH. Alternative therapies for chronic hepatitis B patients with partial virological response to standard entecavir monotherapy. J Clin Gastroenterol 2016;50:338–344.
[130] Viganò M, Invernizzi F, Grossi G, Lampertico P. Review article: the potential of interferon and nucleos(t)ide analogue combination therapy in chronic hepatitis B infection. Aliment Pharmacol Ther 2016;44:653–661.
[131] Chan HL, Ahn SH, Chuang WL, Hui AJ, Tabak F, Mehta R, et al. Predictors of clinical response: Results from a large, randomized controlled study with

tenofovir disoproxil fumarate (TDF) plus peginterferon alfa-2A (PEG) combination for chronic hepatitis B (CHB). J Hepatol 2015;62:S251–S252.
[132] Su W-W, Hsu C-W, Lee C-M, Peng C-Y, Chuang W-L, Kao J-H, et al. Combination therapy with peginterferon alfa-2a and a nucleos(t)ide analogue for HBeAg-positive chronic hepatitis B patients: results of a large, randomised, multicentre, double-blind, placebo-controlled study. J Hepatol 2014;60:S47.
[133] Xie Q, Zhou H, Bai X, Wu S, Chen J-J, Sheng J, et al. A randomized, open-label clinical study of combined pegylated interferon alfa-2a (40KD) and entecavir treatment for hepatitis B "e" antigen-positive chronic hepatitis B. Clin Infect Dis 2014;59:1714–1723.
[134] Brouwer WP, Xie Q, Sonneveld MJ, Zhang N, Zhang Q, Tabak F, et al. Adding pegylated interferon to entecavir for hepatitis B e antigen-positive chronic hepatitis B: A multicenter randomized trial (ARES study). Hepatology 2015;61:1512–1522.
[135] Ning Q, Han M, Sun Y, Jiang J, Tan D, Hou J, et al. Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: a randomised open-label trial (OSST trial). J Hepatol 2014;61:777–784.
[136] Hu P, Shang J, Zhang W, Gong G, Li Y, Chen X, et al. Predictive value of baseline and on-treatment qHBsAg level in HBeAg positive CHB patients who switched from NUCs to pegylated interferon A-2A: A further analysis from new switch study. J Hepatol 2015;62:S251.
[137] Li G-J, Yu Y-Q, Chen S-L, Fan P, Shao L-Y, Chen J-Z, et al. Sequential combination therapy with pegylated interferon leads to loss of hepatitis B surface antigen and hepatitis B e antigen (HBeAg) seroconversion in HBeAg-positive chronic hepatitis B patients receiving long-term entecavir treatment. Antimicrob Agents Chemother 2015;59:4121–4128.
[138] Chi H, Xie Q, Zhang NP, Qi X, Liang C, Guo S, et al. Addition of peginterferon alfa-2B during long-term nucleos(T)ide analogue therapy increases hbeag seroconversion and hbsag decline-week 48 results from a multicenter randomized controlled trial (pegon study). Hepatology 2014;60:1106A.
[139] Lampertico P, Brunetto MR, Craxì A, Gaeta GB, Rizzetto M, Palmieri G, et al. LP25: Add-on peginterferon ALFA-2A significantly reduces hbsag levels in hbeag-negative, genotype d chronic hepatitis b patients fully suppressed on nucleot(s)ide analogue treatment: The HERMES study. J Hepatol 2015;62:S276.
[140] Bourlière M, Rabiega P, Ganne-Carrie N, Serfaty L, Marcellin P, Barthe Y, et al. Effect on HBs antigen clearance of addition of pegylated interferon alfa-2a to nucleos(t)ide analogue therapy versus nucleos(t)ide analogue therapy alone in patients with HBe antigen-negative chronic hepatitis B and sustained undetectable plasma hepatitis B virus DNA: a randomised, controlled, open-label trial. Lancet Gastroenterol Hepatol 2017;2:177–188. http://dx.doi.org/10.1016/S2468-1253(16)30189-3.
[141] Wang FY, Li B, Li Y, Liu H, Qu WD, Xu HW, et al. Entecavir for patients with hepatitis b decompensated cirrhosis in China: a meta-analysis. Sci Rep 2016;6:32722.
[142] Zhang X, Liu L, Zhang M, Gao S, Du Y, An Y, et al. The efficacy and safety of entecavir in patients with chronic hepatitis B- associated liver failure: a meta-analysis. Ann Hepatol 2015;14:150–160.
[143] Miquel M, Núñez Ó, Trapero-Marugán M, Díaz-Sánchez A, Jiménez M, Arenas J, et al. Efficacy and safety of entecavir and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice. Ann Hepatol 2013;12:205–212.
[144] Ye X-G, Su Q-M. Effects of entecavir and lamivudine for hepatitis B decompensated cirrhosis: Meta-analysis. World J Gastroenterol 2013;19:6665–6678.
[145] Cholongitas E, Papatheodoridis GV, Goulis J, Vlachogiannakos J, Karatapanis S, Ketikoglou J, et al. The impact of newer nucleos(t)ide analogues on patients with hepatitis B decompensated cirrhosis. Ann Gastroenterol 2015;28:109–117.
[146] Yue-Meng W, Li YH, Wu HM, Yang J, Xu Y, Yang LH, et al. Telbivudine *vs.* lamivudine and entecavir for treatment-naive decompensated hepatitis B virus-related cirrhosis. Clin Exp Med 2016:1–9.
[147] Welker M-W, Zeuzem S. Pre- and post-transplant antiviral therapy (HBV, HCV). Visc Med 2016;32:105–109.
[148] Jang JW, Choi JY, Kim YS, Woo HY, Choi SK, Lee CH, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. Hepatology 2015;61:1809–1820.
[149] Hyun JJ, Seo YS, Yoon E, Kim TH, Kim DJ, Kang HS, et al. Comparison of the efficacies of lamivudine *vs.* entecavir in patients with hepatitis B virus-related decompensated cirrhosis. Liver Int 2012;32:656–664.
[150] Srivastava M, Rungta S, Dixit VK, Shukla SK, Singh TB, Jain AK. Predictors of survival in hepatitis B virus related decompensated cirrhosis on tenofovir therapy: An Indian perspective. Antiviral Res 2013;100:300–305.
[151] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016;64:433–485.
[152] Perrillo R, Buti M, Durand F, Charlton M, Gadano A, Cantisani G, et al. Entecavir and hepatitis B immune globulin in patients undergoing liver transplantation for chronic hepatitis B. Liver transpl 2013;19:887–895.
[153] Fox AN, Terrault NA. The option of HBIG-free prophylaxis against recurrent HBV. J Hepatol 2012;56:1189–1197.
[154] Wang P, Tam N, Wang H, Zheng H, Chen P, Wu L, et al. Is hepatitis B immunoglobulin necessary in prophylaxis of hepatitis B recurrence after liver transplantation? A meta-analysis. PLoS One 2014;9 e104480.
[155] Fernández I, Loinaz C, Hernández O, Abradelo M, Manrique A, Calvo J, et al. Tenofovir/entecavir monotherapy after hepatitis B immunoglobulin withdrawal is safe and effective in the prevention of hepatitis B in liver transplant recipients. Transpl Infect Dis 2015;17:695–701.
[156] Huprikar S, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, et al. Solid organ transplantation from hepatitis B virus-positive donors: Consensus guidelines for recipient management. Am J Transplant 2015;15:1162–1172.
[157] European AIDS Clinical Society. Treatment Guidelines 2016;8:1. http://www.eacsociety.org/files/guidelines_8.1-english.pdf.
[158] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents 2016. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.
[159] Gallant J, Brunetta J, Crofoot G, Benson P, Mills A, Brinson C, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. J Acquir Immune Defic Syndr 2016;73:294–298.
[160] Triantos C, Kalafateli M, Nikolopoulou V, Burroughs A. Meta-analysis: antiviral treatment for hepatitis D. Aliment Pharmacol Ther 2012;35:663–673.
[161] Heidrich B, Yurdaydın C, Kabaçam G, Ratsch BA, Zachou K, Bremer B, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology 2014;60:87–97.
[162] Wranke A, Serrano BC, Heidrich B, Kirschner J, Bremer B, Lehmann P, et al. Antiviral treatment and liver-related complications in hepatitis delta. Hepatology 2017;65:414–425.
[163] Karaca C, Soyer OM, Baran B, Ormeci AC, Gokturk S, Aydin E, et al. Efficacy of pegylated interferon-α treatment for 24 months in chronic delta hepatitis and predictors of response. Antivir Ther 2013;18:561–566.
[164] Heller T, Rotman Y, Koh C, Clark S, Haynes-Williams V, Chang R, et al. Long-term therapy of chronic delta hepatitis with peginterferon alfa. Aliment Pharmacol Ther 2014;40:93–104.
[165] Wedemeyer H, Yurdaydin C, Ernst S, Caruntu FA, Curescu MG, Yalcin K, et al. O4 prolonged therapy of hepatitis delta for 96 weeks with pegylated-interferon-α-2a plus tenofovir or placebo does not prevent HDVRNA relapse after treatment: the hidit-2 study. J Hepatol 2014;60:S2–S3.
[166] Guedj J, Rotman Y, Cotler SJ, Koh C, Schmid P, Albrecht J, et al. Understanding early serum hepatitis D virus and hepatitis B surface antigen kinetics during pegylated interferon-alpha therapy via mathematical modeling. Hepatology 2014;60:1902–1910.
[167] Keskin O, Wedemeyer H, Tüzün A, Zachou K, Deda X, Dalekos GN, et al. Association between level of hepatitis D virus RNA at week 24 of pegylated interferon therapy and outcome. Clin Gastroenterol Hepatol 2015;13:2342–2349.
[168] Niro GA, Smedile A, Fontana R, Olivero A, Ciancio A, Valvano MR, et al. HBsAg kinetics in chronic hepatitis D during interferon therapy: on-treatment prediction of response. Aliment Pharmacol Ther 2016;44:620–628.
[169] Le Gal F, Brichler S, Sahli R, Chevret S, Gordien E. First international external quality assessment for hepatitis delta virus RNA quantification in plasma. Hepatology 2016;64:1483–1494.
[170] Manesis EK, Vourli G, Dalekos G, Vasiliadis T, Manolaki N, Hounta A, et al. Prevalence and clinical course of hepatitis delta infection in Greece: a 13-year prospective study. J Hepatol 2013;59:949–956.
[171] Caccamo G, Saffioti F, Raimondo G. Hepatitis B virus and hepatitis C virus dual infection. World J Gastroenterol 2014;20:14559–14567.
[172] Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viralinteractions and management. Ann Gastroenterol 2015;28:221–228.
[173] EASL recommendations on treatment of hepatitis C 2016. J Hepatol 2017;66:153–194.
[174] De Monte A, Courjon J, Anty R, Cua E, Naqvi A, Mondain V, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus:

Reactivation of hepatitis B virus coinfection as a further challenge. J Clin Virol 2016;78:27–30.
[175] Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. J Med Case Rep 2015;9:164.
[176] Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. Clin Infect Dis 2015;61:1304–1306.
[177] Kimura H, Ohkawa K, Sakakibara M, Imanaka K, Matsunaga T, Miyazaki M, et al. Sustained hepatitis C virus RNA clearance accompanied by elevation of hepatitis B virus DNA after short-term peginterferon-α, ribavirin and simeprevir therapy in a chronic hepatitis patient having dual infection with hepatitis B and C viruses. Kanzo 2015;56:422–427.
[178] Sulkowski MS, Chuang W-L, Kao J-H, Yang JC, Gao B, Brainard DM, et al. No evidence of reactivation of hepatitis B virus among patients treated with ledipasvir-sofosbuvir for hepatitis C virus infection. Clin Infect Dis 2016;63:1202–1204.
[179] Wang C, Ji D, Chen J, Shao Q, Li B, Liu J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol 2017;15:132–136.
[180] European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol 2017;66, [In press].
[181] Jochum C, Maischack F, Anastasiou OE, Verheyen J, Timm J, Bechmann L, et al. Treatment of fulminant acute Hepatitis B with nucles(t)id analogues is safe and does not lead to secondary chronification of Hepatitis B. Z Gastroenterol 2016;54:1306–1311.
[182] Wang C-Y, Zhao P, Liu W-WAcute Liver Failure Study Team. Acute liver failure caused by severe acute hepatitis B: a case series from a multi-center investigation. Ann Clin Microbiol Antimicrob 2014;13:23.
[183] Wong VW, Wong GL, Yiu KK, Chim AM, Chu SH, Chan H-Y, et al. Entecavir treatment in patients with severe acute exacerbation of chronic hepatitis B. J Hepatol 2011;54:236–242.
[184] Streinu-Cercel A, Sandulescu O, Stefan M, Streinu-Cercel A. Treatment with lamivudine and entecavir in severe acute hepatitis B. Indian J Med Microbiol 2016;34:166–172.
[185] He B, Zhang Y, Lü M-H, Cao Y-L, Fan Y-H, Deng J-Q, et al. Glucocorticoids can increase the survival rate of patients with severe viral hepatitis B: a meta-analysis. Eur J Gastroenterol Hepatol 2013;25:926–934.
[186] Wiegand J, Wedemeyer H, Franke A, Rößler S, Zeuzem S, Teuber G, et al. Treatment of severe, nonfulminant acute hepatitis B with lamivudine *vs.* placebo: a prospective randomized double-blinded multicentre trial. J Viral Hepat 2014;21:744–750.
[187] Ito K, Yotsuyanagi H, Yatsuhashi H, Karino Y, Takikawa Y, Saito T, et al. Risk factors for long-term persistence of serum hepatitis B surface antigen following acute hepatitis B virus infection in Japanese adults. Hepatology 2014;59:89–97.
[188] Goyal A, Murray JM. The impact of vaccination and antiviral therapy on hepatitis B and hepatitis D epidemiology. PLoS One 2014;9 e110143.
[189] Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol 2013;59:814–829.
[190] Jonas MM, Lok AS, McMahon BJ, Brown RS, Wong JB, Ahmed AT, et al. Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis. Hepatology 2016;63:307–318.
[191] Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology 2012;56:2018–2026.
[192] Jonas MM, Chang M-H, Sokal E, Schwarz KB, Kelly D, Kim KO, et al. Randomized controlled trial of entecavir vs placebo in children with Hepatitis B envelope Ag-positive chronic Hepatitis B. Hepatology 2016;63:377–389.
[193] Centers for Disease Control and Prevention (CDC). Updated CDC recommendations for the management of hepatitis B virus infected health-care providers and students. MMWR Recomm Rep 2012;61:1–12.
[194] Gerlich WH. Reduction of infectivity in chronic hepatitis B virus carriers among healthcare providers and pregnant women by antiviral therapy. Intervirology 2014;57:202–211.
[195] Raven SF, de Heus B, Wong A, Zaaijer HL, van Steenbergen JE. Fluctuation of viremia in hepatitis B virus-infected healthcare workers performing exposure-prone procedures in the Netherlands. Infect Control Hosp Epidemiol 2016;37:655–660.
[196] Chen H-L, Lee C-N, Chang C-H, Ni Y-H, Shyu M-K, Chen S-M, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology 2015;62:375–386.
[197] Greenup A-J, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. J Hepatol 2014;61:502–507.
[198] Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016;374:2324–2334.
[199] Sun K-X, Li J, Zhu F-C, Liu J-X, Li R-C, Zhai X-J, et al. A predictive value of quantitative HBsAg for serum HBV DNA level among HBeAg-positive pregnant women. Vaccine 2012;30:5335–5340.
[200] Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012;19:e18–e25.
[201] Wen WH, Huang CW, Chie WC, Yeung CY, Zhao LL, Lin WT, et al. Quantitative maternal hepatitis B surface antigen predicts maternally transmitted hepatitis B virus infection. Hepatology 2016;64:1451–1461.
[202] Liu J, Wang J, Jin D, Qi C, Yan T, Cao F, et al. Hepatic flare after telbivudine withdrawal and efficacy of postpartum antiviral therapy for pregnancies with chronic hepatitis B virus. J Gastroenterol Hepatol 2017;32:177–183.
[203] Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American gastroenterological association institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215–219.
[204] Huang H, Li X, Zhu J, Ye S, Zhang H, Wang W, et al. Entecavir *vs.* lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy. Jama 2014;312:2521.
[205] Cholongitas E, Tziomalos K, Pipili C. Management of patients with hepatitis B in special populations. World J Gastroenterol 2015;21:1738–1748.
[206] Viganò M, Serra G, Casella G, Grossi G, Lampertico P. Reactivation of hepatitis B virus during targeted therapies for cancer and immune-mediated disorders. Expert Opin Biol Ther 2016;16:917–926.
[207] Phipps C, Chen Y, Tan D. Lymphoproliferative disease and hepatitis B reactivation: challenges in the era of rapidly evolving targeted therapy. Clin Lymphoma Myeloma Leuk 2016;16:5–11.
[208] Voican CS, Mir O, Loulergue P, Dhooge M, Brezault C, Dréanic J, et al. Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment. Ann Oncol 2016;27:2172–2184.
[209] Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol 2016;22:219–237.
[210] Grossi G, Loglio A, Viganò M, Cappelletti M, Goldaniga MC, Farina L, et al. Universal prophylaxis with lamivudine prevents hepatitis B reactivation in HBsAg-negative/anti-HBC positive patients undergoing rituximab-based chemotherapy for non-Hodgkin b cell lymphoma – final results. Hepatology 2016;64:88A.
[211] Cerva C, Colagrossi L, Maffongelli G, Salpini R, Di Carlo D, Malagnino V, et al. Persistent risk of HBV reactivation despite extensive lamivudine prophylaxis in haematopoietic stem cell transplant recipients who are anti-HBc-positive or HBV-negative recipients with an anti-HBc-positive donor. Clin Microbiol Infect 2016;22:946.e1–946.e8.
[212] Mozessohn L, Chan KK, Feld JJ, Hicks LK. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for lymphoma: a meta-analysis. J Viral Hepat 2015;22:842–849.
[213] Huang YH, Hsiao LT, Hong YC, Chiou TJ, Bin YuY, Gau JP, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765–2772.
[214] Buti M, Manzano ML, Morillas RM, García-Retortillo M, Martín L, Prieto M, et al. Prevents HBV reactivation with tenofovir in Anti-HBC positive patients with hematologic malignancies treated with rituximab. Results final visit 18-months (preblin study). J Hepatol 2016;64:S369.
[215] Fabrizi F, Martin P, Messa P. Novel perspectives on the hepatitis B virus vaccine in the chronic kidney disease population. Int J Artif Organs 2015;38:625–631.
[216] Lindemann M, Zaslavskaya M, Fiedler M, Wilde B, Heinemann FM, Heinold A, et al. Humoral and cellular responses to a single dose of fendrix in renal transplant recipients with non-response to previous hepatitis B vaccination. Scand J Immunol 2017;85:51–57.
[217] Gajurel K, Stapleton JT. Hepatitis viruses in kidney transplantation. Semin Nephrol 2016;36:386–396.

[218] Ridruejo E. Antiviral treatment for chronic hepatitis B in renal transplant patients. World J Hepatol 2015;7:189–203.
[219] Yap DY, Yung S, Tang CS, Seto WK, Ma MK, Mok MM, et al. Entecavir treatment in kidney transplant recipients infected with hepatitis B. Clin Transplant 2014;28:1010–1015.
[220] De Virgilio A, Greco A, Magliulo G, Gallo A, Ruoppolo G, Conte M, et al. Polyarteritis nodosa: A contemporary overview. Autoimmun Rev 2016;15:564–570.
[221] Boyd A, Lacombe K, Lavocat F, Maylin S, Miailhes P, Lascoux-Combe C, et al. Decay of ccc-DNA marks persistence of intrahepatic viral DNA synthesis under tenofovir in HIV-HBV co-infected patients. J Hepatol 2016;65:683–691.
[222] Lai C-L, Wong D, Ip P, Kopaniszen M, Seto W-K, Fung J, et al. Reduction of covalently closed circular DNA with long-term nucleos(t)ide analogue treatment in chronic hepatitis B. J Hepatol 2017;66:275–281.
[223] Levrero M, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M, et al. Control of cccDNA function in hepatitis B virus infection. J Hepatol 2009;51:581–592.
[224] Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut 2015;64:1972–1984.
[225] Zoulim F, Testoni B, Lebossé F. Kinetics of intrahepatic covalently closed circular DNA and serum hepatitis B surface antigen during antiviral therapy for chronic hepatitis B: lessons from experimental and clinical studies. Clin Gastroenterol Hepatol 2013;11:1011–1013.
[226] Park Y, Hong DJ, Shin S, Cho Y, Kim H-S. Performance evaluation of new automated hepatitis B viral markers in the clinical laboratory: two quantitative hepatitis B surface antigen assays and an HBV core-related antigen assay. Am J Clin Pathol 2012;137:770–777.
[227] Luckenbaugh L, Kitrinos KM, Delaney WE, Hu J. Genome-free hepatitis B virion levels in patient sera as a potential marker to monitor response to antiviral therapy. J Viral Hepat 2015;22:561–570.
[228] Honda M, Shirasaki T, Terashima T, Kawaguchi K, Nakamura M, Oishi N, et al. Hepatitis B Virus (HBV) Core-Related Antigen During Nucleos(t)ide Analog Therapy Is Related to Intra-hepatic HBV Replication and Development of Hepatocellular Carcinoma. J Infect Dis 2016;213:1096–1106.
[229] Wong DK, Seto W-K, Cheung K-S, Chong C-K, Huang F-Y, Fung J, et al. Hepatitis B virus core-related antigen as a surrogate marker for covalently closed circular DNA. Liver Int 2017 (in press).
[230] Maasoumy B, Wiegand SB, Jaroszewicz J, Bremer B, Lehmann P, Deterding K, et al. Hepatitis B core-related antigen (HBcrAg) levels in the natural history of hepatitis B virus infection in a large European cohort predominantly infected with genotypes A and D. Clin Microbiol Infect 2015;21:606 e1–e10.
[231] Tada T, Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, et al. HBcrAg predicts hepatocellular carcinoma development: An analysis using time-dependent receiver operating characteristics. J Hepatol 2016;65:48–56.
[232] Song G, Yang R, Rao H, Feng B, Ma H, Jin Q, et al. Serum HBV core-related antigen is a good predictor for spontaneous HBeAg seroconversion in chronic hepatitis B patients. J Med Virol 2017;89:463–468.
[233] Tanaka E, Matsumoto A. Guidelines for avoiding risks resulting from discontinuation of nucleoside/nucleotide analogs in patients with chronic hepatitis B. Hepatol Res 2014;44:1–8.
[234] Martinot-Peignoux M, Lapalus M, Maylin S, Boyer N, Castelnau C, Giuily N, et al. Baseline HBsAg and HBcrAg titres allow peginterferon-based ''precision medicine'' in HBeAg-negative chronic hepatitis B patients. J Viral Hepat 2016;23:905–911.
[235] Chuaypen N, Posuwan N, Payungporn S, Tanaka Y, Shinkai N, Poovorawan Y, et al. Serum hepatitis B core-related antigen as a treatment predictor of pegylated interferon in patients with HBeAg-positive chronic hepatitis B. Liver Int 2016;36:827–836.
[236] Wang J, Shen T, Huang X, Kumar GR, Chen X, Zeng Z, et al. Serum hepatitis B virus RNA is encapsidated pregenome RNA that may be associated with persistence of viral infection and rebound. J Hepatol 2016;65:700–710.
[237] Giersch K, Allweiss L, Volz T, Dandri M, Lütgehetmann M. Serum HBV pgRNA as a clinical marker for cccDNA activity. J Hepatol 2016;66:460–462.
[238] Wang J, Du M, Huang H, Chen R, Niu J, Jiang J, et al. Reply to: ''Serum HBV pgRNA as a clinical marker for cccDNA activity'': Consistent loss of serum HBV RNA might predict the ''para-functional cure'' of chronic hepatitis B. J Hepatol 2017;66:462–463.
[239] Van Bömmel F, Van Bömmel A, Krauel A, He H, Wat C, Pavlovic V, et al. Serum HBV RNA is an early predictor of HBeAg seroconversion in patients with chronic Hepatitis B (CHB) treated with pegylated interferon alfa-2a (40KD). Hepatology 2015;62:336A.
[240] van Bömmel F, Bartens A, Mysickova A, Hofmann J, Krüger DH, Berg T, et al. Serum hepatitis B virus RNA levels as an early predictor of hepatitis B envelope antigen seroconversion during treatment with polymerase inhibitors. Hepatology 2015;61:66–76.
[241] Zeisel MB, Lucifora J, Mason WS, Sureau C, Beck J, Levrero M, et al. Towards an HBV cure: state-of-the-art and unresolved questions-report of the ANRS workshop on HBV cure. Gut 2015;64:1–13.
[242] Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol 2017. http://dx.doi.org/10.1016/j.jhep.2017.05.008, in press.
[243] Durantel D, Zoulim F. New antiviral targets for innovative treatment concepts for hepatitis B virus and hepatitis delta virus. J Hepatol 2016;64:S117–S131.
[244] Bogomolov P, Alexandrov A, Voronkova N, Macievich M, Kokina K, Petrachenkova M, et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. J Hepatol 2016;65:490–498.
[245] Blank A, Markert C, Hohmann N, Carls A, Mikus G, Lehr T, et al. First-in-human application of the novel hepatitis B and hepatitis D virus entry inhibitor myrcludex B. J Hepatol 2016;65:483–489.
[246] Al-Mahtab M, Bazinet M, Vaillant A, Ip P, Huang F-Y, Lai C-L, et al. Safety and efficacy of nucleic acid polymers in monotherapy and combined with immunotherapy in treatment-naive Bangladeshi patients with HBeAg+ chronic hepatitis B infection. PLoS One 2016;11:e0156667.
[247] Koh C, Canini L, Dahari H, Zhao X, Uprichard SL, Haynes-Williams V, et al. Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial. Lancet Infect Dis 2015;15:1167–1174.