

# Management of chronic hepatitis B: an update

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## Summary

Since the publication in 2009 of clinical practice guidelines for the management of hepatitis B virus (HBV) infection by the *European Association for the Study of the Liver* (EASL), a wealth of new data has emerged regarding the antivirals most commonly used to treat chronic hepatitis B. This review will summarise the most recent knowledge on these drugs, and how this may affect current and future management of HBV infection. Despite the progress in drug development, HBV infection remains a complex entity, characterised by a peculiar interplay between host and viral factors. With the potent drugs currently available, however, its management and control are possible in the majority of cases.

**Key words:** hepatitis B virus; chronic hepatitis B; tenofovir; entecavir; cirrhosis

## Introduction

Hepatitis B virus (HBV) infection is a major cause of acute and chronic hepatitis, and of its long-term complications, i.e. decompensated cirrhosis and hepatocellular carcinoma (HCC) [1, 2]. About 5% of the global population, i.e. 350 million persons, are currently infected with HBV [1]. In Europe, according to a recent technical report of the European Centre for Disease Prevention and Control [3], the HBV prevalence rates vary widely, i.e. between 0.1 and 7.0%, increasing from west to east and from north to south [4], with a significant impact on national healthcare systems [3–5]. In Switzerland, official estimates place the prevalence of HBV at about 0.3% of the general population [6], corresponding to ~20000 infected persons, although some studies seem to suggest higher figures [7–9]. It has to be said that the Swiss epidemiology of HBV is steadily evolving, like in most European countries, due to a significant influx of migrants from highly endemic countries. HBV infection remains a challenging entity, characterised by a complex interplay between host and viral factors. Chronic HBV infection undergoes several phases. More than 95% of persons infected at the adult age recover spontaneously, suggesting that most chronic infections occur either perinatally or during the first few years thereafter. In these cases, the HBV infection proceeds initially through

an *immune tolerant* phase, characterised by little or no signs of liver disease (normal ALT and mild or absent liver necroinflammation) in spite of very active viral replication, with serum HBV DNA levels typically in the range of  $10^7$  to  $10^{10}$  IU/ml. During this phase, the HBeAg is positive. With time, the immune system reacts toward viral antigens exposed at the surface of infected hepatocytes, and the patients enter an *immune reactive* or *immune elimination* phase. Levels of HBV DNA fall while those of ALT increase, mirrored by the appearance of lobular hepatitis. This phase may be hallmarked by the seroconversion from HBeAg to anti-HBe, and progression to an *inactive carrier* state, characterised by low (<2,000 IU/ml) or undetectable levels of HBV DNA in serum, normal liver enzymes, and the disappearance of liver necroinflammation. On the other hand, a prolonged immune reactive phase, with multiple, sequential flares of hepatitis or unremitting necroinflammation, will result in progressive liver fibrosis, ultimately leading to cirrhosis. When seroconversion to anti-HBe occurs, this may not necessarily lead to an inactive carriage: a minority of patients who become anti-HBe-positive maintains both viral replication and hepatitis. This condition, the so-called *HBeAg-negative hepatitis B*, is caused by infection with a mutant strain of HBV incapable of secreting HBeAg, and characterised by significant risk of clinical and histological disease progression in spite of the serological profile. In contrast to inactive carriers patients with HBeAg-negative hepatitis B have higher serum levels of HBV DNA (i.e. >2,000 IU/ml) and HBsAg [10]. Rarely, chronically HBV-infected patients may lose HBsAg and achieve definitive recovery, an event spontaneously occurring in as few as 1–2% of patients annually [11].

In order to assist and streamline the management of HBV infection, in 2009 the *European Association for the Study of the Liver* (EASL) published specific clinical practice guidelines [12], and an update is expected soon. Similarly, Practice Guidelines have been issued by the *American Association for the Study of Liver Diseases* [13]. Recently, a wealth of new data has emerged regarding the antivirals most commonly used to treat chronic hepatitis B (table 1). This article will review some of most recent knowledge on these drugs and how this may affect current and future management of HBV infection.

## Whom to treat and why

The majority of HBsAg-positive persons are inactive HBV carriers and in most cases simply require regular follow-up. This illustrates an important fact: a chronic infection with HBV is not necessarily accompanied by chronic, progressive liver damage warranting pharmacological interventions. It is therefore mandatory to establish a correct diagnosis and a proper indication for treatment. According to the 2009 EASL clinical practice guidelines (5), the decision to treat is primarily based on the combination of three criteria: 1) *serum HBV DNA levels*, 2) *serum alanine aminotransferase (ALT) levels* and 3) *histological grade and stage of the underlying liver disease*. As a consequence, patients should be considered for antiviral treatment only when (i) serum HBV DNA is above 2,000 IU/ml (that is, approximately 10,000 copies/ml), and/or (ii) serum ALT levels are above the upper limit of normal (ULN), and (iii) liver biopsy shows moderate to severe active necroinflammation and/or fibrosis using a standardised scoring system (e.g.  $\geq$  A2 and/or  $\geq$  F2 when using the METAVIR score). Additional considerations include the patient's age and the presence of clinically significant comorbidity. Patients with clinical evidence of cirrhosis should be treated irrespectively of serum HBV DNA level. Special considerations apply also to some patients' categories, where treatment may be postponed. These include

patients in the HBeAg-positive immunotolerant phase, i.e. with high serum levels of HBV DNA (typically higher than  $10^7$  IU/ml) and normal serum ALT, or patients with mild chronic hepatitis B. The latter group falls in a sort of grey zone characterised by mildly elevated ALT (i.e.  $<2$  times the upper level of the norm) and histological lesions not fulfilling the minimal criteria stated above, e.g. less than A2/F2 using the METAVIR score. While these two rules should apply only to young patients, there is no consensus about the minimum age for considering treatment rather than surveillance (the EASL has set the threshold at the age of 30 years).

EASL guidelines rely on liver histology. Thus, even though liver biopsy is an invasive procedure and, as such, poorly accepted by many physicians and patients alike, the assessment of the degree of liver inflammation and fibrosis remains an important mainstay of the diagnostic workup of chronic hepatitis B. Exceptions do apply and ought to be known. A liver biopsy is not necessary if treatment is indicated regardless of liver histology or if there is evidence of cirrhosis.

The *goal* of therapy of chronic hepatitis B is to achieve a sustained suppression of HBV replication, to obtain remission of the underlying liver disease and thus prevent its progression towards cirrhosis and HCC [11–14]. Continuous viral suppression is equally essential in order to avoid the risk of the emergence of antiviral resistance.

**Table 1:** Selected recent advances in the management of chronic hepatitis B.

References	Type of study	Findings
Brunetto et al. [10]	Prospective cohort study	HBsAg serum levels may help distinguishing inactive carriers from patients with HBeAg-negative chronic hepatitis B
Levrero et al. [22] Belloni et al. [32]	Review article Basic research original study	IFN- $\alpha$ may possess indirect antiviral activity by increasing the acetylation of histones bound to viral cccDNA, thus decreasing its transcriptional activity and suppressing HBV replication and HBsAg synthesis
Sonneveld et al. [24]	Clinical assay evaluation	Currently available quantitative assays for serum HBsAg are robust and comparable
Lim et al. [36]	Retrospective cohort study	Seroconversion to anti-HBe in chronic hepatitis B patients treated with nucleos(t)ide analogues is stable over time at a rate comparable to that obtained with IFN- $\alpha$
Chevaliez et al. [41] Zoutendijk et al. [42]	Retrospective study Retrospective study	Achieving HBsAg loss may require decades of therapy with nucleos(t)ide analogues
Liaw et al. [43]	Randomised trial (GLOBE study)	Telbivudine is superior to lamivudine in treating patients with chronic hepatitis B (HBeAg-positive and HBeAg-negative) over a 2-year period (GLOBE study)
Chang et al. [44] Lampertico et al. [46] Yokosuka et al. [47]	Rollover study (ETV-901) Treatment in field practice (Italy) Rollover study (ETV-060) (Japan)	After 5 years of therapy with entecavir (ETV-901 study), 94% (88/94) had HBV DNA $<300$ copies/ml and only one patient had developed resistance. In the field study from Italy, $<1\%$ of patients developed a breakthrough upon therapy with entecavir for an average period of 30 months. In the Japanese study, the 3-year cumulative probability of resistance to entecavir was 3.3%
Heathcote et al. [37] Heathcote et al. [38] Marcellin et al. [39] Snow-Lampart et al. [45] Marcellin et al. [55]	Randomised trials (GS-US-174-0102 and GS-US-174-0103) with open-label follow-on	Chronic hepatitis B patients treated with tenofovir for up to 4 years reached undetectable HBV DNA in 96% and 99% of HBeAg-positive and HBeAg-negative cases, respectively; no viral resistance was detected for up to 4 years; HBsAg loss occurred in 11% of cases
Fung et al. [48]	Randomised trial	Sequential therapy using entecavir followed by lamivudine results in HBV rebound in 24% of patients after 96 weeks, showing that a prior optimal viral suppression with entecavir does not confer any significant advantage in patients who later switch to lamivudine
Reijnders et al. [50] van Bömmel et al. [52] Berg et al. [53]	Prospective cohort study Retrospective multicentre study Randomised trial	The antiviral efficacy of entecavir is unaffected by prior treatment with adefovir, presence of adefovir-resistance or prior treatment with lamivudine in cases where lamivudine-resistance never developed. However, entecavir should not be used in patients with previous lamivudine-resistance, in whom tenofovir is the option of choice
Lazzarin et al. [56] Madruca et al. [57]	Randomised trial (study 934) Randomised trial (study 903)	Long-term therapy with tenofovir-containing regimens of patients infected with HIV shows a stable estimated glomerular filtration rate, and no evidence of clinically significant bone effects
Liaw et al. [58]	Randomised study (interim analysis at 48 weeks)	112 patients with chronic hepatitis B and decompensated liver disease were randomised to receive tenofovir, emtricitabine or entecavir: after 48 weeks, the adverse event and laboratory profiles were consistent with advanced liver disease and complications, with no unexpected safety signals

From the virological standpoint, the ideal endpoint of therapy is the persistent disappearance of HBsAg from serum, accompanied by seroconversion to anti-HBs. Since this is rarely achieved with currently available regimens, surrogate endpoints have been identified. In HBeAg-positive patients, a durable seroconversion to anti-HBe is commonly accepted, since it is associated with improved prognosis [15]. In patients who fail to seroconvert and in those who are anti-HBe-positive *ab initio*, the endpoint consists in the continuous suppression of serum HBV DNA below the detection limit of PCR assays (10–15 IU/ml).

## Current therapy

Seven drugs are available for treatment of chronic hepatitis B (table 2): interferon- $\alpha_{2a}$  (IFN- $\alpha_{2a}$ ), currently marketed in its pegylated form (Pegasys<sup>®</sup>), and six nucleos(t)ide analogues: 1) two L-nucleoside analogues, lamivudine (Zeffix<sup>®</sup>) and telbivudine (Sebivo<sup>®</sup>), 2) a deoxyguanosine analogue called entecavir (Baraclude<sup>®</sup>), and 3) two acyclic nucleoside phosphonates, tenofovir disoproxil fumarate (Viread<sup>®</sup>) and adefovir dipivoxil (Hepsera<sup>®</sup>). The long-term efficacy of these drugs differs because of their particular potency and drug-resistance patterns. While lamivudine, telbivudine, entecavir and tenofovir are approved as first-line therapy for treatment-naïve chronic hepatitis B, the risk of selecting drug resistant viral strains with the first two drugs has effectively reduced the current choice to the potent analogues entecavir and tenofovir. Adefovir is a less efficacious drug, with a moderately high rate of selection of resistant viral strains: for this reason, it should be used only as second-line treatment, in patients with previous treatment failure to lamivudine, telbivudine or entecavir, although today this role has been taken over by tenofovir (see below). Entecavir is marketed as 0.5 or 1 mg tablets, the latter being used in rescue therapy of patients with drug resistant strains.

### Interferon alpha

IFN- $\alpha_{2a}$  has been used against HBV for about 30 years, and is currently approved without limitations in its pegylated form. However, its use should be limited to patients with a favourable baseline profile, i.e. HBeAg-positive patients with the highest chances of seroconverting to anti-HBe, or for anti-HBe-positive patients who may maintain durable suppression of HBV DNA after the end of therapy. The advantages and disadvantages of pegylated IFN- $\alpha_{2a}$  are well-known: while, on the one hand, it achieves a >30% HBeAg seroconversion rate after a finite period of administration (one year) [12], on the other hand it is burdened with

significant side effects and contraindications. In particular, pegylated IFN- $\alpha_{2a}$  should be used with major caution in patients with cirrhosis, and is definitely contra-indicated in cases of decompensated liver disease, owing to its risk of potentially fatal hepatic failure. Thus, it is not surprising that most patients (and doctors) are disinclined to use it, especially since the advent of potent, safer and better tolerated nucleoside and nucleotide analogues. This view should probably be nuanced. Not only does the HBeAg seroconversion rate following IFN- $\alpha_{2a}$  therapy continue to increase during the six months after the discontinuation of treatment [16], but the seroconversion status remains stable over time in 70–87% of patients who had achieved it at the end of therapy [16, 17]. Pegylated IFN- $\alpha_{2a}$  can also result in HBsAg seroconversion in up to 11% of patients followed in the long-term [17]. Although both features have been repeatedly put forward to support the use of pegylated IFN- $\alpha$  rather than of direct antivirals, recent data concerning long-term therapy with some nucleos(t)ide (such as tenofovir) have shown comparable results (see below).

If treatment acceptance is poor for pegylated IFN- $\alpha_{2a}$ , it can be improved either with a better selection of patients, based on validated profiling at baseline [18] or with the implementation of rules for termination of treatment to reduce drug exposure in patients bound to therapy failure, similarly to what has been proposed for the therapy of chronic hepatitis C. However, modelling of HBV DNA kinetics during pegylated IFN- $\alpha$  therapy has shown only limited clinical utility, and reliable prediction of long-term treatment failure is only possible after 24 weeks of therapy, with a negative predictive value of 86% [19]. Alternatively, one may measure the intrahepatic level of the so-called covalently closed circular DNA (cccDNA), the transcriptionally active HBV mini-chromosome that persists in the nucleus of infected hepatocytes and decreases upon therapy [20]. Persistence of intrahepatic cccDNA at the end of treatment is predictive of off-treatment relapse [21]. Unfortunately, the clinical utility of this assay is very limited due to the invasiveness of liver biopsy. A more realistic approach is the measurement of serum HBsAg, which correlates well with intrahepatic cccDNA levels in both HBeAg-positive and negative patients. The cccDNA correlation with serum HBV DNA is poor, especially among HBeAg-negative individuals [22, 23]. This suggests not only a differential regulation of viral and subviral particles in the different phases of HBV infection, but also that serum HBV DNA levels may not predict the status of infection in the liver, especially in HBeAg-negative patients, as reliably as HBsAg. As a result, several studies have analysed the predictive value of quantitative HBsAg measurement in ser-

**Table 2:** Available drugs to treat chronic hepatitis B.

Active substance	Trade name	Registered indication in CH	Risk of viral resistance
Pegylated interferon $\alpha_{2b}$	Pegasys <sup>®</sup>	All stages	No resistance
Lamivudine	Zeffix <sup>®</sup>	Treatment-naïve patients	Highest risk of resistance development, i.e. highest risk of resistance
Telbivudine	Sebivo <sup>®</sup>	Treatment-naïve patients	Intermediate risk of resistance development
Adefovir	Hepsera <sup>®</sup>	Only in patients with treatment-emergent resistance	Intermediate risk of resistance development
Entecavir	Baraclude <sup>®</sup>	Treatment-naïve patients	Very low risk of resistance development in treatment-naïve patient. In L-nucleoside-experienced patients, high risk of cross-resistance
Tenofovir	Viread <sup>®</sup>	Treatment-naïve patients	Very low risk of resistance development (no mutations so far described)

um at baseline and during therapy. This has been made possible by the advent of novel quantitative assays for HBsAg that are highly reproducible and standardised and allow high-throughput automated quantifications at relatively low cost. Recent data show also that the two quantitative assays currently in the market perform comparably [24]. HBsAg serum level decline during pegylated IFN- $\alpha_{2a}$  therapy predicts off-treatment response more accurately than HBV DNA kinetics, both in HBeAg-positive [25] and HBeAg-negative patients [26–28]. Combining HBsAg and HBV DNA measurement has enabled establishing a rule for stopping therapy in HBeAg-negative patients at 12 weeks of therapy with a negative predictive value of 100% [28]. A similar stopping rule was proposed, in this case using HBsAg quantification alone, in HBeAg-positive patients [29]. These encouraging results should be taken with caution, however, and be independently confirmed in larger studies [30, 31]. Besides, some authors have shown that the predictive value of HBsAg decline may not apply equally to all HBV genotypes [31]. Nonetheless, the observations on HBsAg on-treatment kinetics are intellectually stimulating: why should the measurement of HBsAg be a better predictor of success than HBV DNA kinetics? Interestingly, HBsAg decline under nucleos(t)ide analogues, which are otherwise very potent in suppressing HBV DNA, is much weaker (see below). This suggests that IFN- $\alpha$  may act via indirect mechanisms not shared by nucleos(t)ide analogues, either stimulating the immune response or inducing epigenetic changes capable of modulating the transcriptional activity of the HBV cccDNA [22]. Indeed, recent elegant experiments have shown how IFN- $\alpha$  may increase the acetylation of histones bound to cccDNA, thus decreasing its transcriptional activity and suppressing both replication and HBsAg synthesis [32]. If these interesting results were confirmed *in vivo*, they may reinvigorate the interest in IFN- $\alpha$  as a first-line drug in chronic hepatitis B.

### Nucleos(t)ide analogues

When compared to IFN- $\alpha$ , nucleos(t)ide analogues have several advantages and a few pitfalls. The first issue lies in the fact that the length of treatment for nucleos(t)ide analogues is as yet undefined, and may possibly last for life. Nucleos(t)ide analogues induce HBeAg seroconversion rates that are proportional to the length of treatment, but it has been reported that most patients (~80%) serorevert to HBeAg once the treatment is stopped [33]. This provides an unfair picture of analogues' long-term efficacy and conflicts with previous, more optimistic reports [34, 35]. Recently, in a very large longitudinal study, 569 HBeAg-positive chronic hepatitis B patients were observed for a mean follow-up of 8 years [36]. A total of 246 HBeAg seroconversions occurred. Spontaneous seroconversion occurred in 59% of untreated patients compared to 81% on oral nucleos(t)ide therapy (lamivudine, adefovir, entecavir) ( $p = 0.0001$ ), a difference maintained after correction for baseline parameters ( $p = 0.028$ ). Seroconversions were maintained over time in 78% of those who had been treated with nucleos(t)ide analogues and in 97% of those who had seroconverted spontaneously ( $p = 0.0003$ ). These data show that treatment with nucleos(t)ide analogues can achieve a rate of HBeAg seroconversion that is

not only significantly higher than that occurring spontaneously (in untreated patients) but also that seroconversions are stable over time to an extent comparable to that observed after IFN- $\alpha$  therapy [36].

Nonetheless, the ideal endpoint of HBV treatment is not the HBeAg seroconversion but the permanent HBsAg loss, which occurs, as seen above, in 11% of patients treated with IFN- $\alpha_{2a}$  [17]. In this regard, nucleos(t)ide analogues are rapidly catching up. Prolonged therapy with tenofovir of HBeAg-positive patients resulted in HBsAg loss rates of 8% and 11% after 3 [37] and 4 [38] years of therapy, respectively. Some factors predictive of HBsAg loss were recently reported and included a steep slope of HBsAg decline after 12 weeks of therapy, HBeAg loss after 24 weeks of therapy, and a shorter time since diagnosis, which may indicate a shorter duration of infection [39]. Similarly, after 2 years of administration, entecavir showed an HBsAg loss rate of 5% [40]. One must admit that these rates are still disappointingly low, even if they may increase with more prolonged therapy. Furthermore, these data need to be confirmed by additional studies and longer off-treatment follow-up. The increasing rate of HBsAg loss during prolonged nucleos(t)ide analogue therapy raises the issue of the length of therapy. Would the quantitative determination of HBsAg levels be helpful in tailoring nucleos(t)ide treatment duration? In a very detailed study conducted on a small number of patients ( $n = 30$ ) carefully followed for a median of 93 months (range 49–123 months) during treatment with various antivirals, Chevaliez et al. [41] showed a slow but constant decline of HBsAg during therapy. However, when the number of years needed to clear HBsAg after HBV DNA had become undetectable was calculated for each patient, the figure ranged from 6 to a staggering 181 years: in 13 patients, that is, 43% of the total, the time necessary to clear HBsAg was predicted to be more than 30 years. Moreover, the number of years needed to clear HBsAg was not related to pretreatment parameters or to the duration of undetectable HBV DNA. Thus, HBsAg clearance following nucleos(t)ide therapy is an infrequent and often late event. This suggests that the only realistic endpoint using these drugs will remain maintaining HBV DNA at undetectable levels and that, possibly, stopping nucleos(t)ide therapy will be unlikely in the majority of chronic hepatitis B patients. This view was confirmed in another study where a total of 75 patients were followed during treatment with entecavir or tenofovir [42]. The predicted median time needed to reach HBsAg loss for HBeAg-positive patients was 36 years, shortened to a median of 19.5 years in patients with a high baseline ALT. HBsAg decline in HBeAg-negative was slow and barely progressed after 3 years of therapy. Thus, long term HBV DNA suppression by potent nucleos(t)ide therapy leads to HBsAg decline in HBeAg-positive, but not in HBeAg-negative chronic hepatitis B patients. In conclusion, using nucleos(t)ide analogues to achieve HBsAg loss may require decades of therapy in most patients [41, 42].

The price one has to pay for long-term therapy with nucleos(t)ide analogues is dual: emergence of drug resistant strains and safety. The selection of drug-resistant viral strains was one of the most important concerns with the original nucleos(t)ide analogues, especially with lamivud-

ine and adefovir dipivoxyl. The situation improved only marginally with telbivudine: its 2-year administration still results in the selection of drug resistant strains in 25.1% of HBeAg-positive and 10.8% of HBeAg-negative patients [43]. Currently, the most potent antivirals with the highest barrier for resistance mutations are entecavir, with a resistance rate 1.2% after 5 years [44], and tenofovir, with no resistance reported after 4 years [45]. The low rate of resistance during entecavir therapy has been confirmed in two field studies from Italy [46] and Japan [47]. However, prolonged suppression of HBV DNA below the sensitivity level of commercially available assays does not rule out ongoing viral replication. This may account for the late-onset selection of resistant strains, as suggested also by a study where patients treated with entecavir who had achieved undetectable viraemia were switched to lamivudine, resulting into a significant number of virological breakthroughs [48]. Entecavir and tenofovir are the ideal candidates for first-line treatment of chronic hepatitis B and, in any case, represent the treatment of choice whenever resistance occurs. Entecavir and tenofovir are the most potent analogues available, with an on-treatment response (undetectable HBV DNA) of 94% for HBeAg-positive patients treated with entecavir for 5 years [44], and 96% and 99% respectively, for HBeAg-positive and HBeAg-negative patients treated for 4 years with tenofovir [45]. These studies have also clearly shown that the rate of complete viral suppression keeps rising even after the first year of treatment, suggesting that an incomplete response after one year should not necessarily pose the indication for a modification of therapy, unless a prompt and complete abatement of viraemia is clinically indicated, such as in cirrhotic patients. In all patients with a virological breakthrough, the most important step is to assess treatment compliance, as this is the major cause of treatment failure. If compliance is certain and true resistance is suspected, genotypic resistance testing should be carried out and a rescue therapy initiated with the most effective antiviral drug, in order to avoid the risk of selecting multiple drug-resistant viral strains, taking into consideration the respective resistance profile, as discussed previously [49]. Resistant viral strains can present with cross-resistance between drugs, such as seen between L-nucleosides (lamivudine and telbivudine) and entecavir. Although the latter is marketed in 1 mg pills for treatment of resistance emergence, entecavir should never be used to rescue resistance following therapy with an L-nucleoside [50]. The 1 mg dose of entecavir is in any case inappropriate to correct a suboptimal response to 0.5 mg of the same drug [51]. In both cases, the best choice is to switch to tenofovir monotherapy [52, 53] and its potency is independent of HBV genotype [54].

Concerning long-term safety, both entecavir and tenofovir seem well tolerated and safe. In a recent, real-life study on 418 consecutive chronic hepatitis B patients treated with entecavir 0.5 mg for a median of 30 months, no major safety issues were reported. Median serum creatinine remained unchanged during treatment, and a greater than 44  $\mu\text{mol/L}$  increase of serum creatinine occurred in 0.6% of the patients, whereas blood phosphate levels dropped below 0.74 mmol/L in 1% of the patients [46]. A similar safety profile was reported for tenofovir [37]. After four

years of tenofovir therapy, only 2 patients in the study 102 (0.5%) experienced an increase in creatinine greater than 44  $\mu\text{mol/L}$ , which improved when dosing was reduced to every other day [55]. The safety data on long-term tenofovir use are even more solid if one considers the experience gathered in the therapy of HIV infection, for which tenofovir was licensed in 2001. None of 160 HIV-infected patients interrupted an antiretroviral regimen containing efavirenz, emtricitabine and tenofovir administered for 5 years due to renal side effects [56]. In another study, where various antiretroviral regimens containing efavirenz, lamivudine and tenofovir were administered for 10 years to 171 HIV-infected patients [57], none developed a decrease in serum phosphate, while two had self-limited increases of serum creatinine at 97 and 124–142 mg/dL. In this study, seven patients had bone fractures (all were trauma-related) and none deemed tenofovir-related by the investigators: none had any evidence of clinically relevant bone effects as assessed by measurement of bone mineral density. Finally, the safety of tenofovir (but also of emtricitabine and entecavir) was confirmed in patients with decompensated liver disease [58].

## Conclusions

In conclusion, HBV can be effectively managed in most cases, due to the availability of safe and effective drugs. The risk of selecting drug resistant viral strains is currently reduced to a minimum with the two potent analogues entecavir and tenofovir, which should therefore be the preferred oral antiviral agents. Use of IFN- $\alpha$  is today limited to selected cases, although recent data on its mechanism of action may revive the interest in this long-standing pillar of HBV therapy. HBV infection remains a complex entity, with different phases resulting from the interaction between viral and host factors. However, its control is now an objective within reasonable reach for most patients.

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