

# Long-term efficacy and safety of nucleos(t)ide analogues in patients with chronic hepatitis B

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**Abstract:** Nucleos(t)ide analogues with high barrier to resistance are regarded as the principal therapeutic option for chronic hepatitis B (CHB). Treatment with entecavir (ETV), tenofovir disoproxil (TDF) and the later released tenofovir alafenamide (TAF) is highly effective at controlling hepatitis B virus (HBV) infection and, in the vast majority of patients, is well tolerated. No significant differences in viral suppression have been described among the different regimens, although an earlier achievement in biochemical response has been suggested first under TDF and recently under TAF. High barrier to resistance NAs rarely achieve hepatitis B surface antigen sero-clearance, and therefore should be maintained life-long in most cases. This has increased concerns about treatment-related toxicity, especially in patients under TDF with additional risk factors for kidney and bone impairment. TAF has shown a better bone and kidney safety profile than TDF, although it is not yet available worldwide due to its higher cost. Emergence of adverse events should be monitored since treatment-switch to ETV/TAF seems to be effective and safe in HBV mono-infected subjects. Finally, although an effective antiviral treatment leads to a clear improvement in clinical outcome of CHB patients; the risk of developing hepatocellular carcinoma (HCC) is not completely avoided with viral suppression. Whether tenofovir-based regimens provide any additional benefit over ETV in HCC prevention remains unclear and requires further investigation.

**Keywords:** ETV, TDF, TAF, VHB, viral hepatitis

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## Introduction

Chronic hepatitis B (CHB) is still considered a leading cause of mortality worldwide, with approximately 780,000 annual deaths.<sup>1,2</sup> It is estimated that around 30% of 257 million people who are chronically infected also have chronic disease and active viral replication. Therefore, they should be considered candidates for hepatitis B virus (HBV) treatment with either peg-interferon (IFN) or nucleos(t)ide analogues (NAs).<sup>3</sup> Without treatment, up to 40% of these patients will develop long-term complications such as liver cirrhosis and hepatocellular carcinoma (HCC).<sup>4–6</sup> Effective viral suppression using antiviral drugs has shown to improve patients' survival and quality of

life.<sup>7</sup> However, there is no current therapeutic approach that achieves virological cure, which means an eradication of circular covalently closed DNA (cccDNA) from liver cells.<sup>8</sup> High barrier to resistance NAs such as entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) remain as first line treatment in the clinical practice due to multiple contraindications and safety concerns of IFN-based regimens.<sup>9–11</sup> Nevertheless, in most patients, NAs must be chronically maintained since hepatitis B surface antigen (HBsAg) sero-clearance is rarely achieved and indications for NAs withdrawal are limited.<sup>9,10,12</sup> High barrier to resistance NAs in monotherapy have shown an accurate safety

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profile and high rates of viral response in CHB patients. The emergence of TAF, a tenofovir pro-drug, has apparently overcome TDF limitations in long-term kidney and bone related side effects, although it is not widely available and lengthier studies in real-life settings are lacking. Long-term follow-up is required to identify adverse effects early and to ensure a proper HCC surveillance due to the higher risk of liver cancer even in effectively treated patients. The aim of this paper is to summarize the safety and efficacy aspects of high barrier to resistance NA regimens in CHB treatment.

## Efficacy

### *Virological response*

Virological response is defined as the achievement of undetectable HBV-DNA by polymerase chain reaction (currently with a limit of detection of 10 IU/ml), which is clearly related to an improvement in clinical outcomes and patients' survival.<sup>9</sup> Monotherapy with either TDF or ETV at daily dose of 245 mg/300 mg and 0.5 mg respectively has shown high rates of viral suppression in randomized trials and real-life cohorts.<sup>13-16</sup> Viral suppression (defined as HBV-DNA <57 IU/ml) of CHB naïve subjects under ETV reached 94% in hepatitis B e antigen (HBeAg) positive and 95% in HBeAg-negative subjects after 5-year follow-up.<sup>17</sup> On the other hand, a 10-year extension phase of randomized clinical trials (RCTs) with TDF reported a 100% and 98% rate of viral suppression (HBV-DNA <29 IU/ml). A meta-analysis of RCTs yielded a similar rate of HBV-DNA suppression [relative risk (RR) = 1.04, 95% confidence interval (CI) (1.00, 1.09),  $p=0.07$ ] for TDF and ETV respectively.<sup>18</sup> Viral suppression rate in field-practice studies yielded slightly lower suppression rate, generally above 90% in treatment-naïve patients for both ETV and TDF regimens, regardless of HBeAg status.<sup>19-22</sup> A large retrospective Asian study performed in 20,273 patients (from which 84% were under ETV regimens and 17% were treatment-experienced) yielded 86.4% of viral suppression after 4.5 year follow-up.<sup>23</sup> Similar viral suppression rate was reported after 24 months of treatment in a multi-center retrospective study performed in the United States in 557 subjects, with no differences between TDF and ETV groups.<sup>24</sup> Meanwhile, prospective European field studies with up to 4-year follow-up

showed rates of virological response to TDF regimens above 90% of the overall cohorts.<sup>20,25,26</sup>

A single-dose regimen of 25 mg of TAF has been compared with TDF over 96 weeks, achieving similar rates of virological response in both HBeAg positive (73% versus 75%,  $p=0.47$ ) and negative (90% versus 91%,  $p=0.84$ ) subjects.<sup>27-29</sup> Phase III non-inferiority TDF versus TAF studies with up to 144 weeks of follow-up are currently on-going.<sup>30</sup> Preliminary results showed similar suppression rates with TAF in both HBeAg negative and positive subjects [+1.7%, 95% CI (-8.1, +11.4);  $p=0.71$  and +2%, 95% CI (-5.6, +9.6);  $p=0.59$ , respectively]. Nationwide real-life studies with TAF have yielded preliminary results showing high rates of viral suppression at 48 weeks under TAF treatment.<sup>31,32</sup>

### *Biochemical response*

Alanine aminotransferase (ALT) normalization under antiviral treatment has been associated with a decrease in viral replication, tissue damage and necroinflammation.<sup>9</sup> Conventional ALT cut-offs in most laboratories are established at 40 IU/ml; although the American Association for the Study of Liver Diseases (AASLD) settled ALT cut-offs at 30 IU/L for men and 19 IU/L for women. TDF and ETV showed similar efficacy on ALT normalization below traditional cut-offs. Systematic review and meta-analysis of RCT in treatment-naïve patients treated with TDF or ETV revealed an earlier normalization of ALT in the TDF group during the first 24 weeks of treatment [RR=0.87, 95% CI (0.77, 0.98);  $p=0.02$ ] with no differences in weeks 96 and 144 [RR=0.94, 95% CI (0.88, 1.01);  $p=0.08$ ; and RR=0.98, 95% CI (0.92, 1.03);  $p=0.42$ , respectively] applying central laboratories' ALT cut-offs.<sup>18</sup> Meanwhile, phase III non-inferiority trial comparing TAF with TDF showed higher rates of ALT normalization in the TAF group after 96 weeks of treatment, applying both central laboratories' and AASLD cut-offs and in both HBeAg positive and negative patients (75% versus 68%,  $p=0.017$ ; and 81% versus 71%,  $p=0.038$ , respectively).<sup>29</sup> Available results from week 144 showed a significantly higher ALT-normalization with TAF according to the AASLD threshold in HBeAg negative and positive subjects [+12%, 95% CI (-0.7%, +24.6%);  $p=0.052$  and +10.9%, 95% CI (2.4%, 19.9%);  $p=0.010$ ,

respectively].<sup>32</sup> Underlying mechanisms that could explain a deeper decrease of ALT with TAF regimens remain unknown. However, a recent real-world cohort study of 21,182 patients receiving TDF or ETV supports the clinical relevance of ALT normalization. An ALT decline below AASLD thresholds during the first year of treatment was associated with fewer hepatic events after 6-year follow-up (3.51% *versus* 5.70%,  $p < 0.001$ ), including HCC.<sup>33</sup> Persistent ALT elevation despite effective viral suppression is suggested to be related to concomitant conditions such as steatosis and cardiovascular risk factors and it is linked to a lower regression of liver cirrhosis in NA treated patients.<sup>34</sup>

#### Serological response

HBeAg seroconversion is regarded as a hallmark of antiviral treatment since it conveys a lower viral replication and a partial immunological control of the infection. Also, it is regarded as a necessary requisite for HBsAg seroclearance.<sup>35</sup> HBsAg loss is currently considered the primary target for HBV therapies, since it allows treatment withdrawal and entails a clear improvement in clinical outcomes and a decrease in HCC risk. A large multicenter nationwide study performed in Hong Kong including 20,263 treated patients showed that HBsAg clearance confers additional benefits over viral suppression on reducing HCC risk (0.6% *versus* 5.6% at 8 years,  $p < 0.001$ ) but not on liver decompensation, liver transplantation and liver related mortality [adjusted hazard ratio (aHR) 0.99; 95% CI (0.30–3.26);  $p = 0.991$ ].<sup>23</sup> Also, a decline in HBsAg titres under NAs seems to predict HBsAg clearance, although HBsAg titres may be altered by HBeAg status and genotype.<sup>7,36–38</sup> Results from a meta-analysis showed similar rates of HBeAg clearance [RR = 1.05, 95% CI (0.68, 1.62),  $p = 0.82$ ] and seroconversion [RR = 0.93, 95% CI (0.54, 1.61);  $p = 0.80$ ] for TDF and ETV respectively.<sup>18</sup> Data concerning HBsAg loss were not analyzed, although previous studies reported no significant differences between the two regimens, with annual rate of HBsAg loss below 1% for HBeAg negative patients and in HBeAg positive subjects infected at birth.<sup>39</sup> According to a multicenter non-inferiority randomized trial, a steeper decrease in HBsAg was observed under TDF compared with ETV after 48 wks of treatment, with a greater reduction in HBeAg positive

patients ( $-0.365 \pm 0.611$  log<sub>10</sub>IU/ml) than in HBeAg negative subjects ( $0.070 \pm 0.191$ ).<sup>16</sup> Concerning TAF, randomized double-blinded comparison against TDF in both HBeAg negative and positive subjects did not show significant differences in HBeAg loss rate (22% *versus* 18%,  $p = 0.20$ ) and seroconversion to anti-HBeAg (18% *versus* 12%,  $p = 0.05$ ) at week 96; HBsAg loss was reached 1% in both groups ( $p = 0.88$ ) with no differences in HBsAg seroconversion ( $p = 0.88$ ) and similar decrease of HBsAg titres over treatment.<sup>29</sup>

#### Histological response

A significant regression of liver fibrosis and cirrhosis after long-term treatment with high barrier to resistance NAs has been observed. An open-label trial after 5 years of TDF treatment showed histological improvement ( $\geq 2$  point reduction in Knodell score) in 87% of 348 patients, while 51% had regression of fibrosis ( $\geq 1$  decrease by Ishak score) in liver biopsy performed at week 240 ( $p < 0.0001$ ). Seventy-one (74%) out of the 96 patients with cirrhosis (Ishak 5 or 6) at baseline had reversed liver cirrhosis and three (1.2%) out of 252 non-cirrhotic patients developed cirrhosis at the end of follow-up ( $p < 0.0001$ ). Histological improvement was also observed with ETV regimen in 88% of 57 patients (10 with advanced fibrosis or cirrhosis) after a median follow-up of 6 years.<sup>40</sup> Comorbidities such as alcohol or fatty liver seem to play a key role in histological progression of HBV despite an effective viral suppression. Changes in liver stiffness under NAs treatment have also been described, although the correlation with histological activity is uncertain.<sup>41</sup> A systematic review and meta-analysis described a decrease of 5.19 kPa ( $-3.34$  kPa to  $-7.03$  kPa) after 5-year treatment with either high or low barrier to resistance NAs. A greater decrease in liver stiffness was observed in those under TDF or ETV and higher ALT levels and viral load at baseline.<sup>42</sup> No similar studies have been performed with TAF. There are limited data on non-invasive biomarkers during antiviral treatment. A prospective study in 303 HBeAg negative CHB patients showed a significant decrease of both ALT to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) during 5 years of treatment with ETV, suggesting the usefulness of these markers to assess liver fibrosis improvement and treatment efficacy.<sup>43</sup> However, changes in

APRI and FIB-4 were not correlated with changes in liver fibrosis by Ishak score ( $p=0.39$  and  $p=0.05$  for APRI and FIB-4, respectively) after 240 weeks of TDF treatment in a multicenter cohort of 303 patients of two clinical trials.<sup>44</sup> Changes in FIB-4 have not been detected after 48 weeks of TAF treatment in 270 patients in a real-life cohort.<sup>45</sup>

### Clinical outcomes

The ultimate benefit of an effective antiviral treatment is to improve patient survival by reducing liver decompensation, liver transplantation and mortality. Benefits in CHB patients are illustrated by several studies and seem to be more remarkable in patients with cirrhosis. Even regression of small esophageal varices has been described after long-term treatment with TDF/ETV.<sup>46–49</sup> ETV regimen showed significant clinical benefits in 551 cirrhotic patients of a retrospective–prospective Asian study, reducing the risk of hepatic events (HR 0.51,  $p=0.002$ ), HCC (HR, 0.55;  $p=0.049$ ), liver-related mortality (HR 0.26;  $p<0.001$ ) and all-cause mortality (HR 0.34;  $p<0.001$ ) compared with an historical cohort.<sup>48,49</sup> An Asian retrospective study in patients with liver cirrhosis also showed a significant decrease in Model for End-Stage Liver Disease score in 605 subjects with 6-month transplant-free survival (from  $19.8 \pm 4.3$  to  $14.7 \pm 6.0$ ,  $p<0.001$ ) under NAs treatment. No significant differences between ETV ( $n=555$ ) and TDF group ( $n=50$ ) were reported ( $4.9 \pm 6.7$  versus  $7.9 \pm 8.3$ ,  $p=0.069$ ).<sup>50</sup> A multicenter study on 1088 cirrhotic patients also showed benefits of TDF-treated patients compared with a historical cohort of untreated individuals; TDF treatment was independently associated with reduced risks of HCC (aHR 0.46,  $p<0.01$ ), liver decompensations (aHR 0.28,  $p=0.01$ ) and death or liver transplant (aHR 0.06,  $p<0.01$ ).<sup>51</sup> In HIV/HBV co-infected individuals, data have shown high rates of virological and serological long-term response to either TDF- or TAF-based treatments, which were also associated with favorable clinical outcomes in this population.<sup>52–55</sup> Moreover, high barrier to resistance NAs contribute to prevent HBV-reinfection and improve long-term outcome in liver transplant recipients even in those receiving a limited hepatitis B immune globulin regimen. The main international guidelines recommend either TAF or ETV due to kidney liability of these patients.<sup>56,57</sup>

Clinical benefits of NAs seem to increase with the length of the treatment and with a maintained viral suppression. This was proved by a multicenter European study on 1205 subjects – with and without compensated cirrhosis – that described a decrease of HCC risk after 5 years of effective antiviral therapy with ETV/TDF. It was especially effective in patients with cirrhosis or with risk factors such as older age, lower platelets and liver stiffness measurement above 12 KpA.<sup>58</sup> HCC development, however, is still a subject of concern; since oncogenic risk seems to decrease but not disappear in non-cirrhotic CHB patients that achieve treatment response. Persistence of cccDNA with damage in cellular repair and oxidative stress have been proposed as underlying mechanisms that could explain carcinogenesis in patients without significant fibrosis. Hence, HCC is currently considered the main threat for CHB patients' survival.

TDF and ETV appear to have a similar effectiveness preventing hepatic events, as illustrated in a large longitudinal South Korean study including 1325 patients that described similar risk of liver related death or transplant [HR 0.96; 95% CI (0.23–4.07); log-rank  $p=0.955$ ], HCC [HR 1.36; 95% CI (0.72–2.56); log-rank  $p=0.340$ ] and hepatic decompensation [HR 1.64; 95% CI (0.67–4.00); log-rank  $p=0.276$ ] in ETV and TDF patients after 5-year follow-up.<sup>59</sup> Controversially, a higher risk of HCC in ETV-treated patients compared with TDF was described in a large cohort of Asian patients, suggesting a potential carcinogenic effect in ETV.<sup>60</sup> A retrospective nationwide multicenter study including 2897 Asian patients did not reproduce these results and reported a similar annual HCC incidence with ETV and TDF (1.92 versus 1.69 per 100 person-years, respectively;  $p=0.852$ ), without differences in mortality and liver transplantation during follow-up.<sup>61</sup> Another nationwide Korean study including 3022 consecutive patients (34% cirrhotic, 59% HBeAg positive) reported similar results with similar incidence rates of HCC (HR 1.030, propensity score matching model,  $p=0.880$ ) for ETV and TDF groups. Analysis of subgroups did not show differences in cirrhotic subjects.<sup>62</sup> In Europe, a recent multicenter study of 1935 Caucasian patients with CHB and a median follow-up of 7 years also described a similar HCC



incidence under ETV and TDF treatment (6.5% versus 8.0%,  $p=0.211$ ).<sup>63</sup> Similar results were released by a large multicenter French study including 2768 HBeAg positive and negative HBV mono-infected subjects from different ethnicities followed by a median of 45 months which concluded that the incidence of HCC (8.8 versus 9.1), liver decompensation (3.4 versus 4.9), transplantation (2.6 versus 1.3) or death (8.9 versus 11.1) was similar for TDF and ETV respectively, with no differences in univariable and multivariable aHR.<sup>64</sup> A recent meta-analysis analyzing 12 observational studies and one RCT did not find any difference between ETV and TDF groups ( $p>0.05$ ).<sup>65</sup> Concerning TAF, a 5-year comparison of cumulative HCC incidence in clinical trials cohorts did not show differences between TAF and TDF groups.<sup>66</sup>

#### *Treatment failure with high barrier to resistance NAs*

Virological breakthroughs defined by an increase in HBV-DNA levels of  $>1 \log_{10}$  from nadir, or its redetection after becoming undetectable, is rare and usually associated with lack of compliance. It could be more infrequently related to drug resistance emergence, which has been related to poorer clinical outcomes and higher risk of HCC.<sup>67,68</sup> ETV phenotypic resistance is detected in around 1% of treatment-naïve patients as a result of the reverse-transcriptase simultaneous substitutions.<sup>69</sup> Meanwhile, subjects previously exposed to lamivudine (LMV) experienced cross-resistance to ETV treatment in up to 50% of cases after 5-year treatment.<sup>69</sup> M204I/V  $\pm$  L180M mutations confer LMV resistance; a decreased susceptibility to ETV is present when T184, S202, M250 or lately identified A181 are also detected.<sup>69-71</sup> Standard dose of TDF in monotherapy has proved to be as effective as NA-combination therapy to achieve virological suppression after 48 weeks of treatment in patients with resistance to ETV.<sup>68</sup> On the other hand, no TDF resistance was identified in clinical trials with up to 10-year follow-up of monotherapy regimen in either naïve or treatment-experienced subjects.<sup>72-74</sup> Sporadic case-reports have been described, but resistance-associated mutations are not well characterized.<sup>74-76</sup> No reported cases of TAF resistance have been identified up to now in either naïve or treatment-experienced subjects.

















#### **Safety**

Both TDF and ETV have shown an accurate safety profile in pivotal trials and real life cohorts.<sup>15,73</sup> Mild adverse events such as headache, fatigue and nasopharyngitis have been reported with both drugs in less than 10% of cases.<sup>48</sup> Similar frequency of these events was described in randomized trials with TAF.<sup>4,77</sup> Mitochondrial toxicity and specifically lactic acidosis have been reported with all low barrier to resistance NAs, but the incidence with high barrier to resistance drugs seems to be extremely low and associated with concomitant conditions such as kidney failure and end-stage liver disease.<sup>78,79</sup> No cases under TAF have been reported. Main concerns of high barrier to resistance NAs safety are related to kidney and bone side effects, primarily described in HIV cohorts.<sup>80</sup> Based on this, European Association for the Study of the Liver clinical practice guidelines recommended the election or switch of either ETV or TAF over TDF for CHB in groups at higher risk of bone and kidney toxicity. These recommendations gathered patients aged above 60 years and subjects with bone or kidney comorbidities, conditions that could reach up to 66% of real-life HBV cohorts according to a recent European observational study.<sup>81</sup> Table 1 summarizes the safety and monitoring of CHB patients under the recommended NAs in special situations.<sup>82-88</sup>

#### *Kidney-related side effects*

Both TDF and ETV are metabolized through the kidney and must be adjusted in glomerular filtrate rates (GFRs) under 50 ml/min per 1.73 m<sup>2</sup>, while TAF is not approved in GFR below 15 ml/min per m<sup>2</sup>. However, TDF kidney toxicity mechanisms are not based on glomerular function but in tubular-cell damage caused by high intracellular TDF concentrations. Thus, glomerular function markers such as estimated GFR (eGFR) and creatinine clearance are deemed as underestimating TDF-associated kidney injury.<sup>80,89</sup> Proximal tubular dysfunction could be assessed by urinary excretion of glucose, phosphate and low molecular weight proteins such as B2-microglobulin and retinol-binding-protein (RBP). Among them, altered RBP excretion has been suggested to detect early subclinical nephrotoxicity under TDF, according to a cross-sectional real-world study; although it is not generally used in clinical

**Table 1.** Monitoring recommendations and considerations for first line NAs.

	TDF	TAF	ETV
	Monitor with serum creatinine, eGFR and serum P <sup>+</sup> at start and then regularly. Dose adjustment if eGFR <50 ml/min per 1.73 m <sup>2</sup> . Consider switch to TAF or ETV if P <sup>+</sup> <2.5 mmol/dl, eGFR <60 ml/min per 1.73 m <sup>2</sup> or elderly. <sup>70</sup>	No monitoring needed. No dose adjustment needed. Scarce evidence in hemodialysis and eGFR <15 ml/min per 1.73 m <sup>2</sup> . Favorable preliminary data. <sup>71,72</sup>	Monitor with serum creatinine and eGFR at start and then regularly. Dose adjustment if eGFR <50 ml/min per 1.73 m <sup>2</sup> .
	Consider switch to TAF or ETV if P <sup>+</sup> <2.5 mmol/dl, concomitant bone condition or elderly.	No monitoring needed.	No monitoring needed.
	Usual dose. Extreme kidney monitoring.	Scarce evidence. Favorable preliminary data. <sup>73</sup>	Increase usual dose to 1 mg/day. Extreme kidney monitoring.
	Extremely infrequent. Ensure adherence. Switch to ETV or combination therapy.	Not reported.	Resistance in 1% in naïve, 50% LMV-experienced. Ensure adherence. Switch to TDF usual dose in monotherapy.
	Recommended.	Scarce evidence. Limited favorable data in HIV mono-infected women. <sup>74</sup>	Not recommended.
	Above 2 years old.	Scarce experience, above 12 years old.	Above 2 years old.
	As part of HAART.	As part of HAART.	Not recommended in monotherapy.
	No direct anti-HDV activity. <sup>75</sup> Might be added to peg-IFN $\alpha$ and/or new therapies according to HBV replication. <sup>76</sup>	No direct anti-HDV activity. Data extrapolated from other NAs. <sup>75</sup> Might be added to peg-IFN $\alpha$ and/or new therapies according to HBV replication. <sup>76</sup>	No direct anti-HDV activity. <sup>75</sup> Might be added to peg-IFN $\alpha$ and/or new therapies according to HBV replication. <sup>76</sup>
 Kidney safety.  Bone safety.  End-stage liver disease.  Drug resistance.  Pregnancy and childbearing women.  Children.  HIV co-infection.  HDV co-infection. eGFR, estimated glomerular filtrate rate; ETV, entecavir; HAART, high active antiretroviral therapy; HBV, hepatitis B virus; HDV, hepatitis delta virus; HIV, human immunodeficiency virus; IFN, interferon; LMV, lamivudine; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; P <sup>+</sup> , serum phosphate.			

practice.<sup>90</sup> Changes in serum or urinary phosphate were not detected between ETV and TDF groups. Fanconi syndrome is the most severe manifestation of TDF tubular toxicity and has been described only in sporadic HBV-mono-infected cases, with resolution after TDF withdrawal.<sup>91</sup> In HBV-mono-infected patients, an

increase in serum creatinine was described after 10-year TDF-treatment in up to 5% of patients (2% greater than 0.5 mg/dl) and hypophosphatemia was reported in 1.7% of cases.<sup>73</sup> A smaller decline in eGFR was reported (−1.2 versus −4.8 mg/dl; *p* < 0.001) at 96 weeks of phase III studies comparing TAF with TDF and in

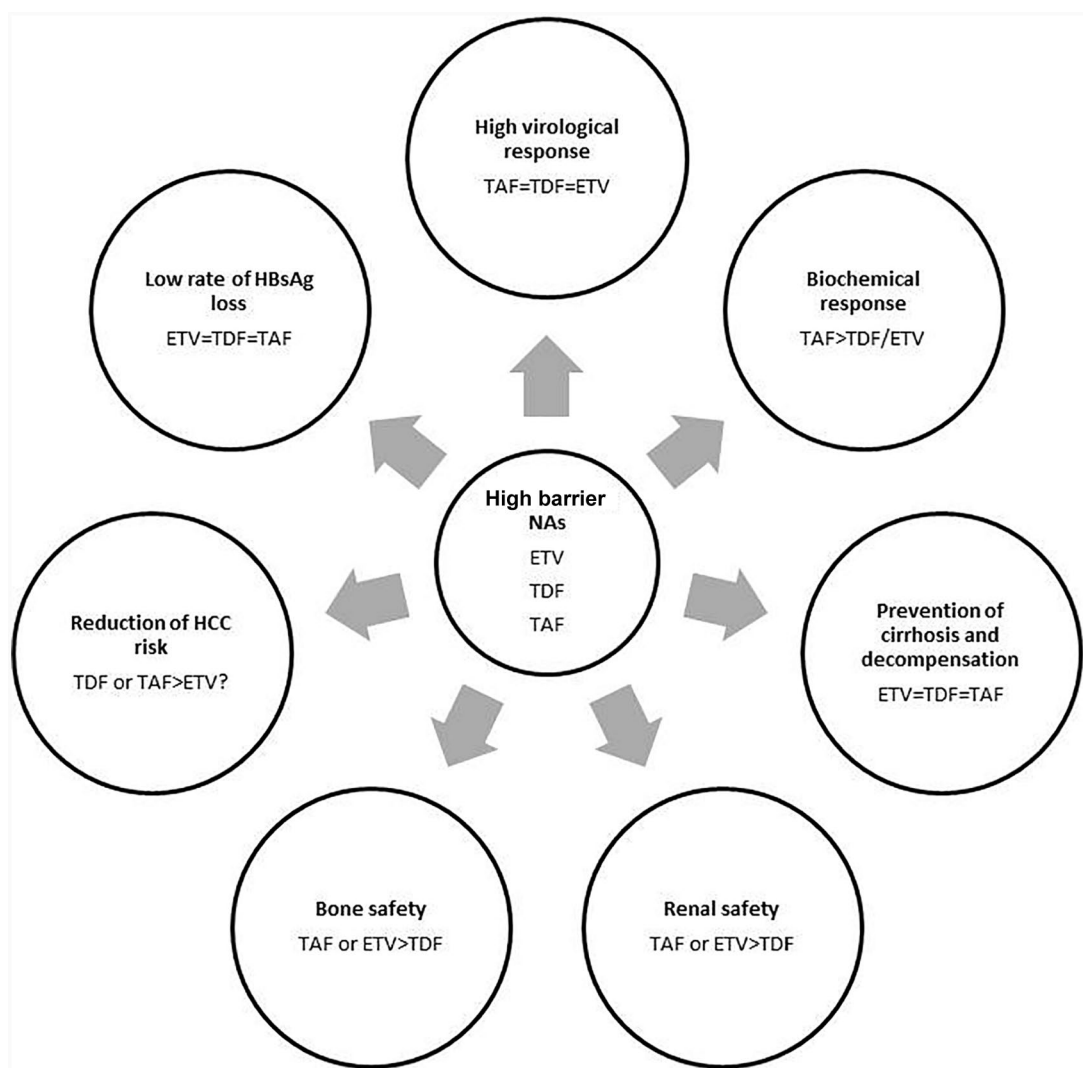
preliminary results of week 144 ( $-1.2$  versus  $-6$ ;  $p < 0.001$ ).<sup>32</sup> Tubular markers (RBP and B2-microglobulin/creatinine ratios) were also significantly lower in TAF group ( $p < 0.001$ ) in results from week 96 and week 144, while no difference was reported in serum phosphate between TDF and TAF groups [ $-0.1$  ( $-0.4, 0.2$ ) versus  $-0.1$  ( $-0.4, 0.3$ )] at week 96.<sup>29</sup> Data also suggest a stabilization or slight improvement of TDF-related kidney damage after treatment-switch to either TAF or ETV. A prospective open-label trial detected significant changes only 12 weeks after the TDF switch to TAF. Urinary B2-microglobulin/creatinine and RBP/creatinine significantly decreased ( $p < 0.01$ ). No differences were found in other tubular markers and in glomerular function estimations.<sup>92</sup> Recently, a phase III non-inferiority study performed in 490 patients yielded slight benefits of switching from TDF to TAF without efficacy impairment: a median change of eGFR by Cockcroft–Gault was statistically significant ( $0.94$  ml/min versus  $2.7$  ml/min,  $p < 0.0001$ ). Changes in tubular and bone turnover markers were also observed between TAF and TDF arms ( $0.0$  versus  $0.02$ ,  $p = 0.0063$  in serum creatinine and  $14\%$  versus  $22\%$ ,  $p = 0.013$  of more than grade 1 proteinuria by dipstick), although no differences were reported in serum phosphate [ $0.0$  ( $-0.3$ – $0.3$ ) versus  $0.0$  ( $-0.2$ – $0.2$ ),  $p = 0.7$ ].<sup>93</sup> Recently released phase II study results of week 48, after switching from TDF to TAF in patients with advance kidney disease and hemodialysis, showed stabilization of eGFR and markers of renal tubular function.<sup>83</sup> Similar results have been recently suggested after switching from ETV in patients with renal failure. A retrospective study of 313 patients treated with ETV or NA combination concluded that eGFR significantly improved after switching to TAF in patients with chronic kidney disease (adjusted slope coefficient difference:  $2.75$  ml/min per  $1.73$  m<sup>2</sup> per 48 weeks;  $p = 0.001$ ).<sup>94</sup> No significant change was observed in subjects with maintained glomerular function. This results are consistent with available evidence from HIV/HBV coinfecting cohorts; a prospective study in 106 HIV/HBV patients showed an increase of  $6.2$  ml/min  $1.73$  m<sup>2</sup> (95% CI  $2.4$ – $10.0$ ) in GFR and a decline in protein-to-creatinine ratio after 1 year of treatment-switch from TDF to TAF in those patients with GFR below  $60$  ml/min  $1.73$  m<sup>2</sup>.<sup>95</sup> Other studies in the real setting have also pointed to concomitant conditions such as diabetes mellitus and previous decreased eGFR as factors associated with renal toxicity.<sup>96</sup>

### Bone-related side effects

Bone effects of TDF regimens are probably related to an increase of phosphate tubular turnover but also to a modulation in osteoclastic/blastic activity.<sup>70</sup> A relative decrease in bone marrow density (BMD) with TDF was detected, with unclear clinical implications.<sup>80,97</sup> Phase III non-inferiority studies comparing TAF with TDF showed that BMD suffered a smaller decline in TAF group in both hip and spine ( $-0.33\%$  versus  $-2.51\%$ ;  $p < 0.001$  and  $-0.75\%$  versus  $-2.57\%$ ;  $p < 0.001$ , respectively) after 96 weeks of treatment.<sup>27,77</sup> Results after 144 weeks have also shown a significantly smaller decrease in hip and spine BMD in the TAF group.<sup>32</sup> Changes in BMD seem to be at least partially reversible after TDF withdrawal according to switching treatment studies. A study in HIV patients above 60 years old showed a statistically significant improvement of around 2% in hip and spine marrow density when switching from TDF containing regimen to TAF.<sup>98</sup> No similar studies have been published with elderly HBV-mono-infected patients. Recently, a phase III non-inferiority study performed in 490 patients yielded slight benefits of switching from TDF to TAF without efficacy impairment. A difference in BMD of 1.17% in hip [95% CI (0.80–1.54);  $p < 0.0001$ ] and 1.85% spine [95% CI (1.24–2.46);  $p < 0.0001$ ] after 48 weeks of switching was reported.<sup>92</sup> A prospective open-label trial detected significant changes only 12 weeks after the TDF switch to TAF. Hip and spine BMD increased 12.9% and 2.4% ( $p < 0.01$ ), respectively. Longer follow-up and wider real-life experience in high-risk populations should be performed to fully understand the clinical relevance of the bone effects of TDF. The efficacy and safety of first line NAs are summarized in Figure 1.

### Conclusion

High barrier to resistance NAs are regarded an accurate therapeutic option for CHB treatment. Emergence of treatment-related adverse events must be monitored, especially in individuals with concomitant conditions who are at higher risk of developing kidney and bone toxicity with TDF. TAF has shown an improved bone and renal safety profile, with beneficial effects even after treatment-switch. However, a better understanding of the clinical relevance of these findings is needed through lengthier real-world studies including special populations and cost-effectiveness assessments. ETV, TDF and TAF have



**Figure 1. Efficacy and safety of high barrier to resistance nucleos(t)ide analogues in chronic hepatitis B.**

Virological response is defined as undetectable HBV-DNA by PCR with a lower limit of detection of 10IU/ml after one year of treatment. Biochemical response is defined as ALT normalization under treatment applying traditional cutoffs and AASLD-proposed cutoffs.

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; ETV entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC hepatocellular; NA, nucleos(t)ides analogue; PCR, polymerase chain reaction; TAF tenofovir alafenamide; TDF tenofovir disoproxil fumarate.

proved to be highly effective, although HCC risk does not seem to be suppressed and active HCC surveillance in clinical practice must be ensured. Further research is needed to establish differences in HCC prevention among available drugs.

#### Author contributions

Concept and design: LR and MB.  
 Drafting of the manuscript: LR and MB.  
 Critical revision of the manuscript for important intellectual content: LR, M R-B, RE and MB.  
 Approved the version to be published: LR, MR-B, RE and MB.

#### Conflict of interest statement

M. Buti and R. Esteban report grant support and/or consultancy and lecture fees from AbbVie, Gilead Sciences, Bristol-Myers Squibb, Janssen and MSD. M. Riveiro-Barciela reports grant support from Gilead Sciences and lecture fees from Gilead Sciences and Grifols.

#### Ethics statement

Our study did not require ethical board approval because it did not involve human or animal trials.



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## References

- World Health Organization. *Global hepatitis report 2017*. Geneva: WHO, 2017.
- Fonseca MA, Ling JZJ, Al-Siyabi O, *et al.* The efficacy of hepatitis B treatments in achieving HBsAg seroclearance: a systematic review and meta-analysis. *J Viral Hepat* 2020; 27: 650–662.
- Petersen J and Buti M. Considerations for the long-term treatment of chronic hepatitis B with nucleos(t)ide analogs. *Expert Rev Gastroenterol Hepatol* 2012; 6: 683–694.
- Tang LSY, Covert E, Wilson E, *et al.* Chronic hepatitis B infection. *JAMA* 2018; 319: 1802.
- Raffetti E, Fattovich G and 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.
- Chayanupatkul M, Omino R, Mittal S, *et al.* Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. *J Hepatol* 2017; 66: 355–362.
- Lok ASF, McMahon BJ, Brown RS, *et al.* Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. *Hepatology* 2016; 63: 284–306.
- Seto WK, Lo YR, Pawlotsky JM, *et al.* Chronic hepatitis B virus infection. *Lancet* 2018; 392: 2313–2324.
- European Association for the Study of the Liver (EASL). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370–398.
- Sarin SK, Kumar M, Lau GK, *et al.* Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; 10: 1–98.
- World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection [Internet]. Geneva: WHO, 2015. Available from: <http://www.who.int/hiv/topics/hepatitis/en/%0A978>
- Terrault NA, Lok ASF, McMahon BJ, *et al.* Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B Guidance American association for the study of liver diseases. *Hepatology* 2018; 67: 1560–1599.
- Marcellin P, Heathcote EJ, Buti M, *et al.* Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008; 359: 2442–2455.
- Lai C-L, Shouval D, Lok AS, *et al.* Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2006; 354: 1011–1020.
- Ahn J, Lee HM, Lim JK, *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.
- Koike K, Suyama K, Ito H, *et al.* Randomized prospective study showing the non-inferiority of tenofovir to entecavir in treatment-naïve chronic hepatitis B patients. *Hepatol Res* 2018; 48: 59–68.
- Chang TT, Lai CL, Yoon SK, *et al.* Entecavir treatment for up to 5 years in patients with hepatitis b e antigen-positive chronic hepatitis B. *Hepatology* 2010; 51: 422–430.
- Chen MB, Wang H, Zheng QH, *et al.* Comparative efficacy of tenofovir and entecavir in nucleos(t)ide analogue-naïve chronic hepatitis B: a systematic review and meta-analysis. *PLoS One* 2019; 14: 1–13.
- Riveiro-Barciela M, Tabernero D, Calleja JL, *et al.* Effectiveness and safety of entecavir or tenofovir in a Spanish cohort of chronic hepatitis B patients: validation of the page-B score to predict hepatocellular carcinoma. *Dig Dis Sci* 2017; 62: 784–793.
- Lampertico P, Soffredini R, Yurdaydin C, *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. *Dig Liver Dis* 2014; 46: e14.
- Ono A, Suzuki F, Kawamura Y, *et al.* Long-term continuous entecavir therapy in nucleos(t)ide-naïve chronic hepatitis B patients. *J Hepatol* 2012; 57: 508–514.
- Park C-H, Kim HY, Lee SW, *et al.* On-treatment and off-treatment efficacy of entecavir in a real-life cohort of chronic hepatitis B patients. *Eur J Gastroenterol Hepatol* 2016; 28: 1179–1187.

23. Yip TC-F, Wong GL-H, Chan HL-Y, *et al.* HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues. *J Hepatol* 2019; 70: 361–370.
24. Ha NB, Trinh HN, Rosenblatt L, *et al.* Treatment outcomes with first-line therapies with entecavir and tenofovir in treatment-naïve chronic hepatitis B patients in a routine clinical practice. *J Clin Gastroenterol* 2016; 50: 169–174.
25. Marcellin P, Zoulim F, Hézode C, *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.
26. Petersen J, Heyne R, Mauss S, *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.
27. Chan HLY, Fung S, Seto WK, *et al.* Tenofovir alafenamide versus 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.
28. Kim HJ, Chan HLY, Lim Y, *et al.* Three-year efficacy and safety of tenofovir alafenamide compared with tenofovir disoproxil fumarate in HBeAg-negative and -positive patients with chronic hepatitis B. *Hepatology* 2018; 68(Suppl. 1): 227A–228A.
29. Agarwal K, Brunetto M, Seto WK, *et al.* 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol* 2018; 68: 672–681.
30. CTRI/2014/01/004329. Double-blind study to evaluate the safety and efficacy of tenofovir alafenamide (TAF) 25 mg QD versus tenofovir disoproxil fumarate (TDF) 300 mg QD for the treatment of HBeAg-positive, chronic hepatitis B. <http://www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2014/01/004329> [Internet], 2014. Available from: <https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01845162/full>
31. Papatheodoridis G, Mimidis K, Spilios Manolakopoulos NG, *et al.* Real-world experience from tenofovir alafenamide use in chronic hepatitis B: an Hellenic multicenter real-life clinical study (HERACLIS-TAF). *J Hepatol Abstr B EASL Conf 2020* 2020; 73: S653–S915.
32. Chan H, Lim Y, Seto W, *et al.* Three year efficacy and safety of tenofovir alafenamide (TAF) compared to tenofovir disoproxil fumarate (TDF) in Hbeag-negative and Hbeag-positive patients with chronic hepatitis B. In: *The Liver Meeting 2018, American Association for the Study of Liver Diseases (AASLD)*, San Francisco, USA, 9–13 November 2018, Abstracts in Hepatology, Vol. 68, Suppl 1, pp. 227A–228A [Internet].
33. Wong GLH, Chan HLY, Tse YK, *et al.* Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B. *J Hepatol* 2018; 69: 793–802.
34. Marcellin P, Gane E, Buti M, *et al.* Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013; 381: 468–475.
35. Wang B, Carey I, Bruce M, *et al.* HBsAg and HBcrAg as predictors of HBeAg seroconversion in HBeAg-positive patients treated with nucleos(t)ide analogues. *J Viral Hepat* 2018; 25: 886–893.
36. Cornberg M, Suk-Fong Lok A, Terrault NA, *et al.* Guidance for design and endpoints of clinical trials in chronic hepatitis B - report from the 2019 EASL-AASLD HBV treatment endpoints conference. *Hepatology* 2019; 71: 1070–1092.
37. Cornberg M, Wong VW-S, Locarnini S, *et al.* The role of quantitative hepatitis B surface antigen revisited. *J Hepatol* 2017; 66: 398–411.
38. Marcellin P, Buti M, Krastev Z, *et al.* Kinetics of hepatitis B surface antigen loss in patients with HBeAg-positive chronic hepatitis B treated with tenofovir disoproxil fumarate. *J Hepatol* 2014; 61: 1228–1237.
39. Grossi G, Viganò M, Loglio A, *et al.* Hepatitis B virus long-term impact of antiviral therapy nucleot(s)ide analogues (NUCs). *Liver Int* 2017; 37: 45–51.
40. Chang T-T, Liaw Y-F, Wu S-S, *et al.* Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology* 2010; 52: 886–893.
41. Fung J, Lai CL, Wong DKH, *et al.* Significant changes in liver stiffness measurements in patients with chronic hepatitis B: 3-year follow-up study. *J Viral Hepat* 2011; 18: e200–5.
42. Facciorusso A, Garcia Perdomo HA, Muscatiello N, *et al.* Systematic review with meta-analysis: change in liver stiffness during anti-viral therapy in patients with hepatitis B. *Dig Liver Dis* 2018; 50: 787–794.


43. Liu R, Guo J, Lu Y, *et al.* Changes in APRI and FIB-4 in HBsAg-negative treatment-naïve chronic hepatitis B patients with significant liver histological lesions receiving 5-year entecavir therapy. *Clin Exp Med* 2019; 19: 309–320.
44. Kim WR, Berg T, Asselah T, *et al.* Evaluation of APRI and FIB-4 scoring systems for non-invasive assessment of hepatic fibrosis in chronic hepatitis B patients. *J Hepatol* 2016; 64: 773–780.
45. Reddy R, Curry M, Bae H, *et al.* Longer-term experience with tenofovir alafenamide (TAF) in HBV-infected patients; changes in EGFR, FIB4, ALT, and DNA suppression. *J Hepatol* 2020; 73: S653–S915.
46. Lampertico P, Invernizzi F, Viganò M, *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.
47. Hosaka T, Suzuki F, Kobayashi M, *et al.* Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology* 2013; 58: 98–107.
48. Wong GL-H, Chan HL-Y, Mak CW-H, *et al.* Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology* 2013; 58: 1537–1547.
49. Su TH, Hu TH, Chen CY, *et al.* Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. *Liver Int* 2016; 36: 1755–1764.
50. Yip TC-F, Lee HW, Wong VW-S, *et al.* Factors associated with improvement in MELD score after antiviral treatment in patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2020; 35: 1610–1618.
51. Liu K, Choi J, Le A, *et al.* Tenofovir disoproxil fumarate reduces hepatocellular carcinoma, decompensation and death in chronic hepatitis B patients with cirrhosis. *Aliment Pharmacol Ther* 2019; 50: 1037–1048.
52. Martín-Carbonero L, Teixeira T, Poveda E, *et al.* Clinical and virological outcomes in HIV-infected patients with chronic hepatitis B on long-term nucleos(t)ide analogues. *AIDS* 2011; 25: 73–79.
53. Kosi L, Reiberger T, Payer BA, *et al.* Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. *J Viral Hepat* 2012; 19: 801–810.
54. Benhamou Y, Fleury H, Trimoulet P, *et al.* Anti-hepatitis B virus efficacy of tenofovir disoproxil fumarate in HIV-infected patients. *Hepatology* 2006; 43: 548–555.
55. Gallant J, Brunetta J, Crofoot G, *et al.* Brief report. *J Acquir Immune Defic Syndr* 2016; 73: 294–298.
56. Li M, Hou Z, Yao G, *et al.* The strategy and efficacy of prophylaxis against hepatitis B virus recurrence after liver transplantation for HBV-related disease in the era of potent nucleos(t)ide analogues: a meta-analysis. *J Dig Dis*. Epub ahead of print 31 October 2020. DOI: 10.1111/1751-2980.12959.
57. Dobrindt EM, Keshi E, Salim Y, *et al.* Hepatitis B immunoglobulin discontinuation in long-term liver transplant patients. *Transpl Infect Dis* 2020; 22: e13303.
58. Papatheodoridis GV, Idilman R, Dalekos GN, *et al.* The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. *Hepatology* 2017; 66: 1444–1453.
59. Kim BG, Park NH, Lee SB, *et al.* Mortality, liver transplantation and hepatic complications in patients with treatment-naïve chronic hepatitis B treated with entecavir vs tenofovir. *J Viral Hepat* 2018; 25: 1565–1575.
60. Choi J, Kim HJ, Lee J, *et al.* Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. *JAMA Oncol* 2019; 5: 30–36.
61. Kim SU, Seo YS, Lee HA, *et al.* A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in South Korea. *J Hepatol* 2019; 71: 456–464.
62. Lee SW, Kwon JH, Lee HL, *et al.* Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and mortality in treatment-naïve patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis. *Gut* 2020; 69: 1301–1308.
63. Papatheodoridis GV, Dalekos GN, Idilman R, *et al.* Similar risk of hepatocellular carcinoma during long-term entecavir or tenofovir therapy in Caucasian patients with chronic hepatitis B. *J Hepatol*. Epub ahead of print 15 June 2020. DOI: 10.1016/j.jhep.2020.06.011.
64. Pol S, ANRS/AFEF HEPATHER Study Group. Tenofovir versus entecavir in HBV chronic infection: impact on HCC and other liver-related complications occurrences. *Hepatology* 2019; 70(Suppl): 129A.

65. Wang XX, Liu X, Dang Z, *et al.* Nucleos(t)ide analogues for reducing hepatocellular carcinoma in chronic hepatitis B patients: a systematic review and meta-analysis. *Gut Liver* 2020; 14: 232–247.
66. Kim WR, Loomba R, Berg T, *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.
67. Huang YJ, Yang SS, Yeh HZ, *et al.* Association of virological breakthrough and clinical outcomes in entecavir-treated HBeAg-positive chronic hepatitis B. *PLoS One* 2019; 14: e0221958.
68. Lim YS, Byun KS, Yoo BC, *et al.* Tenofovir monotherapy versus tenofovir and entecavir combination therapy in patients with entecavir-resistant chronic hepatitis B with multiple drug failure: results of a randomised trial. *Gut* 2016; 65: 852–860.
69. Tenney DJ, Rose RE, Baldick CJ, *et al.* Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology* 2009; 49: 1503–1514.
70. Chen R, Liu Y, Luo D, *et al.* Hepatitis B virus mutation pattern rtA181S+T184I+M204I may contribute to multidrug resistance in clinical practice: analysis of a large cohort of Chinese patients. *Antiviral Res* 2020; 180: 104852.
71. Liu Y, Zhou Y, Li X, *et al.* Hepatitis B virus mutation pattern rtL180M+A181C+M204V may contribute to entecavir resistance in clinical practice. *Emerg Microbes Infect* 2019; 8: 354–365.
72. Fung S, Kwan P, Fabri M, *et al.* Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2014; 146: 980–988.
73. Marcellin P, Wong DK, Sievert W, *et al.* Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. *Liver Int* 2019; 39: 1868–1875.
74. Liu Y, Corsa AC, Buti M, *et al.* No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg– patients with chronic hepatitis B after 8 years of treatment. *J Viral Hepat* 2017; 24: 68–74.
75. Zoulim F and Locarnini S. Optimal management of chronic hepatitis B patients with treatment failure and antiviral drug resistance. *Liver Int* 2013; 33(Suppl. 1): 116–124.
76. Chapman JS and Georgopadkou NH. Routes of quinolone permeation in *Escherichia coli*. *Antimicrob Agents Chemother* 1988; 32: 438–442.
77. Buti M, Gane E, Seto WK, *et al.* Tenofovir alafenamide versus 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.
78. Lange CM, Bojunga J, Hofmann WP, *et al.* Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009; 50: 2001–2006.
79. Jung TY, Jun DW, Lee KN, *et al.* Fatal lactic acidosis in hepatitis B virus-associated decompensated cirrhosis treated with tenofovir. *Medicine* 2017; 96: e7133.
80. Casado JL. Renal and bone toxicity with the use of tenofovir: understanding at the end. *AIDS Rev* 2016; 18: 59–68.
81. Roade L, Loglio A, Borghi M, *et al.* Application of EASL 2017 criteria for switching hepatitis B patients from tenofovir disoproxil to entecavir or tenofovir alafenamide. *Dig Liver Dis* 2020; 52: 1164–1169.
82. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Practice Guideline* 2017; 67: 370–398.
83. Janssen H, Lampertico P, Chen C-Y, *et al.* Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with renal impairment: week 48 results from a phase 2 open label study. *J Hepatol EASL Conf Abstr B* 2020; 70: S653–S915.
84. Mina SF, Scott KF, Edward T, *et al.* Tenofovir alafenamide fumarate is effective and has superior renal safety mainly among stage 2 chronic kidney disease (CKD): real-world study from the Canadian Hepatitis B network (CANHEPB). *Hepatology* 2019; 70.
85. Lim Y-S, Lin C, Heo J, *et al.* Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with hepatic impairment: week 48 results from a phase 2 open label study. *J Hepatol* 2020; 73(Suppl.): S872.
86. Eke AC, Brooks KM, Gebreyohannes RD, *et al.* Tenofovir alafenamide use in pregnant and lactating women living with HIV. *Expert Opin Drug Metab Toxicol* 2020; 16: 333–342.
87. Brancaccio G and Gaeta GB. Treatment of chronic hepatitis due to hepatitis B and hepatitis



- delta virus coinfection. *Int J Antimicrob Agents* 2019; 54: 697–701.
88. Yurdaydin C, Abbas Z, Buti M, *et al.* Treating chronic hepatitis delta: the need for surrogate markers of treatment efficacy. *J Hepatol* 2019; 70: 1008–1015.
  89. Buti M, Roade L, Riveiro-Barciela M, *et al.* Optimal management of chronic hepatitis B patients receiving nucleos(t)ide analogues. *Liver Int* 2020; 40(S1): 15–21.
  90. Rodriguez-Novoa S, Garcia-Samaniego J, Prieto M, *et al.* Altered underlying renal tubular function in patients with chronic hepatitis B receiving nucleos(t)ide analogs in a real-world setting the MENTE study. *J Clin Gastroenterol* 2016; 50: 779–789.
  91. Viganò M, Brocchieri A, Spinetti A, *et al.* Tenofovir-induced Fanconi syndrome in chronic hepatitis B monoinfected patients that reverted after tenofovir withdrawal. *J Clin Virol* 2014; 61: 600–603.
  92. Fong TL, Lee BT, Tien A, *et al.* Improvement of bone mineral density and markers of proximal renal tubular function in chronic hepatitis B patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. *J Viral Hepat* 2019; 26: 561–567.
  93. Lampertico P, Buti M, Fung S, *et al.* Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. *Lancet Gastroenterol Hepatol* 2020; 5: 441–453.
  94. Ogawa E, Nomura H, Nakamuta M, *et al.* Tenofovir alafenamide after switching from entecavir or nucleos(t)ide combination therapy for patients with chronic hepatitis B. *Liver Int* 2020; 40: 1578–1589.
  95. Surial B, Béguelin C, Chave JP, *et al.* Brief report: switching from TDF to TAF in HIV/ HBV-coinfected individuals with renal dysfunction—a prospective cohort study. *J Acquir Immune Defic Syndr* 2020; 85: 227–232.
  96. Min IS, Lee CH, Shin IS, *et al.* Treatment outcome and renal safety of 3-year tenofovir disoproxil fumarate therapy in chronic hepatitis B patients with preserved glomerular filtration rate. *Gut Liver* 2019; 13: 93–103.
  97. Grigsby IF, Pham L, Mansky LM, *et al.* Tenofovir treatment of primary osteoblasts alters gene expression profiles: implications for bone mineral density loss. *Biochem Biophys Res Commun* 2010; 394: 48–53.
  98. Maggiolo F, Rizzardini G, Raffi F, *et al.* Bone mineral density in virologically suppressed people aged 60 years or older with HIV-1 switching from a regimen containing tenofovir disoproxil fumarate to an elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide single-tablet regimen: a multicentre, open-label, phase 3b, randomised trial. *Lancet HIV* 2019; 6: e655–e666.

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