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

Luisa Roade, Mar Riveiro-Barciela, Rafael Esteban and Maria Buti

***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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Correspondence to:
Maria Buti
Liver Unit, Internal Medicine Department, Hospital Universitario Vall d'Hebrón, Vall d'Hebron Barcelona Hospital Campus, Barcelona, 119-129, Spain.

Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto Carlos III, Madrid, Spain
mbuti@vhebron.net

Luisa Roade
Mar Riveiro-Barciela
Rafael Esteban
Liver Unit, Internal Medicine Department, Hospital Universitario Vall d'Hebrón, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain.

Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto Carlos III, Madrid, Spain.

Introduction

Chronic hepatitis B (CHB) is still considered a leading cause of mortality worldwide, with approximately 780,000 annual deaths.[1,2] 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).[3] Without treatment, up to 40% of these patients will develop long-term complications such as liver cirrhosis and hepatocellular carcinoma (HCC).[4–6] Effective viral suppression using antiviral drugs has shown to improve patients' survival and quality of life.[7] However, there is no current therapeutic approach that achieves virological cure, which means an eradication of circular covalently closed DNA (cccDNA) from liver cells.[8] 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.[9–11] 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.[9,10,12] High barrier to resistance NAs in monotherapy have shown an accurate safety

profile and high rates of viral response in CHB patients. The emergence of TAF, a tenofovir prodrug, 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.[9] 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.[13–16] 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.[17] 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.[18] 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.[19–22] 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.[23] Similar viral suppression rate was reported after 24 months of treatment in a multicenter retrospective study performed in the United States in 557 subjects, with no differences between TDF and ETV groups.[24] 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.[20,25,26]

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.[27–29] Phase III non-inferiority TDF *versus* TAF studies with up to 144 weeks of follow-up are currently on-going.[30] 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.[31,32]

Biochemical response

Alanine aminotransferase (ALT) normalization under antiviral treatment has been associated with a decrease in viral replication, tissue damage and necroinflammation.[9] 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.[18] 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).[29] 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].[32] 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.[33] 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.[34]

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.[35] 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); $p = 0.991$].[23] Also, a decline in HBsAg titles under NAs seems to predict HBsAg clearance, although HBsAg titles may be altered by HBeAg status and genotype.[7,36–38] 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.[18] 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.[39] 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 ± 0.611 log10 IU/ml) than in HBeAg negative subjects (0.070 ± 0.191).[16] 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 titles over treatment.[29]

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 (⩾2 point reduction in Knodell score) in 87% of 348 patients, while 51% had regression of fibrosis (⩾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.[40] 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.[41] 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.[42] 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.[43] 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.[44] Changes in FIB-4 have not been detected after 48 weeks of TAF treatment in 270 patients in a real-life cohort.[45]

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.[46–49] 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.[48,49] 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 ± 4.3 to 14.7 ± 6.0, $p < 0.001$) under NAs treatment. No significant differences between ETV ($n = 555$) and TDF group ($n = 50$) were reported (4.9 ± 6.7 *versus* 7.9 ± 8.3, $p = 0.069$).[50] 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, $p < 0.01$).[51] 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.[52–55] 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.[56,57]

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.[58] 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.[59] 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.[60] 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.[61] 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.[62] 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%, $p = 0.211$).[63] 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.[64] A recent meta-analysis analyzing 12 observational studies and one RCT did not find any difference between ETV and TDF groups ($p > 0.05$).[65] Concerning TAF, a 5-year comparison of cumulative HCC incidence in clinical trials cohorts did not show differences between TAF and TDF groups.[66]

Treatment failure with high barrier to resistance NAs

Virological breakthroughs defined by an increase in HBV-DNA levels of >1 log10 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.[67,68] ETV phenotypic resistance is detected in around 1% of treatment-naïve patients as a result of the reverse-transcriptase simultaneous substitutions.[69] Meanwhile, subjects previously exposed to lamivudine (LMV) experienced cross-resistance to ETV treatment in up to 50% of cases after 5-year treatment.[69] M204I/V ± L180M mutations confer LMV resistance; a decreased susceptibility to ETV is present when T184, S202, M250 or lately identified A181 are also detected.[69–71] 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.[68] 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.[72–74] Sporadic case-reports have been described, but resistance-associated mutations are not well characterized.[74–76] 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.[15,73] Mild adverse events such as headache, fatigue and nasopharyngitis have been reported with both drugs in less than 10% of cases.[48] Similar frequency of these events was described in randomized trials with TAF.[4,77] 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.[78,79] 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.[80] 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.[81] Table 1 summarizes the safety and monitoring of CHB patients under the recommended NAs in special situations.[82–88]

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^2, while TAF is not approved in GFR below 15 ml/min per m^2. 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.[80,89] 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
Kidney safety.	Monitor with serum creatinine, eGFR and serum P^+ at start and then regularly. Dose adjustment if eGFR <50 ml/min per 1.73 m^2. Consider switch to TAF or ETV if P^+ <2.5 mmol/dl, eGFR <60 ml/min per 1.73 m^2 or elderly.[70]	No monitoring needed. No dose adjustment needed. Scarce evidence in hemodialysis and eGFR <15 ml/min per 1.73 m2. Favorable preliminary data.[71,72]	Monitor with serum creatinine and eGFR at start and then regularly. Dose adjustment if eGFR <50 ml/min per 1.73 m^2.
Bone safety.	Consider switch to TAF or ETV if P^+ <2.5 mmol/dl, concomitant bone condition or elderly.	No monitoring needed.	No monitoring needed.
End-stage liver disease.	Usual dose. Extreme kidney monitoring.	Scarce evidence. Favorable preliminary data.[73]	Increase usual dose to 1 mg/day. Extreme kidney monitoring.
Drug resistance.	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.
Pregnancy and childbearing women.	Recommended.	Scarce evidence. Limited favorable data in HIV mono-infected women.[74]	Not recommended.
Children.	Above 2 years old.	Scarce experience, above 12 years old.	Above 2 years old.
HIV co-infection.	As part of HAART.	As part of HAART.	Not recommended in monotherapy.
HDV co-infection.	No direct anti-HDV activity.[75] Might be added to peg-IFNα and/or new therapies according to HBV replication.[76]	No direct anti-HDV activity. Data extrapolated from other NAs.[75] Might be added to peg-IFNα and/or new therapies according to HBV replication.[76]	No direct anti-HDV activity.[75] Might be added to peg-IFNα and/or new therapies according to HBV replication.[76]

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^+, serum phosphate.

practice.[90] 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.[91] 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.[73] 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; $p < 0.001$).[32] 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.[29] 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.[92] 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), $p = 0.7$].[93] 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.[83] 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^2 per 48 weeks; $p = 0.001$).[94] No significant change was observed in subjects with maintained glomerular function. This results are consistent with available evidence from HIV/HBV coinfected cohorts; a prospective study in 106 HIV/HBV patients showed an increase of 6.2 ml/min 1.73 m^2 (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^2.[95] 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.[96]

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.[70] A relative decrease in bone marrow density (BMD) with TDF was detected, with unclear clinical implications.[80,97] 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.[27,77] Results after 144 weeks have also shown a significantly smaller decrease in hip and spine BMD in the TAF group.[32] 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[98] 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); $p < 0{\cdot}0001$] after 48 weeks of switching was reported.[92] 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

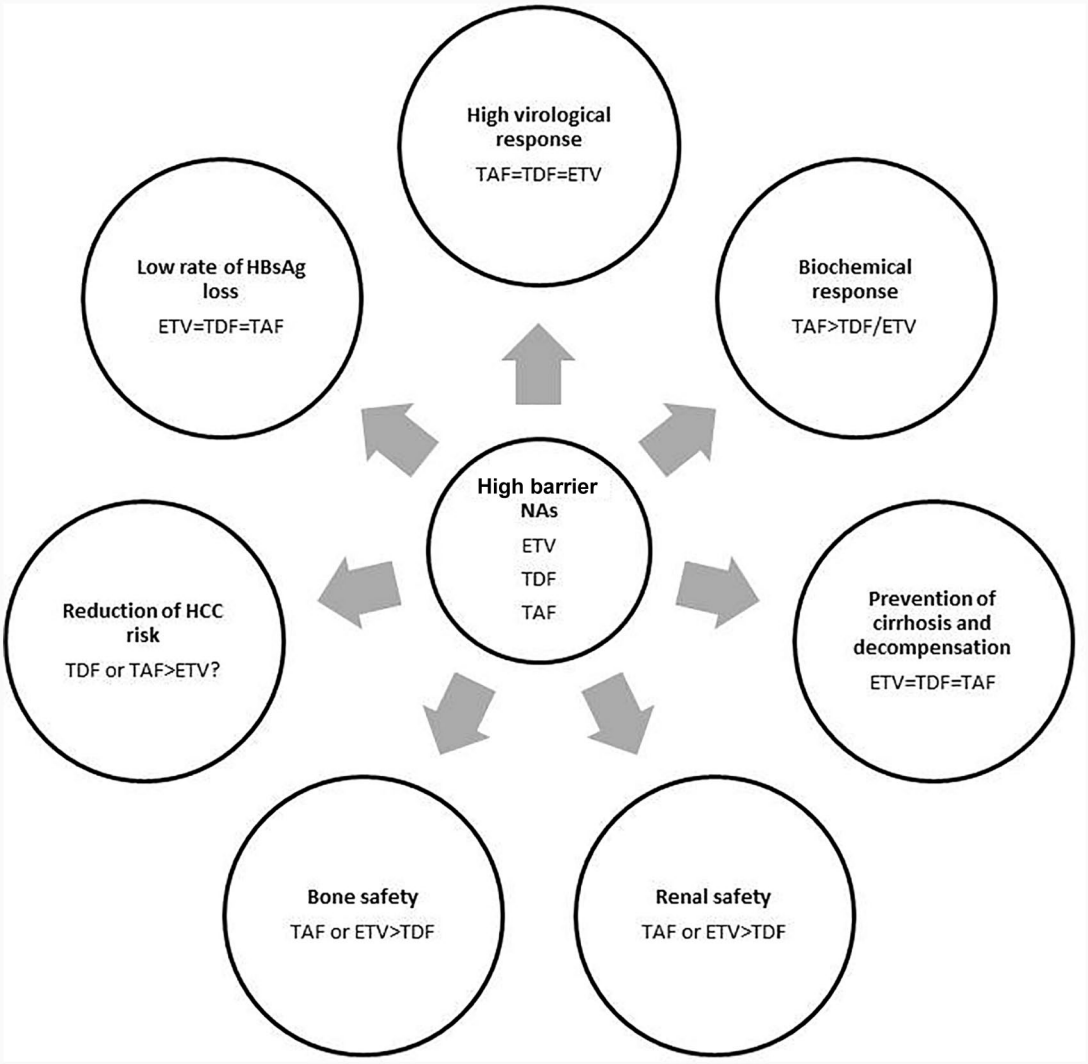

Figure 1. Efficacy and safety of high barrier to resistance nucleos(t)ide analogues in chronic hepatitis B.
Virological response is defined as undetectable HBV-DNA by PCR with a lower limit of detection of 10 IU/ml after one year of treatment. Biochemical response is defined as ALT normalization under 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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ORCID iD

Luisa Roade https://orcid.org/0000-0002-8160-9613

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