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Review article: switching patients with chronic hepatitis B to tenofovir alafenamide—a review of current data

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Summary

Background: The nucleos(t)ide analogues (NAs) entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) are preferred treatment options for patients with chronic hepatitis B infection (CHB). However, resistance to ETV has been reported, especially with prior exposure to other NAs, and long-term TDF treatment has been associated with decline in renal function and loss of bone mineral density in some patients. Consequently, TAF may be preferable to ETV, TDF or other NAs in specific circumstances such as in patients with risk of bone or renal complications, elderly patients or those with previous NA experience.

Aim: To provide a summary of the available efficacy and safety data following switch to TAF from other NAs in patients with CHB in clinical studies and real-world settings.

Methods: Literature searches were performed on PubMed and abstracts from three major international liver congresses between 2019 and 2021. Studies that included efficacy and/or safety data for patients with CHB switching from any NA to TAF were selected.

Results: Thirty-six papers and abstracts were included in this narrative review. Switching from TDF to TAF maintained or improved virological and biochemical responses with improved bone and renal safety. Switching from ETV or other NAs to TAF maintained or improved virological and biochemical responses and varying results for bone and renal safety.

Conclusions: Switching to TAF appears to maintain or improve virological, biochemical and bone- and renal-related safety outcomes. These data support the concept of switching to TAF in some patients with CHB based on their individual circumstances.

The Handling Editor for this article was Professor Geoffrey Dusheiko, and this uncommissioned review was accepted for publication after full peer-review.

The author's complete affiliation list are listed in Appendix.

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1 | INTRODUCTION

Hepatitis B virus (HBV) is a major global health problem.[1] Despite the availability of an effective vaccine, the World Health Organization estimated that in 2015, 257 million people had chronic HBV infection (CHB). HBV infection was responsible for approximately 887 000 deaths primarily due to liver cirrhosis and hepatocellular carcinoma (HCC).[1] Patients with CHB live on average 14 years less than the general population due to multiple causes.[2] The main goal of CHB treatment is to prevent disease progression and HCC development, thereby improving survival and quality of life.[3-6] Hepatitis B surface antigen (HBsAg) loss or seroconversion is the optimal treatment endpoint. However, HBsAg loss rarely occurs with current therapies, so antiviral treatment is generally life-long. Safety is paramount for long-term treatment approaches. Recent studies have shown that the mean age of patients with CHB has increased significantly over the past two decades. This increasing proportion of CHB patients with advanced age carries with it the associated increases in comorbidities, including chronic kidney disease (CKD), osteoporosis, bone fractures and cardiovascular disease (CVD).[7-11] The presence of comorbidities in an ageing CHB patient population means that long-term safety of antiviral therapies must be optimised.

Current preferred antiviral treatments are nucleos(t)ide analogues (NAs) such as entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF).[3-6,12,13] ETV, TDF and TAF are potent NAs with a high barrier to resistance that have demonstrated high long-term antiviral efficacy and a favourable safety profile.[3] However, ETV has a high barrier to resistance only in NA treatment-naïve CHB patients and not in patients previously exposed to NAs with a low barrier to resistance.[3,14-16] TDF resistance has been reported but is rare,[17,18] and no resistance to TAF has been reported.[3] Patients who develop NA resistance should switch NA treatment according to the pattern of prior NA treatments.[3-5] In some patients treated with TDF, declines in renal function[19-23] and reductions in bone mineral density (BMD) have been reported.[19,24-27] These side effects are uncommon but could be problematic for long-term TDF treatment in an ageing CHB population with comorbidities.

TAF is the oral phosphonamidate prodrug of tenofovir and has greater stability in plasma compared with TDF.[28] TAF provides targeted delivery of tenofovir directly to the liver.[29,30] Circulating plasma concentrations of tenofovir in patients with CHB are approximately 90% lower with TAF compared with TDF at approved doses.[31] In Phase 3 trials of patients with CHB, TAF was non-inferior to TDF in terms of antiviral efficacy, with no resistance to treatment reported up to 96 weeks.[19,32,33] TAF treatment was associated with significantly smaller reductions in BMD and improvements in creatinine clearance as well as markers of renal tubular function compared with TDF at Weeks 48 and 96.[19,32,33] In a pooled analysis of patients aged at least 65 years treated in Phase 2 and 3 trials, the efficacy and safety of TAF was generally similar to that reported in younger patients, with small improvements in renal and bone parameters noted in older patients switched from TDF to TAF.[34]

Following widespread regulatory approval from 2016 onward, TAF has become a preferred CHB treatment, alongside TDF and ETV, in updated clinical guidelines.[5,6,12,13,35] Current guidelines recommend TAF or ETV instead of TDF in specific circumstances, including in patients with risk of bone or renal complications, elderly patients and in patients with previous NA treatment. TAF may be preferable to ETV in treatment-experienced patients (Table 1).[3,5,6,12,13] Despite these recommendations, many patients remain on non-TAF therapies.

The aim of this narrative review was to summarise the available virological, biochemical and renal- and bone-related safety data following switch to TAF from other NAs in clinical studies and real-world settings.

1.1 | Search strategy and selection criteria

PubMed searches were performed using search terms "tenofovir alafenamide", "hepatitis B OR HBV OR CHB" and "switch OR switching". Abstracts from three major international liver congresses (The International Liver Congress, The Liver Meeting and The Conference of the Asian Pacific Association for the Study of the Liver) in 2019, 2020 and 2021 were searched using the term 'alafenamide'. Studies that included efficacy and/or safety data for patients with CHB switching from any NA to TAF were selected. Data from the most recent abstract or any subsequently published papers were included. Thirty-six papers and abstracts were included in this narrative review.

1.2 | Switching from TDF to TAF

Approximately half of the publications on TAF switching come from studies in CHB patients previously treated with TDF, including the only Phase 3, randomised, double-blind, non-inferiority study and several sub-analyses of this study and its extension. Results have shown that switching from TDF to TAF maintained or improved virological and biochemical response with improved renal and bone safety (Table 2, Figures 1 and 2).[36-52]

1.2.1 | Virological and biochemical response

In studies of CHB patients with undetectable HBV DNA at baseline, switching from TDF to TAF maintained virological and biochemical responses (Table 2).[36,43,47] In a double-blind Phase 3 study in 488 patients with CHB who had received TDF for at least 48 weeks, patients were randomised to continue TDF treatment or switch to TAF.[36] At Week 48, over 99% of patients in both treatment groups had HBV DNA below 20 IU/ml. More patients achieved alanine aminotransferase (ALT) normalisation with TAF compared with TDF. Further analyses were performed at Week 96 after all patients had received open-label TAF for an additional

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TABLE 1 Summary of indications for selecting ETV or TAF over TDF

Guideline	Recommendations

EASL 2017[3]	• Age > 60 years
	• Bone disease
	  • Chronic steroid use or use of other medications that reduce BMD
	  • History of fragility fracture
	  • Osteoporosis
	• Renal alteration[a]
	  • eGFR <60 ml/min/1.73 m^2
	  • Albuminuria >30 mg/24 h or moderate dipstick proteinuria
	  • Low phosphate (<2.5 mg/dl)
	  • Haemodialysis
	• TAF should be preferred to ETV in patients with previous NA exposure

AASLD 2018[5]	• Consider TAF[b] or ETV in patients with or at risk of renal dysfunction or bone disease • In cases of suspected TDF-associated renal dysfunction and/or bone disease, TDF should be discontinued and substituted with TAF or ETV, with consideration for previous known drug resistance

KASL 2019[6]	• Bone disease
	  • Chronic steroid use
	  • Use of medication that worsens BMD
	  • Osteoporosis or osteopenia
	• Renal alteration[b]
	  • eGFR <60 ml/min/1.73 m^2
	  • Dipstick proteinuria or urine albumin/creatinine >30 mg/g
	  • Low serum phosphate (<2.5 mg/dl)
	• TAF should be preferred to ETV in patients with previous NA exposure
	• In treatment-adherent patients with partial virological response, switch from one NA to another NA option with no cross resistance
	• For ETV-resistant CHB, switch to tenofovir monotherapy or add tenofovir

CSH/CMA/CSID 2019[12]	• In patients with CKD, renal failure or receiving renal replacement therapy, ETV or TAF is recommended • Patients treated with TDF should switch to ETV or TAF if they suffer from renal or bone disease, or are at high risk
JSH 2019[13]	• TAF and ETV are preferred first-line drugs for patients with renal impairment, hypophosphataemia or osteopenia/osteoporosis at treatment initiation • Switching from TDF to TAF is recommended for patients with renal impairment, hypophosphataemia or osteopenia/osteoporosis • Switching from combination therapy with ETV + TDF to ETV + TAF is recommended for patients with renal impairment, hypophosphataemia or osteopenia/osteoporosis

AASLD, American Association for the Study of Liver Diseases; BMD, bone mineral density; CHB, chronic hepatitis B virus infection; CKD, chronic kidney disease; CMA, Chinese Medical Association; CrCl, creatinine clearance; CSH, Chinese Society of Hepatology; CSID, Chinese Society of Infectious Disease; EASL, European Association for the Study of the Liver; eGFR, estimated glomerular filtration rate; ETV, entecavir; JSH, Japan Society of Hepatology; KASL, Korean Association for the Study of the Liver; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]ETV dose needs to be adjusted if eGFR <50 ml/min; no TAF dose adjustment is required in adults or adolescents (aged ≥12 years or ≥ 35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis;

[b]TAF is not recommended in patients with CrCl <15 ml/min or those on dialysis.

48 weeks. The proportion of patients with virological suppression was maintained, and rates of ALT normalisation increased in both groups. These results were supported by results from two prospective single-centre studies of patients with at least 12 months of TDF treatment and HBV DNA below 20 IU/ml, in which virological and biochemical responses were maintained to Week 24 after switching.[43,47]

In studies where some patients had detectable HBV DNA at baseline, similar efficacy results were reported (Table 2).[42,44-46,48,50-52] Results from an international retrospective study of 834 patients who switched to TAF after at least 12 months of TDF showed that virological and biochemical parameters were stable over 24 months.[51] Maintenance of virological response 24 weeks after switching from TDF to TAF was also

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TABLE 2 Studies of patients switching from TDF to TAF

				Effectiveness		Safety	
Study	**Type of study**	**Pt population**	**Prior NAs**	**HBV DNA**	**ALT**	**Bone effects**	**Renal effects**
Lampertico 2020a[36]	Phase 3, randomised, double-blind, Week 48 analysis GS-US-320-4018	TAF: n = 243 TDF: n = 245 Mean age: 51 y Male: 71% HBV DNA <20 IU/ml and HBV DNA < LLOQ for ≥12 weeks at screening HBeAg +ve: 32% Median ALT level at BL, U/L: 23 (TAF), 24 (TDF)	TDF: 100% LAM: 39% ADV: 38% ETV: 20% TBV: 10% Other: 5%	HBV DNA ≥20 IU/ml in 1 pt (<1%) at Week 48 in each group (difference in proportion 0.0%, 95% CI, −1.9 to 2.0)	ALT normalisation rate at Week 48 (AASLD)[a] • TAF: 50% • TDF: 26%; $P = 0.014$	Mean % change in spine BMD at Week 48 • TAF: +1.74 • TDF: −0.11; $P < 0.0001$ Mean % change in hip BMD at Week 48 • TAF: +0.66 • TDF: −0.51; $P < 0.0001$Improved markers of bone turnover (CTX, P1NP) TAF vs TDF	Median change in $eGFR_{CG}$ at Week 48, ml/min • TAF: +0.94 • TDF: −2.74; $P < 0.0001$ Pts with Grade ≥ 1 proteinuria at Week 48 • TAF: 14% • TDF: 22%; $P = 0.013$Improved markers of tubular function (urinary RPB/Cr and β2M/Cr ratios) TAF vs TDF
Buti 2019[37]	Phase 3, randomised, double-blind, Week 48 analysis GS-US-320-4018	TAF: n = 180 TDF: n = 178 Pts with ≥1 risk factor for TDF toxicity[b] Mean age: 53 y (TAF), 54 y (TDF) Male: 66% HBV DNA <20 IU/ml and HBV DNA < LLOQ for ≥12 weeks at screening HBeAg +ve: 29% Median ALT level at BL, U/L: 23	TDF: 100%Other: NR See Lampertico 2020a for full study population	Pts with HBV DNA <20 IU/ml at Week 48 • TAF: 97% • TDF: 97%; $P = 0.96$	Pts with normal ALT (AASLD)[a] at Week 48 • TAF: 79% • TDF: 76%	Mean % change in spine BMD at Week 48 • TAF: +1.81 • TDF: −0.33; $P < 0.001$ Mean % change in hip BMD at Week 48 • TAF: +0.67 • TDF: −0.53; $P < 0.001$	Median change in $eGFR_{CG}$ at Week 48, ml/min • TAF: +1.86 • TDF: −2.70; $P < 0.001$
Ahn 2020[38]	Phase 3, randomised, double-blind, Week 48 Asian subset analysis GS-US-320-4018	TAF: n = 143 TDF: n = 145 Pts of Asian ethnicity with ≥1 risk factor for TDF toxicity[b] Mean age: 53 y (TAF), 54 y (TDF) Male: 64% HBV DNA <20 IU/ml and HBV DNA < LLOQ for ≥12 weeks at screening HBeAg +ve: 35% Median ALT level at BL, U/L: 23	TDF: 100% Other: NR See Lampertico 2020a for full study population	Pts with HBV DNA <20 IU/ml at Week 48 • TAF: 97% • TDF: 97%	Pts with normal ALT (AASLD)[a] at Week 48 • TAF: 76% • TDF: 73%	Mean % change in spine BMD at Week 48 • TAF: +1.92 • TDF: −0.52; $P < 0.0001$ Mean % change in hip BMD at Week 48 • TAF: +0.64 • TDF: −0.73; $P < 0.0001$	Median change in $eGFR_{CG}$ at Week 48, ml/min • TAF: +2.61 • TDF: −2.67; $P < 0.0001$

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TABLE 2 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Lampertico 2020b[39d]	Phase 3, open-label extension, Week 96 analysis GS-US-320-4018	TAF-TAF: n = 243 TDF-TAF: n = 245 HBeAg +ve: 32% See Lampertico 2020a for study details	TDF: 100% LAM: 39% ADV: 38% ETV: 20% TBV: 10% Other: 5%	Pts with HBV DNA <20 IU/ml at Week 96 • TAF-TAF: 95% • TDF-TAF: 94%	ALT normalisation rate at Week 96 (AASLD)[a] • TAF-TAF: 56% • TDF-TAF: 74%; $P = 0.051$	Mean % change in spine BMD at Week 96 • TAF-TAF: +2.33 • TDF-TAF: +1.73; $P = 0.097$ Mean % change in hip BMD at Week 96 • TAF-TAF: +1.16 • TDF-TAF: +0.18; $P < 0.001$Similar improvements in CTX and P1NP between groups	Median change in $eGFR_{CG}$ from Week 0 to 96, ml/min • TAF-TAF: +0.51 • TDF-TAF: −0.39; $P = 0.871$
Ahn 2021[40]	Phase 3, open-label extension, Week 96 Asian subset analysis GS-US-320-4018	TAF: n = 189 TDF: n = 198 Pts of Asian ethnicity Median age: 52 y (TAF), 51 y (TDF) Male: 70% HBV DNA <20 IU/ml and HBV DNA < LLOQ for ≥12 weeks at screening HBeAg +ve: 35% Median ALT level at BL, U/L: 24	TDF: 100% Other: NR See Lampertico 2020a for full study population	Pts with HBV DNA <20 IU/ml at Week 96 • TAF-TAF: 95% • TDF-TAF: 94%	Pts with normal ALT (central)[a] at Week 96 • TAF-TAF: 88% • TDF-TAF: 91% Pts with normal ALT (AASLD)[a] at Week 96 • TAF-TAF: 79% • TDF-TAF: 86%	Median % change in spine BMD at Week 96 • TAF-TAF: +2.47 • TDF-TAF: +1.55 Median % change in hip BMD at Week 96 • TAF-TAF: +1.23 • TDF-TAF: +0.12	Median change in $eGFR_{CG}$ at Week 96, ml/min • TAF-TAF: +1.26 • TDF-TAF: +0.01
Ãtelen 2020[41]	Retrospective, multicentre, real world	N = 480 Mean age: 47 y Male: NR HBV DNA level at BL: NR HBeAg +ve: 20% ALT level at BL: NR	TDF: 86% Other: NR	NR	NR	Significant improvement in spine and hip BMD at month 6 ($P = 0.05$)	Significant improvement in eGFR and phosphorus levels at Month 6 ($P = 0.05$)
Byun 2021[42]	Randomised, multicentre	TAF: n = 87 TDF: n = 87 Mean age: 55 y Male: 81% Pts with detectable HBV DNA (>15 IU/ml) at BL: 14.9% HBeAg +ve: 62% Median ALT level at BL, IU/L, 25	LAM/ETV/ADV: 71% LAM/ADV: 12% LAM/ETV: 10% ETV/ADV: 4% ETV: 3% ADV: 1% Genotypic resistance to ADV and/or ETV	Pts with HBV DNA <60 IU/ml • BL: TAF 96.6% vs TDF 92.0% • Week 48: TAF 98.9% vs TDF 97.7%; $P > 0.99$	Median (IQR) ALT change at Week 48, IU/L • TAF: −3 (−8, 3) • TDF: −2 (−5, 6); $P = 0.02$ Pts with normal ALT (central)[a] at Week 48 • TAF: 88.5% • TDF: 81.2%; $P = 0.26$	Mean % change in spine BMD at Week 48 • TAF: +1.8 • TDF: +0.2; $P = 0.02$ Mean % change in hip BMD at Week 48 • TAF: −0.2 • TDF: −0.3; $P = 0.90$	Median % change in $eGFR_{CG}$ at Week 48 • TAF: +7.3 • TDF: +1.9; $P = 0.047$ Median change in sCr at Week 48, mg/dl • TAF: −0.1 • TDF: 0.0; $P = 0.09$

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TABLE 2 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Farag 2021[44]	Real-world, multicentre (CANHEPB network)	N = 176 Mean age: 52 y Male: 73% Pts with detectable HBV DNA at BL: 36% HBeAg +ve: 20% Median ALT level at BL, U/L: 27 Pts with CKD Stage 1: 29% Stage 2: 36% Stage 3a: 20% Stage 3b+: 15%	TDF: 73% ETV: 3% LAM: 2% Other: 4% Naïve: 19%	Pts with HBV DNA <20 IU/ml (prior TDF cohort) • BL: 72% • Week 52: 84%	NR	NR	eGFR change, ml/min/month • Pre-TAF: −0.18; $P = 0.008$ • TAF: 0.00; $P = 1.0$Kidney function deterioration was halted after switching to TAF
Fong 2019[43]	Prospective, single arm, open label	N = 75 Median age: 58 y Male: 65% Pts with HBV DNA <20 IU/ml at BL: 100% HBeAg +ve: NR Median ALT at BL, U/L: 23	TDF: 100% ADV: 0% Other: NR	Pts with HBV DNA < 20 IU/ml at Week 24 • 97%[c]	No significant change from BL	Mean % change in BMD at Week 24 • Spine: +3.1; $P < 0.01$ • Hip: +12.8; $P < 0.01$Significant improvements in hip and lumbar total *T*-scores ($P < 0.01$)	No significant change in $eGFR_{CG}$ from BL to Week 24 Significant improvements in urinary RPB/Cr and β2M/Cr ratios at weeks 12 and 24 ($P < 0.01$)
Huynh 2020[45]	Retrospective, single centre	N = 60 Mean age: 55 y Male: 28% Mean HBV DNA at BL: 450 IU/ml HBeAg +ve: 28% Mean ALT at BL, IU/L: 25	TDF: 100% Other: NR	NR	Pts with normal ALT (AASLD)[a] • BL: 78% • Week 96: 86.5%	NR	NR
Kaneko 2019[46]	Prospective, single centre	N = 36 Median age: 55 y Male: 75% Median HBV DNA at BL: 0 IU/ml HBeAg +ve: 25% Median ALT level at BL, U/L: 24	TDF: 100% Other: NR	No elevation in HBV DNA levels at Week 24	NR	NR	Mean change in eGFR, ml/min/1.73 m^2 • Week 4: +3.93; $P = 0.008$ • Week 12: +3.88; $P = 0.039$ • Week 24: +2.89; $P = 0.020$Significant decline in β2M/Cr ratio at Weeks 12 and 24 post switch ($P = 0.002$ and $P = 0.027$, respectively)

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TABLE 2 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Lee 2021[47]	Prospective, single centre	N = 61 Median age: 57 y Male: 59% Pts with HBV DNA <20 IU/ml at BL: 100% HBeAg +ve: NR Median ALT level at BL, U/L: 24	TDF: 100% ADV: 0% Other: NR	NR	Pts with normal ALT (AASLD)[a] • BL: 74% • Week 24: 77% • Week 72: 80%	Mean % change in BMD at Week 24: • Spine: +3.3; $P < 0.01$ • Hip: +13.5; $P < 0.01$	Mean % change in $eGFR_{CG}$: • Week 24: −0.6 • Week 72: −5.2; $P < 0.01$
Loglio 2020[48]	Prospective, observational	N = 146 Median age: 69 y Male: 71% Pts with undetectable HBV DNA at BL: 94% HBeAg +ve: 6% Median ALT level at BL, IU/L: 21	TDF: 100% LAM or ETV: 100% ADV: 65% Other: NR	Virological control maintained over 6 months	Median ALT level at, IU/L • Month 2: 21 • Month 6: 2	NR	$eGFR_{CG}$ level, ml/min • BL: 68 • Month 6: 67 $eGFR_{MDRD}$ level, ml/min • BL: 66 • Month 6: 66 Urinary β2M/Cr ratio, mg/g • BL: 658 • Month 6: 315 UP/Cr ratio, mg/g • BL: 82 • Month 6: 52
Notsumata 2020[49]	Single centre	N = 26 No details provided	NR	NR	NR	FGF23, pg/ml • BL: 29.6 • Week 4: 38.6; $P = 0.001$ • Week 12: 46.7; $P = 0.012$	Urinary L-FABP, μg/gCr • BL: 20.53 • Week 4: 8.9; $P = 0.022$ • Week 12: 3.01; $P = 0.008$
Reddy 2019[50]	Multicentre (TRIO cohort)	N = 270 Mean age: 53 y Male: 59% Pts with HBV DNA ≤2000 IU/ml at BL: 97% HBeAg +ve: NR Mean ALT level at BL, U/L: 28	TDF: 82% ETV: 8% ADV: 1% TBV: <1%	Pts with HBV DNA ≤2000 IU/ml at Week 48 • 100%; $P = 0.011$	Mean ALT level, U/L • BL: 28 • Week 48: 24; $P = 0.013$ Pts with normal ALT (AASLD)[a] • BL: 78% • Week 48: 83%; $P = 0.053$	NR	Pts with eGFR <60 ml/min • BL: 7% • Week 48: 9%; $P = 0.366$

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TABLE 2 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Toyoda 2021[51]	Retrospective, multicentre	N = 834 Mean age: 55 y Male: 57% Pts with HBV DNA <20 IU/ml at BL: 88.2% HBeAg +ve: 31% Mean ALT level at BL, U/L: 29 eGFR ≥90 ml/min: n = 463 eGFR 60–89 ml/min: n = 267 eGFR <60 ml/min: n = 85	TDF: 100% ETV: 45% ADV: 33% LAM: 14% Other: 7%	Pts with HBV DNA <20 IU/ml at Week 96 • 94.9%; $P < 0.001$	Pts with normal ALT (AASLD)[a] • BL: 69.6% • Week 96: 77.8%; $P = 0.003$	NR	Pts with eGFR ≥90 ml/min at BL: 11.2% changed to eGFR 60–89 ml/min at Week 96 Pts with eGFR 60–89 ml/min at BL: 4.9% changed to eGFR <60 ml/min at Week 96; 20.6% improved to eGFR ≥90 ml/min at Week 96 Pts with eGFR <60 ml/min at BL: 1.2% improved to eGFR ≥90 ml/min at Week 96; 35.3% improved to eGFR 60–89 ml/min at Week 96
Yeh 2019[52]	Retrospective, multicentre	N = 121 Mean age: 55 y Male: 72% Pts with HBV DNA <20 IU/ml at BL: 89.3% HBeAg +ve: 21% Mean ALT level at BL, U/L: 36	TDF: 75% ETV: 5% LAM: 3% Other: 18%	Pts with HBV DNA <20 IU/ml at Month 12: • 96.2%; $P = 0.016$	Pts with normal ALT (AASLD)[a] • BL: 58.7% • Month 12: 70.2%; $P = 0.029$	NR	Mean % change in eGFR at Month 12 • Total cohort: −1.0%; $P = 0.278$ • CKD cohort: +2.8%; $P = 0.02715.1\%$ of pts with CKD stage 2 and 33.3% of pts with CKD stage 3 had one CKD stage improvement

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ADV, adefovir; ALT, alanine aminotransferase; β2M/Cr, β2 microglobulin to creatinine; BL, baseline; BMD, bone mineral density; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CTX, C-type collagen sequence; EASL, European Association for the Study of the Liver; eGFR, estimated glomerular filtration rate; $eGFR_{CG}$, estimated glomerular filtration rate Cockcroft-Gault formula; $eGRF_{MDRD}$, estimated glomerular filtration rate Modification of Diet in Renal Disease; ETV, entecavir; FGF, fibroblast growth factor; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IQR, interquartile range; LAM, lamivudine; L-FABP, liver-type fatty acid-binding protein; LLOQ, lower limit of quantification; NA, nucleos(t)ide analogue; NR, not reported; P1NP, procollagen type 1 N-terminal propeptide; pt, patient; RBP/Cr, retinol binding protein to creatinine; sCr, serum creatinine; TAF, tenofovir alafenamide; TBV, telbivudine; TDF, tenofovir disoproxil fumarate; UP/Cr, urine protein to creatinine; y, years.

[a]According to EASL and AASLD guidelines.

[b]According to EASL and AASLD guidelines.

[c]Two patients had HBV DNA >21 IU/ml; both patients were non-compliant as measured by pill count.

[d]In the extension study, patients switched to TAF at baseline continued treatment with TAF (TAF-TAF) and patients treated with TDF during the initial randomised study were switched to TAF at Week 48 (TDF-TAF).

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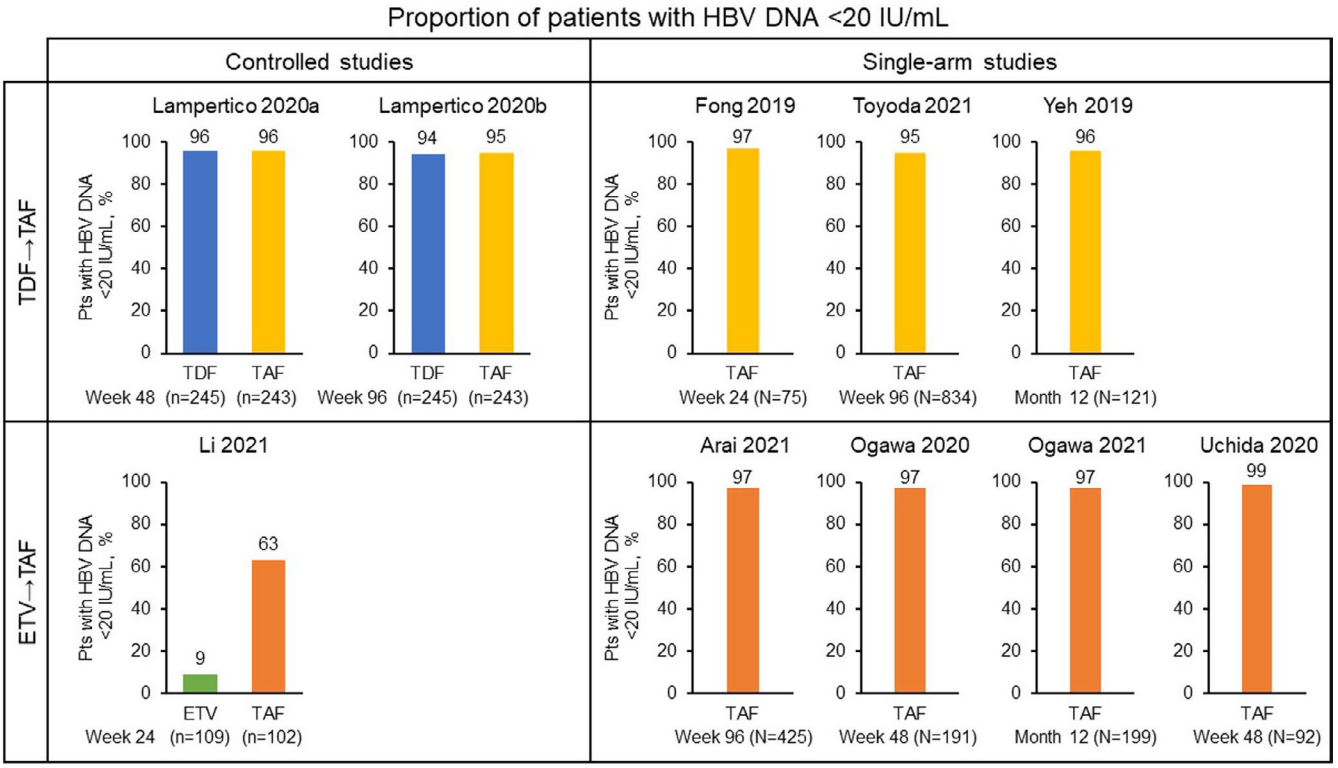

FIGURE 1 Schematic showing the proportion of patients with HBV DNA < 20 IU/ml in studies in patients with CHB switching from TDF or ETV to TAF. The upper panels show results from TDF to TAF switching studies and the lower panels show results from ETV to TAF switching studies. Results from comparative studies are shown in the panels on the left and results from single-arm studies are shown in the panels on the right. Only those studies reporting the proportion of patients with HBV DNA <20 IU/ml are included. No direct comparisons between study results can be made due to differences in study designs and patient populations. Primary endpoints were the proportion of patients with HBV DNA <20 IU/ml (Lampertico 2020a,[36] Lampertico 2020b,[39] Yeh 2019,[52] Li 2021,[58] Arai 2021,[54] Ogawa 2020[59]), complete response defined as the HBV DNA <20 IU/ml plus ALT normalisation (≤35 U/L for males and ≤ 25 U/L for females; Toyoda 2021,[51] Ogawa 2021[60]) or not specified (Fong 2019,[43] Uchida 2020[61]). ALT, alanine aminotransferase; CHB, chronic hepatitis B infection; ETV, entecavir; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

reported in a prospective, single-centre study of 36 patients.[46] In a retrospective, single-centre study of 60 patients treated with TDF and then switched to TAF for 2 years, the authors reported an increase in the proportion of patients with ALT improvements from baseline at Week 96.[45] Improvements in virological and biochemical responses were also reported in a retrospective study of 121 patients switched to TAF after at least 12 months of treatment with another NA (75% prior TDF)[52] and a study of 270 patients switched to TAF in routine clinical practice and remaining on TAF for at least 48 weeks.[50]

1.2.2 | Renal and bone safety

In all studies where renal safety outcomes were reported, improvements were generally observed upon switching from TDF to TAF (Table 2).[36,39-42,46,47,51] In the Phase 3 TDF to TAF switching study, TAF-treated patients had significantly improved renal safety parameters at Week 48 compared with TDF-treated patients.[34] In other studies, evaluations of estimated glomerular filtration rate (eGFR) mostly showed improvements upon switching from TDF to TAF.[41,46,47,51]

Not all TDF to TAF switching studies reported bone-related safety outcomes; however, those that did generally reported improvements (Table 2).[36,39-43,47] In a prospective, single-arm study, BMD significantly increased from baseline to Week 24 in 75 patients switched from TDF to TAF.[43] Forty percent of patients had osteopenia at baseline, but no change in BMD in this patient population was reported. Results from the Phase 3 TDF to TAF switching study showed that patients who switched to TAF had significant improvements in BMD at Week 48 compared with patients continuing TDF.[36]

1.2.3 | Additional safety outcomes of interest

Fasting lipid analysis was performed in the Phase 3 TDF to TAF switching study at Week 96.[39] In patients switched to TAF at baseline, total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels increased after switch. In patients who switched to TAF at Week 48, corresponding increases in total, LDL and HDL cholesterol levels after switch were observed. Levels of total, LDL and HDL cholesterol were similar between treatment groups at Week 96. The total to HDL cholesterol ratio remained

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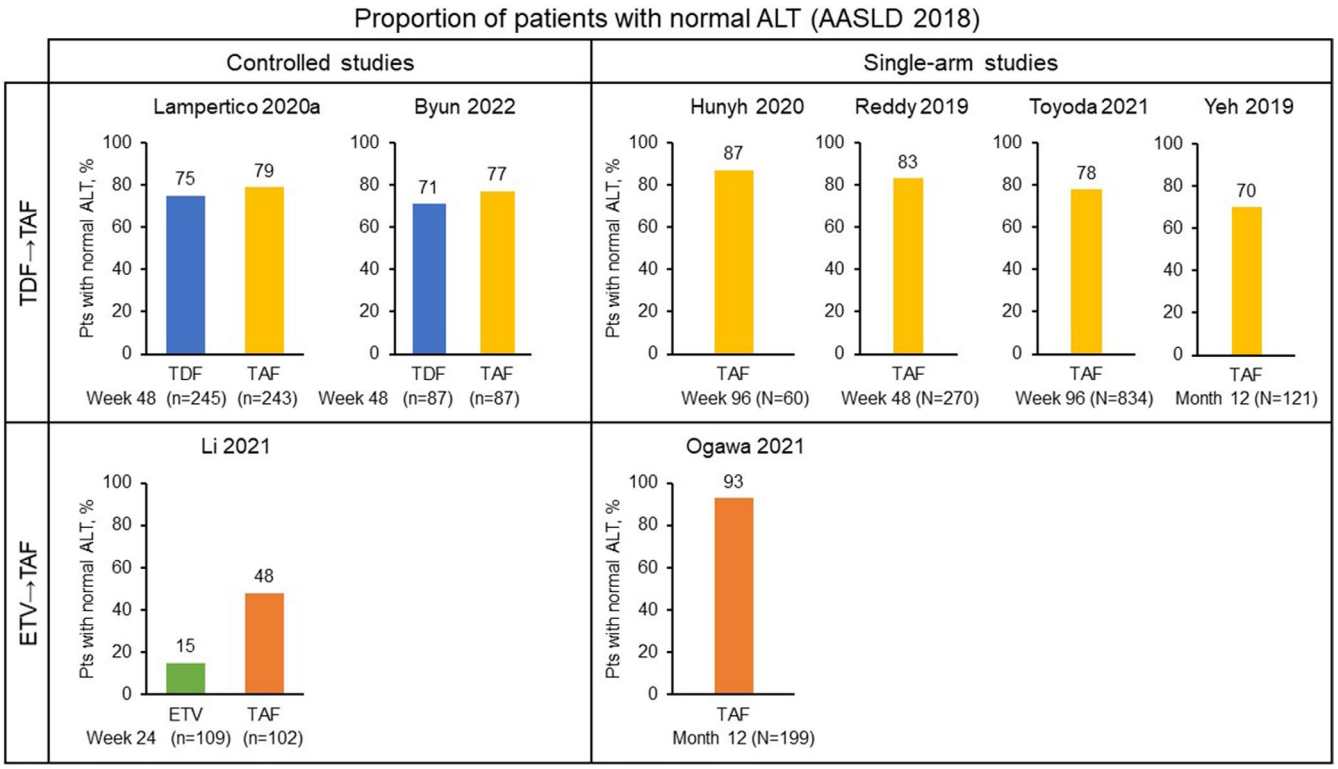

FIGURE 2 Schematic showing the proportion of patients with normal ALT according to the AASLD 2018 criteria in studies in patients with CHB switching from TDF or ETV to TAF. The upper panels show results from TDF to TAF switching studies and the lower panels show results from ETV to TAF switching studies. Results from comparative studies are shown in the panels on the left and results from single-arm studies are shown in the panels on the right. Only those studies reporting the proportion of patients with normal ALT according to AASLD 2018 criteria are included. No direct comparisons between study results can be made due to differences in study designs and patient populations. AASLD 2018 criteria are ≤35 U/L for males and ≤ 25 U/L for females. Primary endpoints were the proportion of patients with HBV DNA <20 IU/ml at Week 48 (Lampertico 2020a,[36] Yeh 2019,[52] Li 2021[58]), HBV DNA <60 IU/ml (Byun 2022[42]), complete response defined as the HBV DNA <20 IU/ml plus ALT normalisation (AASLD 2018 criteria; Toyoda 2021,[51] Ogawa 2021[60]) or not specified (Huynh 2020,[45] Reddy 2019[50]). AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CHB, chronic hepatitis B infection; ETV, entecavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

unchanged. Median change in body weight at Week 96 increased by 1.4 and 1.0 kg in patients who switched from TDF to TAF at baseline and at Week 48, respectively. Increased fasting lipids were also reported in a 5-year analysis of the TAF registrational studies upon switching from TDF to TAF.[53] Results from a randomised study of 176 patients with multidrug-resistant HBV showed greater increases in total, LDL and HDL cholesterol levels from baseline to Week 48 in patients switched to TAF compared with patients continuing TDF ($P < 0.01$ for all).[42] However, the total to HDL cholesterol ratio decreased slightly upon TAF switching. Body mass index (BMI) changed significantly over the study in the TAF group vs TDF group (+0.71 kg vs −0.37 kg; $P = 0.01$). BMI also significantly increased (+0.6 kg; $P < 0.01$) in 61 patients enrolled in a prospective, single-centre study at Week 72 after switching from TDF to TAF.[47]

1.2.4 | Special patient populations

Several studies have evaluated switching from TDF to TAF in specific patient populations (Table 2).[38,42-44,48,51,52] A prospective, real-world study evaluated 146 patients switched from TDF to TAF according to European Association for the Study of the Liver (EASL) criteria.[3,48] Patients were switched because of age (80% were over 60 years old), osteoporosis or steroid treatment (34%) or renal disease (56%). In this population, virological and biochemical parameters were maintained over 6 months of TAF treatment. Estimated GFR remained stable over 6 months, but rapid improvements were seen in β2 microglobulin (β2M)/creatinine and urine protein/creatinine ratios. The authors concluded that switching from TDF to TAF rapidly improves proximal tubular function in an elderly population with long-term exposure to TDF. As part of the Phase 3 TDF to TAF switching study,[36] a subgroup analysis of patients with risk factors for TDF toxicity was performed.[37] Risk factors included age over 60 years, osteoporosis, stage 2 and above CKD, albuminuria, hypophosphataemia, obesity or comorbidities associated with CKD. These risk factors are similar to the EASL switching criteria. For patients included in this analysis, antiviral efficacy was maintained and significant improvements in bone and renal safety parameters were observed after TAF switching.

Various guidelines support switching from TDF to TAF in patients with CKD (Table 1). In a study of 176 patients with CKD from

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TABLE 3 Studies of patients switching from ETV to TAF

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Arai 2021[54]	Multicentre, multinational, real world	N = 425 Mean age: 61 years Male: 60% Pts with HBV DNA <20 IU/ml at BL: 91.9% HBeAg +ve: NR Mean ALT level at BL, U/L: 19 Pts with CKD Stage 1: 55.6% Stage 2: 35.7% Stages 3–5: 8.8% 8.3% of pts had HCC	ETV: 100% Other: 0%	Pts with HBV DNA <20 UI/ml • Week 48: 95.6%; $P = 0.03$ • Week 96: 97.2%; $P = 0.02$	No significant change in ALT levels	NR	11% of CKD stage 1 pts changed to stage 2 8% of CKD stage 2 pts changed to stages 3–5 and 18% changed to stage 1 19% of CKD stage 3–5 pts changed to stage 2
Chen 2021[55]	Single centre	N = 38 Mean age: NR Male: NR HBV DNA <20 IU/ml at BL, n = 24 HBV DNA 20–2000 IU/ml at BL, n = 14 HBeAg +ve: NR ALT level at BL: NR	ETV: 100% Other: NR	HBV DNA suppression rate • BL: 55.3% • Week 24: 92.1%; $P < 0.05$	ALT normalisation rate[a] • BL: 94.7% • Week 24: 94.7%	NR	No significant difference in eGFR
Hagiwara 2019[56]	Prospective, single centre, comparative	N = 48 (24 switched to TAF) Mean age: 61 y (TAF), 55 y (ETV) Male: 25% (TAF), 42% (ETV) HBV DNA-positive for ≥6 months prior to ETV treatment HBV DNA <1.3 $\log_{10}$ IU/ml at switch HBeAg +ve: 15% Mean ALT level at BL, IU/L: 20 (TAF), 18 (ETV)	ETV: 100% Other: 0%	NR	No significant difference between groups	No significant change in lumbar vertebrae or femur bone mineralisation was seen over 48 weeks in either group	No significant difference in changes in eGFR, UA/Cr ratio or phosphorus levels between groups
Itokawa 2020[57]	Retrospective, multicentre	TAF: n = 71 ETV: n = 71 Median age: 61 y (TAF), 58 y (ETV) Male: 63% (TAF), 59% (ETV) HBV DNA <1.3 $\log_{10}$ IU/ml for >6 months prior to switch HBeAg +ve: 9% Median ALT level at BL, IU/L: 20 (TAF), 19 (ETV)	ETV: 100% Other: 0%	NR	No significant difference between groups	NR	Median change in eGFR at Week 48, ml/min/1.73 m^2 • TAF: −1.0 • ETV: −0.5; $P = 0.604$

(Continues)

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TABLE 3 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Li 2021[58]	Prospective, single centre	N = 211 (102 switched to TAF) Mean age: 48 y Male: 81% Persistent low level viraemia (HBV DNA >20–<2000 IU/ml) Mean HBV DNA at BL, log_{10} IU/ml: 2.3 HBeAg +ve: 68% Mean ALT at BL, U/L: 33	ETV: 100% Other: 0%	Pts with HBV DNA <20 IU/ml at Week 24 • TAF: 62.7% • ETV: 9.3%; $P < 0.001$ Mean HBV decrease at Week 24, log_{10} IU/ml • TAF: 1.99 • ETV: 0.76; $P = 0.002$	Pts with normal ALT (central)[b] at Week 24 • TAF: 47.6% • ETV: 10.5%; $P = 0.027$ Pts with normal ALT (AASLD)[b] at Week 24 • TAF: 48.0% • ETV: 14.8%; $P = 0.022$	NR	Mean % change in sCr at Week 24 • TAF: +3.0% • ETV: +1.7%; $P = 0.278$ Mean % change in eGFR at Week 24 • TAF: +1.1% • ETV: +1.5%; $P = 0.707$ eGFR <50 ml/min/1.73 m^2 in one pt per group No significant changes in serum phosphorus or urinary β2M levels
Notsumata 2020[49]	Single centre	N = 38 No details provided	NR	NR	NR	Mean FGF23 level, pg/ml • BL: 34.7 • Week 12: 42.5; $P = 0.004$	Mean urinary L-FABP level, μg/gCr • BL: 4.32 • Week 4: 2.96; $P = 0.039$ No significant change in eGFR, fractional tubular reabsorption of phosphate or serum phosphorus
Ogawa 2020[59]	Multicentre, retrospective, cohort	N = 191 Median age: 62 y Male: 63% Pts with HBV DNA level at BL, IU/ml • <20: 75.9% • 20–2000: 19.9% • >2000: 4.2%HBeAg +ve: 12% Median ALT level at BL, U/L: 20 History of HCC: 9.4%	ETV: 100% Other: 40%	Pts with HBV DNA <20 IU/ml at Week 48 • 96.9% Pts with HBV DNA <20 IU/ml at Week 48 by BL level • 20–2000 (n = 34): 97.1% • >2000 (n = 12); 75.0%	Pts with normal ALT[c] • BL: 55.5% • Week 48: 73.8%; $P < 0.001$	NR	Mean change in eGFR at Week 48, ml/min/1.73 m^2 • eGFR <60 at BL: +0.40 • eGFR ≥60 at BL: −1.75 Mean change in sCr at Week 48, mg/dl • eGFR <60 at BL: +0.004 • eGFR ≥60 at BL: +0.014 Pts with serum phosphorus <2.5 mg/dl • BL: 2.6% • Week 48: 4.2%
Ogawa 2021[60]	Prospective, multicentre Interim analysis	N = 199 Mean age: 58 y Male: 58% Pts with HBV DNA <20 UI/ml at BL: 93.5% HBeAg +ve: 16% Mean ALT level at BL, U/L: 25	ETV: 100% Other: NR	Pts with HBV DNA <20 IU/ml • Month 12: 96.8%	Pts with normal ALT (AASLD)[b] • BL: 87.9% • Month 12: 93.0%	NR	NR
Uchida 2020[61]	Prospective, single centre	N = 92 Median age: 62 y Male: 52% Pts with HBV DNA <20 IU/ml at BL: 96.7% HBeAg +ve: 14% Median ALT level at BL, U/L: 16	ETV: 100% Other: 0%	Pts with HBV DNA <20 IU/ml at Week 48 • 98.9%	Median ALT levels, IU/L • BL: 16 • Week 8: 17; $P = 0.002$ • Week 24: 17; $P = 0.038$ • Week 48: 16; P = ns	NR	No significant difference in eGFR or phosphate levels at Week 48

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TABLE 3 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Yan 2021[62]	Retrospective, single centre	N = 499 (switched to TAF n = 104) Mean age: 46 y (TAF), 42 y (ETV) Male: 65% (TAF), 72% (ETV) Mean HBV DNA level at BL, log IU/ml: 3.2 (TAF), 3.0 (ETV) HBeAg +ve: NR Mean ALT level at BL, U/L: 39 (TAF), 34 (ETV)	ETV: 100% Other: NR	Pts with HBV DNA <30 IU/ml at Week 12 • TAF: 41.8% • ETV: 8.0%; $P < 0.001$ Pts with HBV DNA <30 IU/ml at Week 24: • TAF: 79.4% • ETV: 9.1%; $P < 0.001$	Pts with normal ALT (central)[b] at Week 24 • TAF: 92.6% • ETV: 80.6%; $P < 0.05$	NR	NR

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; β2M, β2 microglobulin; BL, baseline; CKD, chronic kidney disease; CR, creatinine; eGFR, estimated glomerular filtration rate; ETV, entecavir; FGF, fibroblast growth factor; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; L-FABP, liver-type fatty acid-binding protein; NA, nucleos(t)ide analogue; NR, not reported; ns, not significant; pt, patient; sCr, serum creatinine; TAF, tenofovir alafenamide; UA/Cr, urinary albumin to creatinine; y, years.

[a]<50 U/L.

[b]Central laboratory (≤40 U/L), AASLD 2018 (≤35 IU/L for males; ≤ 25 IU/L for females).

[c]≤30 IU/L for males; ≤19 IU/L for females.

the Canadian Hepatitis B Network who switched to TAF (126 patients switched from TDF), HBV DNA decreased, ALT significantly decreased and eGFR stabilised after TAF switching.[44] The effect on eGFR was most pronounced in patients with stage 2 CKD. A similar result was also reported in a retrospective analysis of 121 patients switched from TDF or other NAs (prior TDF: n = 91) to TAF, 51% of whom had eGFR below 90 ml/min at baseline.[52] While no significant change in eGFR from baseline was observed in the total population, eGFR significantly increased in the subgroup with CKD after switch. CKD stage improvements have also been reported in other studies.[36,43,51] In the Phase 3 TDF to TAF switch study, the proportion of patients with at least one CKD stage improvement was significantly higher in TAF-treated patients compared with TDF-treated patients (25% vs 8%, $P < 0.0001$), and the proportion of patients with at least one CKD stage worsening was significantly higher in TDF-treated patients compared with TAF-treated patients (14% vs 6%, $P < 0.0001$).[36] In a retrospective analysis of switching, patients with reduced eGFR (<90 ml/min) at baseline had significant decreases in eGFR while on TDF, but not after TAF switch.[51] After Week 96 of switching to TAF, approximately one-fifth of patients with mildly decreased eGFR (60–89 ml/min) improved to normal range, and approximately one-third of patients with moderately decreased eGFR (below 60 ml/min) improved to eGFR 60–89 ml/min. Multivariate analysis showed that worsening eGFR was associated with older age, male sex and poor baseline eGFR (60–89 ml/min and below 60 ml/min vs at least 90 ml/min) at switch ($P < 0.001$ for all).

1.3 | Switching from ETV to TAF

Data on switching from ETV to TAF are more limited compared with switching from TDF to TAF. However, available results have demonstrated improved or maintained virological and biochemical responses after switching from ETV to TAF. Renal safety measures either declined or improved slightly, or were stable. Bone safety measures were not reported in most studies (Table 3, Figures 1 and 2).[49,54-62]

1.3.1 | Virological and biochemical response

Results from a retrospective study of 191 patients with CHB who switched to TAF after at least 2 years of ETV treatment showed that most patients with partial virological response to ETV at baseline achieved HBV DNA suppression at Week 48.[59] Similar results were reported from a real-world study of 425 patients switched from ETV to TAF.[54] The proportion of patients with HBV DNA below 20 IU/ml significantly increased at 96 weeks after TAF switching. In a retrospective study of 499 patients with suboptimal response to ETV, significantly more patients switched to TAF had HBV DNA below 30 IU/ml and normal ALT at Week 24 compared with those continuing on ETV.[62] Results from a prospective, single-centre study of 92 patients following switch

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TABLE 4 Switching of patients from other NAs/combinations of NAs to TAF

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Lim 2019[63]	Prospective, multicentre, open-label, Week 24 analysis GS-US-320-4035	N = 31 Median age: 57 y Male: 68% Pts with hepatic impairment CPT class A: 61% CPT class B: 29% CPT class C: 10% Pts with HBV DNA <20 IU/ml at BL: 100% HBeAg +ve: 10% Median ALT level at BL, U/L: 27	TDF: 68% ETV: 45% LAM: 45% ADV: 32% TBV: 6% CLV: 3%	Pts with HBV DNA <20 IU/ml at Week 24 • 100%	Pts with normal ALT (AASLD)[a] at Week 24: • 81% ALT normalisation at Week 24: • 60%	Median % change to Week 24 • Spine BMD: +1.53 • Hip BMD: +0.64 • CTX: −12.8 • P1NP: −11.9	Median change to Week 24 • $eGFR_{CG}$: + 3.0 ml/min • sCr: 0.0 mg/dl • Phosphate: 0.0 mg/dl • RBP/Cr ratio: −10.9% • β2M/Cr ratio: −21.3%
Lim 2020[64]	Prospective, multicentre, open-label, Week 48 analysis GS-US-320-4035	N = 31 See Lim 2019 for study details	TDF: 68% ETV: 45% LAM: 45% ADV: 32% TBV: 6% CLV: 3%	Pts with HBV DNA <20 IU/ml at Week 48 • 100%	Pts with normal ALT (AASLD)[a] at Week 48 • 81% ALT normalisation at Week 48 • 60%	Median % change to Week 48 • Spine BMD: +0.54 • Hip BMD: −0.19	Median change to Week 48 • sCr: 0.0 mg/dl • Phosphate: −0.1 mg/dl
Janssen 2020[65]	Prospective, multicentre, open-label, Week 48 analysis GS-US-320-4035	N = 93 Median age: 65 y Male: 74% Pts with renal impairment Mod-sev RI:[b] n = 78 ESRD:[b] n = 15 HBV DNA <20 IU/ml for ≥6 months HBeAg +ve: 17% Median ALT level at BL, U/L: 17	TDF: 62% ETV: 46% LAM: 49% ADV: 49% TBV: 6% CLV: 2%	Pts with HBV DNA <20 IU/ml • Mod-sev RI BL: 99% Week 48: 92% • ESRD BL: 93% Week 48: 93%	Pts with normal ALT (AASLD)[a] at Week 48 • Mod-sev RI: 87% • ESRD: 80%	Median % change in spine BMD at Week 48 • Mod-sev RI: +1.06 • ESRD: −0.04 Median % change in hip BMD at Week 48 • Mod-sev RI: +0.27 • ESRD: −1.74 Median % change in spine BMD at Week 48 in mod-sev RI group • Prior TDF: +2.1 • Prior other NA: −0.01 Median % change in hip BMD at Week 48 in mod-sev RI group • Prior TDF: +1.0 • Prior other NA: −0.9	Median change to Week 48 in mod-sev RI group • $eGFR_{CG}$: +0.8 ml/min • Serum phosphorus: 0.0 mg/dl • RPB/Cr ratio: −42.4% • β2M/Cr ratio: −50.9% • sCr, mg/dl: All: −0.05 • Prior TDF: −0.04 • Prior other NA: −0.05
Alghamdi 2020[66]	Retrospective, single centre	N = 71 Mean age: 45 y Male: 56% Mean HBV DNA level at BL, IU/ml: 839 HBeAg +ve: 11% Mean ALT level at BL, U/L: 29	NR	Mean HBV DNA level at Month 6, IU/ml • 17; $P = 0.043$	Mean ALT level at Month 6, U/L • 27; $P = 0.328$	NR	Non-significant decline in sCr levels at Month 6

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TABLE 4 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Bernstein 2021[67]	Observational, multicentre TARGET-HBV cohort	N = 500 Median age: 55 y Male: 66% Pts with undetectable HBV DNA at BL: 58% HBeAg +ve: 24% Median ALT level at BL, U/L: 29	Any NA: 82% TDF: 72%	Pts with undetectable HBV DNA (prior NA cohort) • BL: 77.3% • Month 12–18: 82.8%	Pts with normal ALT (central; prior NA cohort)[a] • BL: 79.8% • Month 12–18: 85.5%	NR	Pts with CrCl >60 ml/min (prior NA cohort) • BL: 85.5% • Month 12–18: 85.5%
Komorizono 2020[68]	Retrospective, single centre	N = 104 Median age: 64 y Male: 41% HBV DNA negative HBeAg +ve: NR Median ALT level at BL, IU/L: 31	ETV: 64% TDF: 24% LAM/ADV: 8% LAM/TDF: 2% ETV/ADV: 2%	HBV DNA negative pts • BL: 100% • Week 24: 100%No difference according to prior NA	No significant difference in ALT levels ($P = 0.449$)	NR	No significant difference in eGFR ($P = 0.124$) No significant difference in serum phosphorus levels ($P = 0.119$), except for the TDF-TAF group, which showed a significant increase ($P = 0.014$)
Ogawa 2020[59]	Retrospective, multicentre	N = 122 Median age: 61 y Male: 66% HBV DNA level (IU/ml) at BL: • <20: 92.6% • 20–2000: 7.4% • >2000: 0%HBeAg +ve: 23% Median ALT level at BL, U/L: 20 History of HCC: 18.0%	LAM/ADV: 36% LAM/TDF: 32% ETV/TDF: 30% ETV/ADV: 3% Median prior NA treatment duration: 4.3 years	Pts with HBV DNA <20 IU/ml • BL: 92.6% • Week 48: 98.4% HBV DNA <20 IU/ml at Week 48 by BL level • 20–2000 (n = 9): 77.8%	Pts with normal ALT[c]: • BL: 63.7% • Week 48: 69.4%; $P = 0.35$	NR	Mean change in eGFR at Week 48, ml/min/1.73 m^2 • eGFR <60 at BL: +2.68 • eGFR ≥60 at BL: −0.61; $p < 0.001$ Mean change in sCr at Week 48, mg/dl • eGFR <60 at BL: −0.061 • eGFR ≥60 at BL: +0.008 Pts with serum phosphorus < 2.5 mg/dl • BL: 18.9% • Week 48: 12.3%; $P = 0.15$Urinary β2M/Cr ratio significantly reduced in both groups ($P < 0.001$); no significant difference between groups
Ogawa 2021[60]	Prospective, multicentre Interim analysis	N = 71 Mean age: 57 y Male: 55% Pts with HBV DNA <20 IU/ml at BL: 100% HBeAg +ve: NR Mean ALT level at BL, U/L: 24	TDF or ADV: 87% Other: 13% (not included in analysis)	Pts with HBV DNA <20 IU/ml at Month 12 • 100%	Pts with normal ALT[c] • BL: 74.2% • Month 12: 84.2%	NR	NR

(Continues)

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TABLE 4 (Continued)

Study	Type of study	Pt population	Prior NAs	Effectiveness		Safety	
				HBV DNA	ALT	Bone effects	Renal effects
Sano 2021[69]	Retrospective, single centre	N = 33 Mean age: 62 y Male: 70% Pts with HBV DNA >20 IU/ml at BL: 0% HBeAg +ve: 33% Mean ALT level at BL, U/L: 23	TDF: 73% ADV: 64% LAM: 58% ETV: 36% Long-term (>10 years) prior treatment: n = 19 Short-term prior treatment: n = 14	Pts with HBV DNA >20 IU/ml at Month 6 • 0%	No significant change in mean ALT levels in either group	Mean BAP levels, μg/L • Long-term group • BL: 21.1 • Month 6: 19.2; p = 0.0678 • Short-term group • BL: 17.9 • Month 6: 15.5; p = 0.0016	Significant improvements in β2M/Cr ratio in long-term group ($P = 0.0017$) and short-term group ($P = 0.0052$) Non-significant improvements in eGFR
Sripongpun 2020[70]	Retrospective	N = 11 Mean age: 62 y Male: 73% Pts with undetectable HBV DNA at BL: 100% HBeAg +ve: NR Mean ALT level at BL, U/L: 41 Pts after liver transplant	TDF: 100% ETV: 18% Mean prior NA treatment duration: 4.1 years	Pts with unidentifiable HBV DNA at Week 48 • 100%	Median change in ALT at Week 48, U/L • −6; $P = 0.04$	NR	Median change in GFR at Week 48, ml/min/1.73 m^2 • +2.5; $P = 0.2$
Yeh 2020[71]	Prospective, multicentre, open label Interim results	N = 24 Median age: 53 y Male: 29% Median HBV DNA at BL: 64 IU/ml HBeAg +ve: 42% Median ALT level at BL, U/L: 24 Pts with advanced fibrosis and partial virological response	ETV: 58% TDF: 38% LAM: 4%	Pts with undetectable HBV DNA • BL: 0% • Week 24: 75%	Pts with normal ALT (central)[a] • BL: 91.7% • Week 24: 100%	NR	No significant changes in sCr or eGFR levels from BL to Week 24
Zhao 2021[72]	Real world	N = 34 Mean age: 49 y Male: 91% HBV DNA level at BL: NR HBeAg +ve: NR ALT level at BL: NR Pts with diabetes mellitus	TDF: 38% ETV: 21%	NR	NR	NR	16 pts had renal injury including 9 with TDF-related kidney injury Urine β2M decreased upon switching from TDF to TAF ($P = 0.005$)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ADV, adefovir; ALT, alanine aminotransferase; β2M/Cr, β2 microglobulin to creatinine; BAP, bone-specific alkaline phosphatase; BL, baseline; BMD, bone mineral density; CLV, clevudine; CPT, Child-Pugh Score; CrCl, creatinine clearance; CTX, C-type collagen sequence; eGFR, estimated glomerular filtration rate; $eGFR_{CG}$, estimated glomerular filtration rate Cockcroft-Gault formula; ESRD, end-stage renal disease; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LAM, lamivudine; NA, nucleos(t)ide analogue; NR, not reported; P1NP, procollagen type 1 N-terminal propeptide; pt, patient; RBP/Cr, retinol binding protein to creatinine; RI, renal impairment; TAF, tenofovir alafenamide; TBV, telbivudine; TDF, tenofovir disoproxil fumarate; sCr, serum creatinine; y, years.

[a]Central laboratory (≤40 U/L), AASLD 2018 (≤35 IU/L for males; ≤ 25 IU/L for females).

[b]Moderate–severe RI defined as $eGFR_{CG}$ 15–<60 ml/min and ESRD defined as $eGFR_{CG}$ < 15 ml/min on chronic haemodialysis;

[c]≤30 IU/L for males, ≤19 IU/L for females.

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from ETV to TAF showed that two patients with HBV DNA above 20 IU/ml at baseline achieved HBV DNA below 20 IU/ml after TAF switching.[61] Multivariate analysis found that HBV genotype and serum aspartate aminotransferase level at the time of switching were associated with superiority of TAF over ETV. Results from a prospective study of 199 patients switched to TAF after at least 12 months of ETV showed that virological response numerically increased over 12 months.[60] A prospective study compared TAF switching with continuing ETV in 211 ETV-treated CHB patients with low-level viraemia (HBV DNA 20–2000 IU/ml).[58] Significant improvements in the proportion of patients with HBV DNA below 20 IU/ml at Week 24 and ALT normalisation were reported in the TAF group compared with the ETV group. Switching from ETV to TAF favoured HBV DNA level below 20 IU/ml at Week 24 regardless of sex, age, CHB family history, HBV DNA and liver cirrhosis.

1.3.2 | Renal and bone safety

Renal parameters slightly decreased, increased or were maintained in ETV to TAF switching studies (Table 3).[49,54-59,61] Results from a retrospective study showed that patients had small numerical increases in serum creatinine from baseline to Week 48 after switching from ETV to TAF.[59] Estimated GFR slightly increased in patients with eGFR below 60 ml/min; approximately 20% of these patients improved to eGFR of at least 60 ml/min after 48 weeks of TAF. In a prospective ETV to TAF switch study, no significant changes in eGFR or inorganic phosphate levels were reported.[61] In another prospective study, similar renal safety was observed in patients switching to TAF or continuing ETV treatment.[58] A prospective single-centre study of 48 patients treated with ETV for at least 2 years who either switched to TAF or continued ETV excluded patients with eGFR below 60 ml/min.[56] Results from this study showed no significant difference in markers of glomerular or kidney tubule function after 48 weeks between treatment groups. Mean eGFR levels in the ETV group were slightly reduced over 48 weeks compared with stable levels in the TAF group.

1.3.3 | Additional safety outcomes of interest

Results from a prospective study of CHB patients with low-level viraemia showed that 4% of TAF-treated patients experienced Grade 3 elevations in fasting LDL cholesterol, but the authors concluded that these were isolated events in patients with a history of dyslipidaemia and/or elevated LDL cholesterol.[58] Results from a retrospective study of patients with suboptimal response to ETV did not show any significant changes in lipids after 24 weeks of TAF.[62]

1.3.4 | Special patient populations

A retrospective real-world study of 425 patients switched from ETV to TAF included patients with CKD; 55.6% had stage 1 CKD, 35.7% had stage 2 CKD and 8.8% had stage 3–5 CKD.[54] There was a significant decrease in eGFR levels after switching from ETV to TAF, but no significant change in the distribution of CKD groups. Multivariate analysis showed that stage 2 and stage 3–5 CKD at baseline were associated with lower eGFR after switching from ETV to TAF, but most patients had stage 1 CKD throughout the study.

1.4 | Switching from other NAs or combinations of NAs to TAF

Studies evaluating switching from other NAs or combinations of NAs to TAF have shown improved or maintained virological and biochemical responses. Most study results showed that renal safety measures were stable or improved upon switching to TAF. Bone-related safety outcomes were not reported (Table 4).[59,60,63-72]

1.4.1 | Virological and biochemical response

Results from a retrospective review of 104 patients with CHB who switched to TAF from various NAs showed that all patients still tested negative for HBV DNA at Week 24.[68] No significant changes in ALT levels were reported. Virological response was maintained in a prospective multicentre study of 62 patients switched to TAF after at least 12 months of any NA treatment.[59] Improvements in efficacy upon switching to TAF were also reported in several other studies (Table 4).[60,66,67,69,71] A retrospective observational study evaluated 71 patients who switched to TAF after at least 6 months of treatment with various NAs.[66] HBV DNA levels decreased significantly over 6 months after TAF switching. Reasons for TAF switching included TDF unavailability (82%), side effects (14%), lack of efficacy, safety concerns and physician preference (1% each). Results from the US TARGET-HBV cohort study showed that switching to TAF was well tolerated and associated with further improvement in serum ALT and a decrease in HBV DNA to undetectable levels.[67] Reasons for switching included perceived safety profile (35%), physician choice (23%), renal insufficiency or disease (11%) and risk of bone disease (6%).

1.4.2 | Renal and bone safety

Limited renal safety data are available for studies of switching to TAF from other NAs (Table 4).[59,63,65-69,71] Results from a retrospective review of 104 patients who switched to TAF from various NAs showed maintenance of eGFR and serum phosphorus after switching, although a significant increase in serum phosphorus was reported in those with prior TDF treatment.[68] In two Phase 2 studies conducted in virally suppressed patients with hepatic impairment and eGFR of at least 30 ml/min[64] or moderate–severe renal impairment or end-stage renal disease,[65] bone and renal safety parameters were stable

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or improved after switching to TAF from a diverse mix of NAs.[64,65] Creatinine clearance increased slightly after TAF switching in an observational study,[67] while a non-significant decline in serum creatinine levels was reported in another study.[66] A retrospective study showed that patients with eGFR below 60 ml/min showed the greatest improvement in renal glomerular and proximal tubular function after TAF switching.[59] Estimated GFR at Week 48 after TAF switching was significantly improved in patients with CKD compared with patients without CKD.

1.4.3 | Special patient populations

A Phase 2 study enrolled CHB patients with renal impairment who had received oral antivirals for at least 48 weeks and were virally suppressed for at least 6 months prior to TAF switching.[65] Two cohorts were included: the first cohort included 78 patients with moderate to severe renal impairment (eGFR between 15 and 60 ml/min) and the second cohort included 15 patients with end-stage renal disease (eGFR below 15 ml/min) on chronic haemodialysis. Viral suppression was maintained in both cohorts. Renal parameters were stable over 48 weeks and switching to TAF caused numerical increases in BMD. Numerical increases in total, LDL and HDL cholesterol and a small decrease in total to HDL cholesterol ratio were reported at Week 48. Greater increases in total, LDL and HDL cholesterol were observed in patients with prior TDF treatment, and decreases in these parameters were observed in patients who received prior treatment with other NAs compared with the overall population. Median body weight increased by 1 kg over the 48-week study.

A phase 2 study in 31 virally suppressed patients with hepatic impairment and eGFR of at least 30 ml/min evaluated switching to TAF.[63,64] Hepatic impairment was defined as a Child–Turcotte–Pugh (CTP) score of between 7 and 12 or a documented CTP score of at least 7 in the past and any CTP score of 12 or below at screening. After TAF switching, viral suppression was maintained and improvements in renal and bone safety were reported. Estimated GFR_{CG} levels increased, tubular markers decreased, BMD increased and bone turnover markers decreased. Numerical increases in total, LDL and HDL cholesterol were reported at Week 48 with greater increases observed in patients who received prior TDF treatment compared with the overall population. No difference in total to HDL cholesterol ratio was reported. Median body weight increased by 2 kg over the 48-week study. No changes in CTP score were reported.

Preliminary results from a prospective cohort of 24 CHB patients with advanced fibrosis have been reported.[71] Patients with detectable HBV DNA after at least 1 year of NA treatment were included. After 24 weeks of TAF treatment, three-quarters of patients had undetectable HBV DNA. ALT normalisation rates increased after TAF switching, but no significant changes in serum creatinine or eGFR levels were observed. A retrospective study evaluated TAF switching in 11 patients after liver transplant.[70] At Week 48, all patients had unidentifiable HBV DNA, and ALT levels significantly decreased.

2 | DISCUSSION AND CLINICAL IMPLICATIONS

TAF has been available since 2016, is the most recently approved NA and is now included, along with TDF and ETV, as a preferred treatment option for patients with CHB in guidelines.[3-6,12,35] These guidelines recommend TAF or ETV instead of TDF in patients with risk of bone or renal complications, and in elderly patients. TAF is preferred over ETV in patients with previous NA exposure because of the lower risk of drug resistance. The purpose of this narrative review was to assess the available data for switching from other NAs to TAF in CHB patients and the clinical implications of these data.

Given guideline recommendations, it is not surprising that studies evaluating the efficacy and safety of TAF switching in CHB patients have predominantly been performed in those previously treated with TDF.[36-52] Phase 3 study results in patients switched to TAF or continued on TDF showed maintenance of virological suppression at Week 48 in both groups.[36] ALT normalisation and improvements in bone and renal safety outcomes upon switching to TAF were also reported. Similar results have been reported in other studies, where virological, biochemical and bone and renal safety outcomes were improved or maintained in patients upon switching from TDF to TAF.[40-44,46-52]

There are several reasons why a patient with CHB may switch NA treatment, including safety, resistance concerns and guideline recommendations. Most studies identified in this narrative review did not specify reasons for TAF switching. However, where reasons were given, these were most commonly related to safety issues.[41,55,67,73] Efficacy has also been reported as a reason for TAF switching.[55,73] Virological breakthrough on NA treatment may be related to medication non-adherence.[4,5] Results from a meta-analysis of 30 studies of CHB patients where ETV was the most common NA used showed that NA adherence was 74.6%.[74] Results from a population-based historical cohort study of CHB patients treated with ETV in Korea found that 18.6% of patients had adherence levels below 80%.[75] However, lack of adherence is not necessarily a reason to switch NA treatment based on the available data. Another reason for TAF switching is resistance concerns with ETV and older antiviral agents. Data presented within this review support the use of TAF as an alternative to TDF in patients with multidrug-resistant CHB.[42] It should be noted that a recent study of two patients with viral breakthrough on TDF identified a quadruple mutation associated with tenofovir resistance.[17] This quadruple mutation could have a negative impact on TAF antiviral potency. However, in another study of 3886 patients enrolled in HBV clinical studies, only two patients carried the quadruple resistance mutation at baseline, and both patients achieved viral suppression after TDF or TAF treatment.[18] No evidence of resistance to TDF or TAF and no selection of those mutations after starting TDF or TAF was observed.

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Treatment guidelines provide recommendations on which patients should be considered for TAF switching (Table 1).[3,5,6,12,13] One study switched patients to TAF according to EASL criteria.[3,48] Virological and biochemical parameters remained stable after TAF switching, and improvements in renal function were reported.[48] Results from the studies summarised herein support the concept of switching to TAF based on guideline criteria. However, there appears to be a reluctance to switch patients despite evidence-based guidelines. A cross-sectional study performed in two European hospitals estimated that two-thirds of patients who could benefit from switching to ETV or TAF based on EASL guideline criteria remained on TDF.[76] Several studies have evaluated TAF switching in special patient populations, such as those with CKD, hepatic impairment, liver fibrosis or transplantation.[44,51,52,54,63-65,70,71] Pregnant women and children are also important patient populations to consider with respect to NA treatment. While there are no TAF switching studies in pregnant women, studies of TAF during pregnancy have been conducted. Three studies that evaluated TAF treatment in pregnant women reported that TAF could effectively reduce maternal HBV transmission with no observed safety concerns,[77-79] suggesting that TAF switching may be appropriate in these patients, although it is not indicated for such use. ETV and TDF have been studied in children with CHB,[3-5] while TAF is currently under investigation in this setting. Findings from an ongoing study of TAF efficacy and safety in children and adolescents with CHB (NCT02932150) will inform future clinical guidance in this population.

To date, few studies have evaluated switching from ETV, or NAs other than TDF, to TAF, but this evidence base is growing. Improvements in virological outcomes upon switching from ETV to TAF have been shown in several studies.[54,55,58-62] Low-level viraemia during ETV monotherapy is associated with a high risk of HCC and disease progression,[16,80] and the American Association for the Study of Liver Diseases guidelines recommend that patients with low-level viraemia on ETV switch to another antiviral monotherapy with a high barrier to resistance or add a second antiviral drug that lacks cross resistance.[5] Current data suggest that switching these patients to TAF may help avoid poor long-term outcomes. Improvements or maintenance in virological outcomes upon switching from other NAs or combinations of NAs to TAF have been reported.[59,60,63-65,67-71] TDF and/or ETV were the most commonly reported prior NAs, but several studies included a high proportion of patients treated with other prior NAs.[59,60,63-65,69] No differences in efficacy or safety of TAF switching according to prior NA were reported in most studies. However, it is necessary to acknowledge that 'other NA' populations represent a diverse group. Changes in lipids and renal and bone safety in patients with prior TDF were reported in some studies.[63-65,68,72] One study included TDF-treated patients with resistance to adefovir and/or ETV who continued on TDF or switched to TAF. Virological outcomes were comparable between the two treatment groups, but improvements in biochemical, bone and renal outcomes were reported in the TAF group compared with the TDF group. These results suggest that TAF switching may be appropriate in patients with multidrug-resistant CHB.[42]

TDF has a favourable long-term safety profile, but renal tubular dysfunction and BMD loss have been reported in some patients.[19-27] In Phase 3 studies of CHB patients, TAF demonstrated improved renal and bone safety compared with TDF.[19] Several studies showed that switching from TDF to TAF improved both renal and bone safety.[36-41,43,44,46-52] Bone safety was not reported in most studies of TAF switching from ETV or other NAs. With respect to renal safety, switching from ETV or other NAs to TAF had no clear benefit.[49,54-59,61,63-72]

Significant lipid changes were not observed in patients switching from ETV to TAF,[62] but patients who switched from TDF to TAF had greater increases in total, LDL and HDL cholesterol compared with those who continued TDF treatment.[39,42] This could be due to high plasma tenofovir levels in TDF-treated patients, which has been linked to lipid reductions in patients on TDF.[19,81] Therefore, it is possible that changes in lipid levels after TAF switching represent "returning to normal". It should be noted that the total to HDL cholesterol ratio did not increase after switching from TDF to TAF,[39,42] suggesting no increased risk of CVD.[82] The clinical impact of lipid changes upon switching from TDF to TAF is uncertain, but nevertheless, a patient's individual CVD risk should be considered when switching to TAF. Some studies reported body weight increase in patients who switched from TDF to TAF.[39,42,47,64,65] The reported weight gains were in line with the reported average of 1 kg per year,[83,84] although among patients with hepatic impairment, the median weight (Q1, Q3) at baseline was 71 kg (59, 87) and 73 kg (61, 89) in TDF- and TAF-treated patients, respectively.[64] It is uncertain whether TAF affects body weight, particularly given the lipid- and weight-suppressive effects of TDF. The observed rise in lipids and weight following switch from TDF to TAF and not ETV to TAF might be reflective of this effect.

Although maintenance or improvements in virological, biochemical and safety outcomes upon TAF switching were observed, long-term studies are required to determine whether these translate to long-term benefits. High viral suppression rates are associated with improved long-term outcomes in CHB patients, and normal ALT levels are associated with lower HCC incidence.[85-92] Long-term outcomes of patients may improve upon TAF switching, but further investigation is warranted. The CHB patient population is ageing, with an increasing incidence of comorbidities.[7-11] Analysis of TAF efficacy and safety in geriatric (aged 65 years and above) vs non-geriatric patients enrolled in TAF clinical studies showed no clinically significant differences.[34] Consequently, it is imperative for physicians to choose a NA treatment that will continue to suppress viral load, not cause resistance and which has a favourable bone and renal safety profile. Emerging data support TAF as a valuable treatment option in this arena. Results from studies modelling the potential health consequences of NA treatment projected fewer liver, renal and bone complications in patients treated with TAF compared with TDF or ETV over 10 years.[93-95] The renal and bone benefits associated with TAF treatment have the potential to address comorbidities associated with an ageing CHB population. However, a discussion of the economic factors surrounding TAF is beyond the scope of this

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article. Additional long-term real-world data on TAF effectiveness and safety will provide further evidence among switch and naïve patients, as well as in the setting of transplantation and prophylaxis for HBV reactivation.

3 | CONCLUSIONS

This narrative review summarises study results evaluating the efficacy and safety of switching from TDF, ETV or other NAs to TAF in patients with CHB. Switching to TAF appears to maintain or improve virological, biochemical and bone- and renal-related safety outcomes. These data, together with recommendations from various CHB treatment guidelines,[3,5,6,12,13] support the concept of switching to TAF in individual patients with CHB, including those at risk of bone or renal complications, elderly patients and those with previous NA treatment.

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AUTHORSHIP

Guarantors of the article: Young-Suk Lim and Pietro Lampertico.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this narrative review article

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APPENDIX

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