






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

Young-Suk Lim¹ | Wai-Kay Seto^{2,3}  | Masayuki Kurosaki⁴ | Scott Fung⁵ |
Jia-Horng Kao⁶  | Jinlin Hou⁷  | Stuart C. Gordon⁸ | John F. Flaherty⁹ |
Leland J. Yee⁹  | Yang Zhao⁹ | Kosh Agarwal¹⁰ | Pietro Lampertico^{11,12} 

¹University of Ulsan College of Medicine, Seoul, South Korea

²The University of Hong Kong, Hong Kong

³The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

⁴Musashino Red Cross Hospital, Musashino, Japan

⁵University of Toronto, Toronto, Canada

⁶National Taiwan University Hospital, Taipei, Taiwan

⁷Nanfang Hospital, Southern Medical University, Guangzhou, China

⁸Henry Ford Health System and Wayne State University School of Medicine, Detroit, MI, USA

⁹Gilead Sciences, Foster City, CA, USA

¹⁰King's College Hospital, London, UK

¹¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

¹²University of Milan, Milan, Italy

Correspondence

Young-Suk Lim, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea.

Email: limys@amc.seoul.kr

Pietro Lampertico, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy.

Email: pietero.lampertico@unimi.it

Funding information

Gilead Sciences

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.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *Alimentary Pharmacology & Therapeutics* published by John Wiley & Sons Ltd.

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 function¹⁹⁻²³ 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 phosphoramidate 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

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

Guideline	Recommendations
EASL 2017 ³	<ul style="list-style-type: none"> • Age > 60 years • Bone disease <ul style="list-style-type: none"> • Chronic steroid use or use of other medications that reduce BMD • History of fragility fracture • Osteoporosis • Renal alteration^a <ul style="list-style-type: none"> • eGFR <60 ml/min/1.73 m² • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Bone disease <ul style="list-style-type: none"> • Chronic steroid use • Use of medication that worsens BMD • Osteoporosis or osteopenia • Renal alteration^b <ul style="list-style-type: none"> • eGFR <60 ml/min/1.73 m² • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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.

^aETV 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;

^bTAF 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

TABLE 2 Studies of patients switching from TDF to TAF

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

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 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 PINP 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 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		
Átelen 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 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		

(Continues)

TABLE 2 (Continued)

Study	Type of study	Pt population	Effectiveness			Safety		
			Prior NAs	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	TDF: 73% ETV: 3% LAM: 2% Other: 4% Native: 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 urinary RPB/Cr and β 2M/Cr ratios at weeks 12 and 24 (P < 0.01)	No significant change in eGFR _{CG} from BL to Week 24 Significant improvements in urinary RPB/Cr and β 2M/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 β 2M/Cr ratio at Weeks 12 and 24 post switch (P = 0.002 and P = 0.027, respectively)	

TABLE 2 (Continued)

Study	Type of study	Pt population	Effectiveness			Safety	
			Prior NAs	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 β 2M/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, μ g/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 \leq 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 \leq 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

(Continues)

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_{CR}, estimated glomerular filtration rate Cockcroft-Gault formula; eGFR_{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.

^aAccording to EASL and AASLD guidelines.

^bAccording to EASL and AASLD guidelines.

^cTwo patients had HBV DNA >21 IU/ml; both patients were non-compliant as measured by pill count.

^dIn 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).

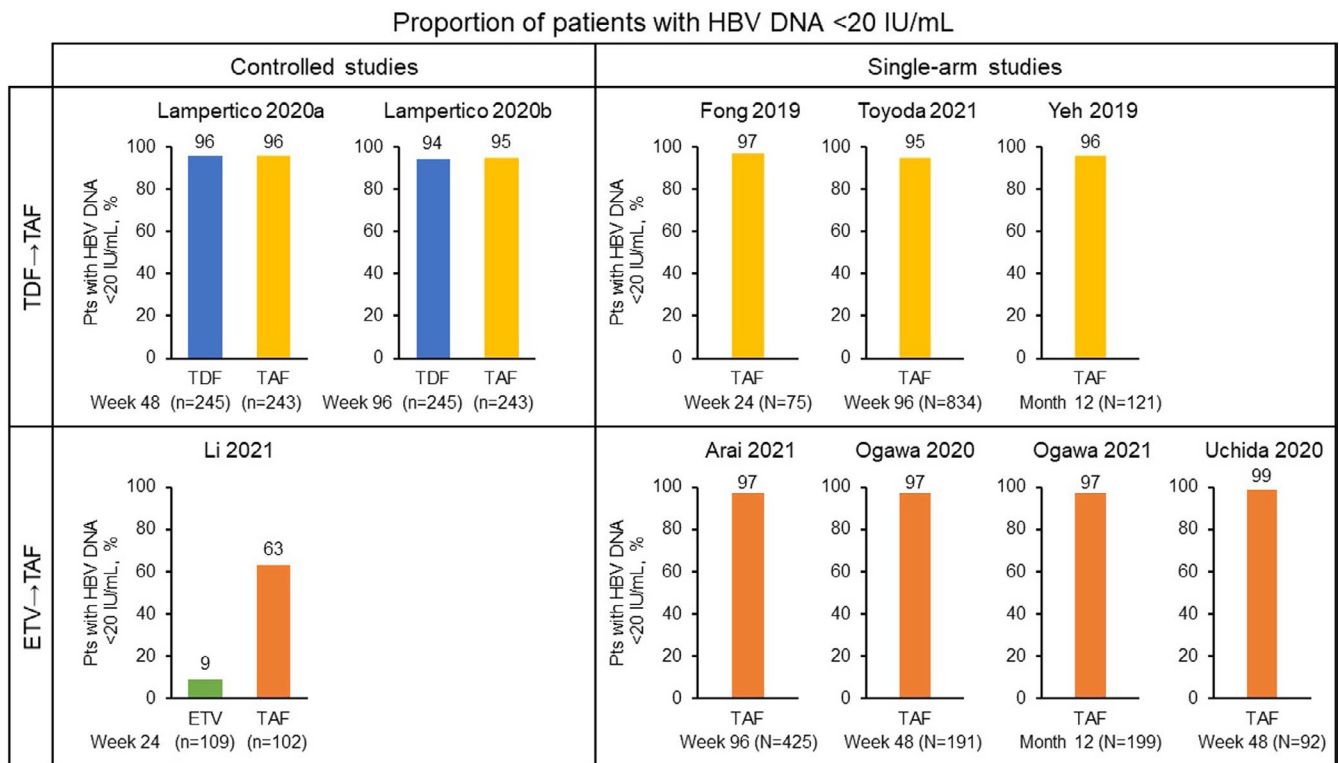


FIGURE 1 Schematic showing the proportion of patients with HBV DNA < 20 IU/ml in studies in patients with CHB switching from TDF or ETV to TAF. The upper panels show results from TDF to TAF switching studies and the lower panels show results from ETV to TAF switching studies. Results from comparative 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 2020⁵⁹), 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 2021⁶⁰) or not specified (Fong 2019,⁴³ Uchida 2020⁶¹). 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

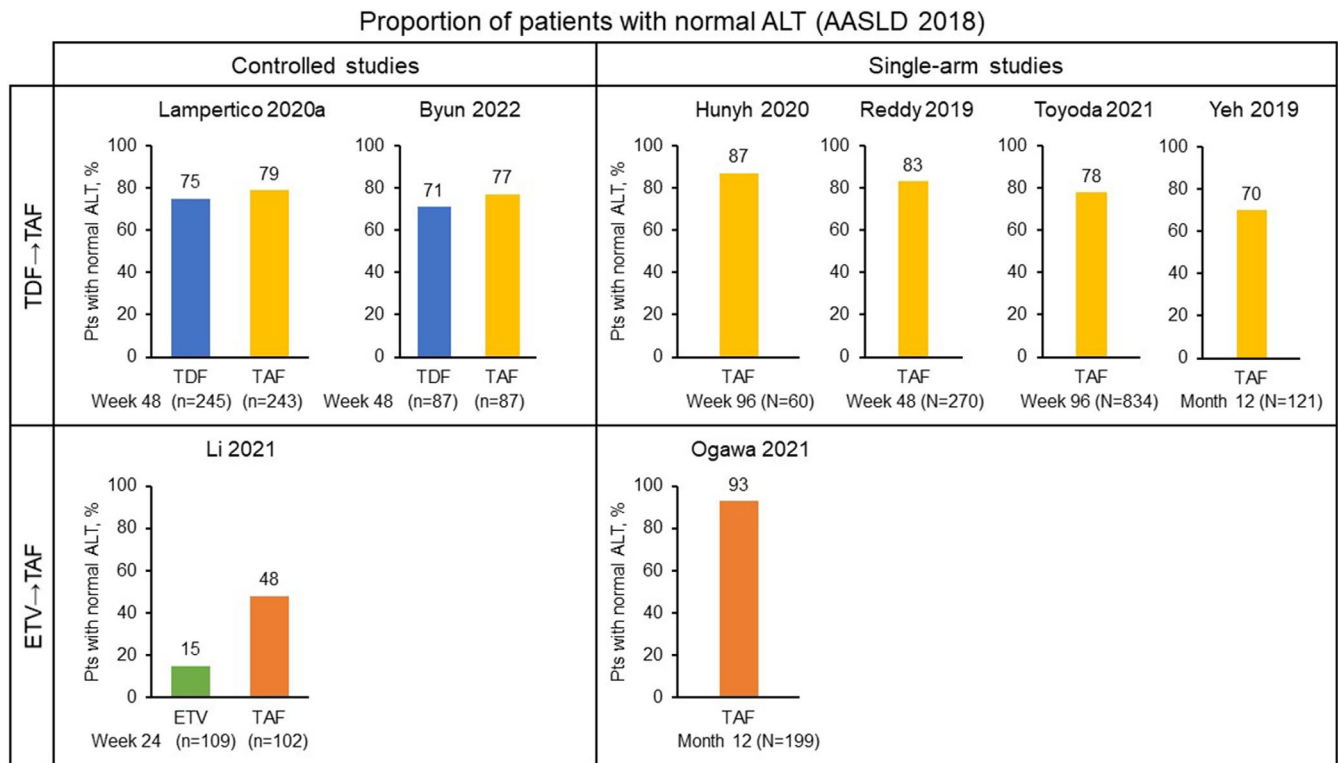


FIGURE 2 Schematic showing the proportion of patients with normal ALT according to the AASLD 2018 criteria in studies in patients with CHB switching from TDF or ETV to TAF. The upper panels show results from TDF to TAF switching studies and the lower panels show results from ETV to TAF switching studies. 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 2021⁵⁸), HBV DNA < 60 IU/ml (Byun 2022⁴²), complete response defined as the HBV DNA < 20 IU/ml plus ALT normalisation (AASLD 2018 criteria; Toyoda 2021,⁵¹ Ogawa 2021⁶⁰) or not specified (Huynh 2020,⁴⁵ Reddy 2019⁵⁰). 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 β_2 microglobulin (β_2 M)/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

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, IU/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 IU/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)

TABLE 3 (Continued)

Study	Type of study	Pt population	Effectiveness			Safety		
			Prior NAs	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 4: 2.96; P = 0.039 • 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	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 IU/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	

TABLE 3 (Continued)

Study	Type of study	Pt population	Effectiveness			Safety		
			Prior NAs	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	NR

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; β 2M, β 2 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.

^bCentral laboratory (\leq 40 U/L), AASLD 2018 (\leq 35 IU/L for males; \leq 25 IU/L for females).

^c \leq 30 IU/L for males; \leq 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

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

Study	Type of study	Pt population	Effectiveness			Safety		
			Prior NAs	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 • 81% • 100% ALT normalisation at Week 48 • 60%	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	

TABLE 4 (Continued)

Study	Type of study	Pt population	Effectiveness			Safety	
			Prior NAs	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: 85.5% 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%
Komorzono 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)

TABLE 4 (Continued)

Study	Type of study	Pt population	Effectiveness			Safety		
			Prior NAs	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; CrCl, 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.

^aCentral laboratory (≤40 U/L), AASLD 2018 (≤35 IU/L for males; ≤ 25 IU/L for females).

^bModerate-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.

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/min⁶⁴ or moderate–severe renal impairment or end-stage renal disease,⁶⁵ bone and renal safety parameters were stable

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.

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

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.

ACKNOWLEDGEMENTS

Medical writing support was provided by Karen Beckett PhD of Elements Communications and financially supported by Gilead Sciences.

Declaration of personal interests: Professor Lim has served as a speaker, advisory board member, consultant and/or has received research support from Assembly Biosciences, Gilead Sciences, GlaxoSmith Kline, Olix Pharmaceuticals, Vaccitech and Vir Biotechnology. Professor Seto has served as a speaker, consultant and/or advisory board member for AbbVie, AstraZeneca, CSL Behring, Gilead Sciences and Mylan. Dr Kurosaki has served as a speaker, consultant and/or advisory board member for AbbVie, Bayer, Chugai Pharmaceutical, Eisai, Eli Lilly, Gilead Sciences and Otsuka Pharmaceutical. Professor Fung has served as a speaker, consultant and/or advisory board member for AbbVie, Assembly Biosciences, Gilead Sciences, Janssen Pharmaceuticals and Spring Bank Pharmaceuticals. Professor Kao has served as a speaker, consultant and/or advisory board member for AbbVie, Arbutus Biopharma, Bristol Myers Squibb, Fujirebio, Gilead Sciences, Johnson & Johnson, MSD, Polaris, Sysmex and Roche. Professor Hou has served as a consultant for Assembly Biosciences, AbbVie, Ascentage Pharma, Bristol Myers Squibb, Gilead Sciences, GlaxoSmithKline, Johnson & Johnson, Qilu Pharmaceutical and Roche, and has received grants from Bristol Myers Squibb and Johnson & Johnson. Dr Gordon has served as a speaker, consultant and/or advisory board member for CymaBay Therapeutics. Dr Agarwal has served as a speaker, consultant and/or advisory board member for Assembly Bio, Arbutus Biopharma, Aligos Therapeutics, Boehringer Ingelheim, Gilead Sciences, Immunocore, Janssen Pharmaceuticals, Merck, Roche, Sandoz, Sobi, Shionogi and Vir Biotechnology. Professor Lampertico has nothing to declare. John Flaherty, Leland J. Yee and Yang Zhao are employees of Gilead Sciences and own stock in Gilead Sciences.

AUTHORSHIP

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

Author contributions: All authors contributed to review of the published data, drafting of the manuscript and critical revision of the manuscript. All authors approved the final version of the article.

DATA AVAILABILITY STATEMENT

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

ORCID

Wai-Kay Seto  <https://orcid.org/0000-0002-9012-313X>

Jia-Horng Kao  <https://orcid.org/0000-0002-2442-7952>

Jinlin Hou  <https://orcid.org/0000-0001-8230-8583>

Leland J. Yee  <https://orcid.org/0000-0002-0369-5878>

Pietro Lampertico  <https://orcid.org/0000-0002-1026-7476>

REFERENCES

- World Health Organization. Hepatitis B fact sheet. Published online 27 July, 2020. Accessed 25 November, 2020. <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>
- Bixler D, Zhong Y, Ly KN, et al. Mortality among patients with chronic hepatitis B infection: the chronic hepatitis cohort study (CHeCS). *Clin Infect Dis*. 2019;68:956-963.
- European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370-398.
- Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10:1-98.
- Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560-1599.
- Korean Association for the Study of the liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. *Clin Mol Hepatol*. 2019;25:93-159.
- Nguyen MH, Lim JK, Burak Ozbay A, et al. Advancing age and comorbidity in a US insured population-based cohort of patients with chronic hepatitis B. *Hepatology*. 2019;69:959-973.
- Oh H, Jun DW, Lee IH, et al. Increasing comorbidities in a South Korea insured population-based cohort of patients with chronic hepatitis B. *Aliment Pharmacol Ther*. 2020;52:371-381.
- Wong GLH, Wong VWS, Yuen BWY, et al. An aging population of chronic hepatitis B with increasing comorbidities: a territory-wide study from 2000 to 2017. *Hepatology*. 2020;71:444-455.
- Sanai FM, Alghamdi H, Alswat KA, et al. Greater prevalence of comorbidities with increasing age: cross-sectional analysis of chronic hepatitis B patients in Saudi Arabia. *Saudi J Gastroenterol*. 2019;25:194-200.
- Tseng CH, Hsu YC, Ho HJ, Nguyen MH, Wu CY. Increasing age and nonliver comorbidities in patients with chronic hepatitis B in Taiwan: a nationwide population-based analysis. *Dig Dis*. 2021;39:266-274.
- Chinese Society of Infectious Diseases, Chinese Medical Association, Chinese Society of Hepatology, Chinese Medical Association. The guidelines of prevention and treatment for chronic hepatitis B [2019 version]. *Zhonghua Gan Zang Bing Za Zhi*. 2019;27:938-961.
- Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. Japan Society of Hepatology guidelines for the management of hepatitis B virus infection (2019 update). *Hepatol Res*. 2020;50:892-923.
- Pan CQ, Hu KQ, Yu AS, Chen W, Bunchorntavakul C, Reddy KR. Response to tenofovir monotherapy in chronic hepatitis B

- patients with prior suboptimal response to entecavir. *J Viral Hepat.* 2012;19:213-219.
15. Yip B, Chaung K, Wong CR, et al. Tenofovir monotherapy and tenofovir plus entecavir combination as rescue therapy for entecavir partial responders. *Dig Dis Sci.* 2012;57:3011-3016.
 16. Kim JH, Sinn DH, Kang W, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. *Hepatology.* 2017;66:335-343.
 17. Park ES, Lee AR, Kim DH, et al. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. *J Hepatol.* 2019;70:1093-1102.
 18. Liu Y, Chang S, Martin R, Flaherty J, Mo H, Feierbach B. Characterization of hepatitis B virus polymerase mutations A194T and CYEI and tenofovir disoproxil fumarate or tenofovir alafenamide resistance. *J Viral Hepat.* 2021;28:30-39.
 19. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol.* 2018;68:672-681.
 20. Gara N, Zhao X, Collins MT, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. *Aliment Pharmacol Ther.* 2012;35:1317-1325.
 21. Jung WJ, Jang JY, Park WY, et al. Effect of tenofovir on renal function in patients with chronic hepatitis B. *Medicine (Baltimore).* 2018;97:e9756.
 22. Min IS, Lee CH, Shin IS, et al. Treatment outcome and renal safety of 3-year tenofovir disoproxil fumarate therapy in chronic hepatitis B patients with preserved glomerular filtration rate. *Gut Liver.* 2019;13:93-103.
 23. Tien C, Xu JJ, Chan LS, et al. Long-term treatment with tenofovir in Asian-American chronic hepatitis B patients is associated with abnormal renal phosphate handling. *Dig Dis Sci.* 2015;60:566-572.
 24. Ahn SH, Kim W, Jung YK, et al. Efficacy and safety of besifovir dipivoxil maleate compared with tenofovir disoproxil fumarate in treatment of chronic hepatitis B virus infection. *Clin Gastroenterol Hepatol.* 2019;17:1850-1859.
 25. Fung S, Kwan P, Fabri M, et al. Tenofovir disoproxil fumarate (TDF) vs. emtricitabine (FTC)/TDF in lamivudine resistant hepatitis B: a 5-year randomised study. *J Hepatol.* 2017;66:11-18.
 26. Gill US, Zissimopoulos A, Al-Shamma S, et al. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: can the fracture risk assessment tool identify those at greatest risk? *J Infect Dis.* 2015;21:374-382.
 27. Seto WK, Asahina Y, Brown TT, et al. Improved bone safety of tenofovir alafenamide compared to tenofovir disoproxil fumarate over 2 years in patients with chronic HBV infection. *Clin Gastroenterol Hepatol.* 2018;20:S1542-3565(18)30633-5. doi: 10.1016/j.cgh.2018.06.023
 28. Lee WA, He GX, Eisenberg E, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. *Antimicrob Agents Chemother.* 2005;49:1898-1906.
 29. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. *Mol Pharm.* 2013;10:459-466.
 30. Murakami E, Wang T, Park Y, et al. Implications of efficient hepatic delivery by tenofovir alafenamide (GS-7340) for hepatitis B virus therapy. *Antimicrob Agents Chemother.* 2015;59:3563-3569.
 31. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. *J Hepatol.* 2015;62:533-540.
 32. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.
 33. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:185-195.
 34. Fung S, Brunetto M, Buti M, et al. Safety and efficacy of tenofovir alafenamide in geriatric patients with chronic hepatitis B: experience from four ongoing phase 2 and phase 3 clinical trials. *J Hepatol.* 2020;73:S883-S884.
 35. Lau G. APASL HBV reactivation 2021 Guidelines. Presented on 6 February, 2021 at APASL 2021 Bangkok (Virtual Meeting). Accessed 27 April, 2021. <https://www.youtube.com/watch?v=fbpVoQX1hYk>
 36. Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. *Lancet Gastroenterol Hepatol.* 2020;5:441-453.
 37. Buti M, Lampertico P, Lim YS, et al. Safety and efficacy at 48 weeks after switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) in chronic HBV patients with risk factors for TDF use. *Hepatology.* 2019;70:301A.
 38. Ahn SH, Kao JH, Hann HW, et al. 48-week safety and efficacy of switching to tenofovir alafenamide (TAF) from tenofovir disoproxil fumarate (TDF) in chronic HBV Asian patients with TDF risk factors (RF). *Hepatol Int.* 2020;14:S87.
 39. Lampertico P, Buti M, Ramji A, et al. A phase 3 study comparing switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) with continued TDF treatment in virologically-suppressed patients with chronic hepatitis B (CHB): final week 96 efficacy and safety results. *J Hepatol.* 2020;73:S67-S68.
 40. Ahn SH, Kao JH, Lampertico P, et al. 96-week efficacy and safety of tenofovir disoproxil fumarate to tenofovir alafenamide switch vs continued TDF treatment among virologically-suppressed hepatitis B patients of Asian ethnicity. *Hepat Int.* 2021;15:S54.
 41. Atelan MK. Pisagor cohort: tenofovir alafenamide real life data in hepatitis B. *Hepatol Int.* 2020;14:S54.
 42. Byun KS, Choi J, Kim JH, et al. Tenofovir alafenamide for drug-resistant hepatitis B: a randomized trial for switching from tenofovir disoproxil fumarate. *Clin Gastroenterol Hepatol.* 2022;20:427-437.
 43. Fong TL, Lee BT, Tien A, et al. Improvement of bone mineral density and markers of proximal renal tubular function in chronic hepatitis B patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. *J Viral Hepat.* 2019;26:561-567.
 44. Farag MS, Fung S, Tam E, et al. Effectiveness and renal safety of tenofovir alafenamide fumarate among chronic hepatitis B patients: real-world study. *J Viral Hepat.* 2021;28:942-950.
 45. Huynh T, Hu KQ. Tenofovir disoproxil fumarate switching to tenofovir alafenamide for 2 years resulted in both ALT and AST, and APRI score improvement in patients with chronic hepatitis B. *Hepatology.* 2020;72:497A.
 46. Kaneko S, Kurosaki M, Tamaki N, et al. Tenofovir alafenamide for hepatitis B virus infection including switching therapy from tenofovir disoproxil fumarate. *J Gastroenterol Hepatol.* 2019;34:2004-2010.
 47. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients. *JGH Open.* 2021;5:258-263.
 48. Loglio A, Viganò M, Borghi M, et al. Early changes in proximal tubule markers in CHB patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide according to EASL 2017 criteria: a real-life study. *Hepatology.* 2020;72:481A.
 49. Notsumata K, Nomura Y, Tanaka A, et al. Early changes in tubular dysfunction markers and phosphorus metabolism regulators as a result of switching from entecavir to tenofovir alafenamide fumarate nucleoside analog therapy for chronic hepatitis B patients. *Hepatol Res.* 2020;50:402-404.

50. Reddy R, Curry M, Bae H, et al. Longer-term experience with tenofovir alafenamide (TAF) in HBV-infected patients; changes in eGFR, FIB4, ALT, and DNA suppression. *J Hepatol*. 2019;70:S309A.
51. Toyoda H, Leong J, Landis C, et al. Treatment and renal outcomes up to 96 weeks after tenofovir alafenamide switch from tenofovir disoproxil fumarate in routine practice. *Hepatology*. 2021;74:656-666.
52. Yeh ML, Trinh S, Huang CF, et al. Improvement in virologic, biochemical and renal outcomes in chronic hepatitis B (CHB) patients switched to tenofovir alafenamide (TAF) in routine clinical practice. *Hepatology*. 2019;70:295A-296A.
53. Chan H, Buti M, Agarwal K, et al. Maintenance of high levels of viral suppression and improved safety profile of tenofovir alafenamide relative to tenofovir disoproxil fumarate in chronic hepatitis B patients treated for 5 years in two ongoing phase 3 studies. *Hepatology*. 2020;72:490A.
54. Arai T, Atsukawa M, Ishikawa T, et al. Real-world outcomes of sequential therapy with tenofovir alafenamide following long-term entecavir. *Hepatol Int*. 2021;15:H-28.
55. Chen P, Wei W, Zhu Y, et al. Switching to tenofovir alafenamide (TAF) from entecavir in Chinese chronic hepatitis B (CHB) patients. *Hepatol Int*. 2021;15:H-43.
56. Hagiwara S, Nishida N, Ida H, et al. Switching from entecavir to tenofovir alafenamide versus maintaining entecavir for chronic hepatitis B. *J Med Virol*. 2019;91:1804-1810.
57. Itokawa N, Atsukawa M, Tsubota A, et al. Sequential therapy from entecavir to tenofovir alafenamide versus continuous entecavir monotherapy for patients with chronic hepatitis B. *JGH Open*. 2020;5:34-40.
58. Li ZB, Li L, Niu XX, et al. Switching from entecavir to tenofovir alafenamide for chronic hepatitis B patients with low-level viraemia. *Liver Int*. 2021;41:1254-1264.
59. Ogawa E, Nomura H, Nakamuta M, et al. Tenofovir alafenamide after switching from entecavir or nucleos(t)ide combination therapy for patients with chronic hepatitis B. *Liver Int*. 2020;40:1578-1589.
60. Ogawa E, Toyoda H, Jun DW, et al. Sequential therapy with tenofovir alafenamide (TAF) in patients with chronic hepatitis B (CHB): an interim analysis of an ongoing multinational prospective study. *Hepatol Int*. 2021;15:H-40.
61. Uchida Y, Nakao M, Tsuji S, et al. Significance of switching of the nucleos(t)ide analog used to treat Japanese patients with chronic hepatitis B virus infection from entecavir to tenofovir alafenamide fumarate. *J Med Virol*. 2020;92:329-338.
62. Yan D, Yang R. Significance of switching from ETV to TAF for CHB patients with suboptimal response to ETV: a retrospective cohort study. *Hepatol Int*. 2021;15:H-36.
63. Lim YS, Lampertico P, Bae HS, et al. Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with hepatic impairment: Week 24 results from a Phase 2 study. *Hepatology*. 2019;70:316A-317A.
64. Lim YS, Lin CY, Heo J, et al. Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with hepatic impairment: week 48 results from a phase 2 open label study. *J Hepatol*. 2020;73:S872.
65. Janssen H, Lampertico P, Chen CY, et al. Safety and efficacy of switching to tenofovir alafenamide (TAF) in virally suppressed chronic hepatitis B (CHB) patients with renal impairment: week 48 results from a phase 2 open label study. *J Hepatol*. 2020;73:S866-S867.
66. Alghamdi AS, Alothmani HS, Mogharbel M, Albiladi H, Babatin M. Clinical characteristics of hepatitis B virus patients after switching to tenofovir alafenamide fumarate: a retrospective observational study. *Cureus*. 2020;12:e10380.
67. Bernstein DE, Trinh HN, Schiff ER, et al. Safety and effectiveness of tenofovir alafenamide in usual clinical practice confirms results of clinical trials: TARGET-HBV. *Dig Dis Sci*. 2021. doi:10.1007/s10620-021-07033-y
68. Komorizono Y, Nakashima K, Sako K, Shibata T. Switching from prior nucleos(t)ide analogues (NAs) to tenofovir alafenamide alone in patients with chronic hepatitis B in clinical practice. *Hepatology*. 2020;72:496A.
69. Sano T, Amano K, Ide T, et al. Short-term efficacy after switching from adefovir dipivoxil and tenofovir disoproxil fumarate therapy to tenofovir alafenamide for chronic hepatitis B. *Biomed Rep*. 2021;14:12.
70. Sripongpun P, Mannalithara A, Kwo PY, Kim WR. Potential benefits of switching liver transplant recipients to tenofovir alafenamide prophylaxis. *Clin Gastroenterol Hepatol*. 2020;18:747-749.
71. Yeh ML, Chen C, Cheng PN, et al. Efficacy and safety of switching to tenofovir alafenamide for chronic hepatitis B patients with advanced fibrosis and partial virologic response to oral nucleos(t)ide analogues (ESTAB-AFPVR) - an interim report. *J Hepatol*. 2020;73:S878.
72. Zhao J, Wei LL, Gao W, Xu B. A real-world clinical study of lipid changes on TAF treatment in Chinese chronic hepatitis B patients with diabetes mellitus. *Hepatol Int*. 2021;15:H-02.
73. Curry M, Bae H, Dietrich D, et al. Differential tenofovir alafenamide (TAF) adoption in HBV-infected populations; assessment of care in US clinical practice. *Hepatology*. 2019;70:308A-309A.
74. Ford N, Scourse R, Lemoine M, et al. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis B infection: a systematic review and meta-analysis. *Hepatol Commun*. 2018;2:1160-1167.
75. Lee J, Cho S, Kim HJ, Lee H, Ko MJ, Lim YS. High level of medication adherence is required to lower mortality in patients with chronic hepatitis B taking entecavir: a nationwide cohort study. *J Viral Hepat*. 2021;28:353-363.
76. Roade L, Loglio A, Borghi M, et al. Application of EASL 2017 criteria for switching hepatitis B patients from tenofovir disoproxil to entecavir or tenofovir alafenamide. *Dig Liver Dis*. 2020;52:1164-1169.
77. Ding Y, Cao L, Zhu L, et al. Efficacy and safety of tenofovir alafenamide fumarate for preventing mother-to-child transmission of hepatitis B virus: a national cohort study. *Aliment Pharmacol Ther*. 2020;52:1377-1386.
78. Zeng QL, Yu ZJ, Ji F, et al. Tenofovir alafenamide to prevent perinatal hepatitis B transmission: a multicenter, prospective, observational Study. *Clin Infect Dis*. 2021;73:e3324-e3332.
79. Li B, Liu Z, Liu X, et al. Efficacy and safety of tenofovir disoproxil fumarate and tenofovir alafenamide fumarate in preventing HBV vertical transmission of high maternal viral load. *Hepatol Int*. 2021;15:1103-1108.
80. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology*. 2012;142:1140-1149.
81. Santos JR, Saumoy M, Curran A, et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2015;61:403-408.
82. Millán J, Pintó X, Muñoz A, et al. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag*. 2009;5:757-765.
83. Flegal KM. Trends in body weight and overweight in the U.S. population. *Nutr Rev*. 1996;54:S97-S100.
84. Lewis CE, Jacobs DR, McCreath H, et al. Weight gain continues in the 1990s: 10-year trends in weight and overweight from the CARDIA study. Coronary artery risk development in young adults. *Am J Epidemiol*. 2000;151:1172-1181.
85. Coffin CS, Rezaeeaval M, Pang JX, et al. The incidence of hepatocellular carcinoma is reduced in patients with chronic hepatitis B on long-term nucleos(t)ide analogue therapy. *Aliment Pharmacol Ther*. 2014;40:1262-1269.
86. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013;58:98-107.
87. Kim WR, Loomba R, Berg T, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. *Cancer*. 2015;121:3631-3638.

88. Lampertico P, Invernizzi F, Viganò M, et al. The long-term benefits of nucleos(t)ide analogs in compensated HBV cirrhotic patients with no or small esophageal varices: a 12-year prospective cohort study. *J Hepatol*. 2015;6:1118-1125.
89. Papatheodoridi A, Sypsa V, Dalekos GN, et al. Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis B. *J Hepatol*. 2020;72:1088-1096.
90. Su TH, Hu TH, Chen CY, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. *Liver Int*. 2016;36:1755-1764.
91. Wu CY, Lin JT, Ho HJ, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. *Gastroenterology*. 2014;147:143-151.
92. Wong GLH, Chan HLY, Tse YK, et al. Normal on-treatment ALT during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B. *J Hepatol*. 2018;69:793-802.
93. Han Y, Wu B, Hu M, Hou F, Yang Y, Wang L. Projection of health outcomes over 5-year and 10-year period using tenofovir alafenamide (TAF) for the management of chronic hepatitis B (CHB) in China. *Hepatol Int*. 2019;13:S53-S54.
94. Han Y, Yu B, Hu M, Hou F, Yang Y, Wang L. Projection of long-term bone and renal outcomes using tenofovir alafenamide (TAF) for the management of chronic hepatitis B (CHB) in China. Poster P-52 presented at APASL STC 2019.
95. Su TH, Smith N, Hsu LI, Lee IH, Hsu YC. Projection of 10-year liver, bone, and renal outcomes using tenofovir alafenamide for the management of chronic hepatitis B in Taiwan. *Gut Liver*. 2019;13:85.

How to cite this article: Lim Y-S, Seto W-K, Kurosaki M, et al. Review article: switching patients with chronic hepatitis B to tenofovir alafenamide—a review of current data. *Aliment Pharmacol Ther*. 2022;55:921-943. doi: [10.1111/apt.16788](https://doi.org/10.1111/apt.16788)

APPENDIX

The authors' complete affiliation list

Young-Suk Lim, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Wai-Kay Seto, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong; State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong; Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China; Masayuki Kurosaki, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino, Japan; Scott Fung, Department of Medicine, Division of Gastroenterology and Hepatology, University of Toronto, Toronto, Canada; Jia-Horng Kao, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Department of Medical Research, Hepatitis Research Centre, National Taiwan University Hospital, Taipei, Taiwan; Jinlin Hou, Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan; Stuart C. Gordon, Department of Infectious Diseases, Institute of Hepatology, Nanfang Hospital, Southern Medical University, Guangzhou, China; John F. Flaherty, Leland J. Yee, Yang Zhao, Division of Gastroenterology and Hepatology, Henry Ford Health System and Wayne State University School of Medicine, Detroit, Michigan, USA; Gilead Sciences, Foster City, California, USA; Kosh Agarwal, Institute of Liver Studies, King's College Hospital, London, UK; Pietro Lampertico, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.