



Cost-effectiveness of switching from tenofovir disoproxil fumarate to tenofovir alafenamide versus entecavir for chronic hepatitis B patients in Greece

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Aim: This study assessed the clinical impact and cost-effectiveness of switching from tenofovir disoproxil fumarate (TDF) to either tenofovir alafenamide (TAF) or entecavir (ETV) in a Greek chronic hepatitis B (CHB) population. **Patients & methods:** A Markov model from the perspective of a third-party payer in Greece quantified the health and economic benefits of switching from TDF to either TAF or ETV over a lifetime horizon. **Results:** Over a lifetime, patients who switch from TDF to TAF versus patients who switch from TDF to ETV had an overall lower incidence of compensated cirrhosis (0.4% lower), decompensated cirrhosis (0.04% lower) and hepatocellular carcinoma (0.25% lower). Chronic kidney disease and end-stage renal disease were also lower in patients who switch to TAF; major osteoporotic fractures were similar for both groups. While total costs were higher for switching from TDF to TAF versus TDF to ETV due to the higher cost of TAF, switching from TDF to TAF versus ETV was cost effective with an incremental cost-effectiveness ratio of €17,113 per quality-adjusted life year. **Conclusion:** Switching from TDF to TAF in patients living with CHB is a cost effective strategy to reduce adverse liver disease outcomes, while improving bone- and renal-related safety outcomes.

Plain language summary

What is this article about? Chronic hepatitis B (CHB) is a major public health issue. Antiviral treatments are effective at treating CHB and include tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and entecavir (ETV); TAF is associated with a lower incidence of bone and renal complications compared with TDF. This study evaluated the benefits and costs of switching from TDF to TAF versus TDF to ETV for the treatment of CHB in a Greek population.

What were the results? This study found that patients switching from TDF to TAF versus ETV had lower estimated incidence of liver disease outcomes, as well as fewer cases of chronic kidney disease and end-stage renal disease; the number of cases of major osteoporotic fractures was similar for patients switching to TAF and ETV.

What do the results of the study mean? Considering these clinical benefits, while total costs for TAF were higher, it was still considered good value for money.

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Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV). Approximately 5% of infected adults develop chronic hepatitis B (CHB), which is characterized by hepatic inflammation that persists for more than 6 months after acute infection with HBV [1]. CHB continues to be a major public health issue despite the availability of an effective vaccine and potent antiviral treatments.



CHB can cause progressive liver damage that, when left unmanaged, may lead to serious adverse clinical outcomes such as cirrhosis, liver failure, hepatocellular carcinoma (HCC) or death. CHB is a lifelong disease that requires long-term or indefinite therapy [2]. Though implementation of universal vaccination against HBV has reduced the prevalence of infection, approximately 20–30% of patients who become infected ultimately develop complications of cirrhosis and HCC [1]. In addition to the significant morbidity, CHB results in considerable economic consequences. Thus, the overall goal for the treatment of CHB is to induce a functional cure by reducing viral levels (viremia) to an undetectable level to minimize the risk of developing adverse liver events such as compensated cirrhosis (CC), decompensated cirrhosis (DCC) and HCC.

While the worldwide prevalence of HBV has decreased in many parts of the world, infection with HBV is a major public health concern in Greece. Surveillance data estimates the prevalence of HBV in Greece to be between 1.9 [3] and 3.5% [4]. Further, recent data suggest a rise in the number of patients diagnosed with advanced liver disease [3]. According to the Viral Hepatitis Scientific Committee of the National Public Health Organization of Greece, the recommended first-line treatment for CHB in adults is antiviral monotherapy with entecavir (ETV), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) due to their beneficial efficacy profile and high barrier for developing treatment resistance [5]. Based on two head-to-head non-inferiority Phase III trials, where TAF demonstrated an added benefit of improved bone and renal outcomes [6,7], guidelines recommend switching people who are at high risk for bone and renal disease from TDF to either TAF or ETV [8]. As the mean age of Greek CHB patients is reported to be 50 years, reducing the incidence of bone and renal complications are important considerations when deciding treatment options [3]. This study thus assessed the cost-effectiveness of switching from TDF to TAF versus ETV for the treatment of Greek CHB patients using *de novo* model to account for advanced liver disease.

Methods

Model overview

A Markov Model was constructed from the perspective of a third-party payer in Greece over a lifetime horizon (50 years) to quantify the health and economic benefit of switching from TDF to either TAF or ETV. The model used a cycle length of 1 year (with half-cycle correction applied); costs and outcomes were discounted at 3.5%.

The model assigns patients to treatment, upon which, active CHB patients (treatment-naïve [TN] or treatment experienced [TE]) are determined to be responders or non-responders by week 48 (Supplementary Figure 1). Based on the response status, the model updates the patient's HBV DNA level and ALT level categories. Responders who achieve viral suppression with an undetectable HBV DNA level by week 48 (Supplementary Table 1), or may achieve HBsAg or HBeAg seroconversion [9]. HBeAg seroconverted patients may transition to HBsAg seroconverted or move back to active CHB, at which time their HBV DNA and ALT levels are reset to baseline. Patients who achieve HBsAg seroconversion are assumed to discontinue their antiviral therapy after 6 months. Patients who do not achieve viral suppression at week 48 immediately discontinue to receive best supportive care (BSC). If treatment resistance occurs, it is assumed that patients will have uncontrolled HBV DNA and ALT levels (i.e., HBV DNA viral load >1,000,000 IU/ml and ALT level >44 IU/ml) for 3 months. A proportion of patients who develop resistance will experience acute flare, some of whom will develop DCC.

Patient population

The population in the model was patients 60 years of age or older, with CHB, of whom 1.6% of patients are HBeAg-positive [3], 21% have cirrhosis [10] and 57% of the population have had some treatment for CHB in the past (TE) [10]. As there is a strong correlation between reduction in ALT levels and viral load levels with antiviral therapies, two patient profiles were created: virally suppressed patients or viremic patients. Based on the treatment outcome (i.e., virally suppressed or viremic), a corresponding HBV DNA-ALT level profile was sampled based on the 320–0108 and 320–0110 trial data [6,7]. Due to the absence of patient-level data for ETV, it is assumed that the HBV DNA-ALT profiles for ETV are the same as the TDF arm of the 320–0108 and 320–0110 trials [6,7].

Treatment efficacy

In order to use the most robust datasets available, treatment efficacy was sourced from randomized controlled trials (for comparative effectiveness data on TAF vs TDF) and meta-analyses based on randomized controlled trials (for TDF vs ETV). Treatment efficacy was defined using two different parameters: undetectable viral loads (i.e., viral suppression) with corresponding ALT levels (Supplementary Table 2) and HBeAg seroconversion (Supplementary

Table 3). Efficacy estimates for TAF and TDF were obtained from the 320–0108/320–0110 trials for the overall population and individual subgroups of interest. ETV efficacy estimates were obtained from published literature and the TDF arm of the 320–0108/320–0110 studies, to which a relative adjustment has been applied. Based on a recent meta-analysis, HBsAg seroconversion is assumed to be independent of treatment and can occur at low baseline rate [11].

Liver related disease

The hazard ratio for the rate of HCC was based on the treatment strategy (TAF, TDF or ETV). Several recent studies have suggested that there is lower rate of HCC events in TDF compared with ETV, with HRs varying between 0.75 and 0.87 [12–19]. A treatment-specific HR of 0.75 was used in the base case for the transition from non-compensated cirrhosis to compensated cirrhosis, based on the mean across the meta-analyses/SLRs considered, for both TDF and ETV. Using clinical trial data [20], an HR of 0.65 was then applied for the TAF versus TDF-specific transitions, resulting in annual transition probability of 0.49 for both. For BSC, REACH-B was used to calculate HCC risk.

Major osteoporotic fracture

Compared with the general population, CHB patients are at a higher risk of osteoporosis; this risk increases with the presence of coexisting cirrhosis [21]. Existing antiviral therapies, such as TDF, may expedite bone mineral loss further increasing the risk of fractures [22]. In order to capture the deterioration of bone density, and also the impact of antiviral therapies, risk of a fracture for each patient was estimated based on a fracture risk profile assigned at baseline (low, medium or high). This profile was based on the fracture risk estimated by the FRAX score, as reported by the Foundation for Osteoporosis Research and Education (Table 1) [23]. The distributions of risk profiles were estimated using real-world data [24].

Major osteoporotic fracture (MOF) risk reduction associated with TAF, as compared with TDF, is incorporated into the model by applying a hazard ratio, derived from the 320–0108 and 320–0110 trials [6,7]. Due to limited bone measurement data for ETV, it was conservatively assumed that the fracture risk for ETV is the same as that for TAF. In the base case, it was also conservatively assumed that a previous fracture was not a risk factor for a subsequent fracture. Bone damage was assumed to be cumulative; that is, if a patient switches therapies, bone deterioration will continue from where the previous therapy left off.

Renal disease

Similar to bone complications, CHB patients are at a higher risk for renal complications compared with the general population and anti-viral therapies such as TDF may also negatively impact renal function [36]. Given the limited number of studies on the long-term renal outcomes of HBV treatments, a biomarker of kidney function, estimated glomerular filtration rate (eGFR), was modeled to estimate the impact on long-term renal outcomes as a consequence of treatment. eGFR in the model was dependent on both treatment and baseline eGFR. Baseline eGFR at model start was determined from the normal distribution of clinical trial eGFR scores prior to treatment. Patients then experience a decline in eGFR for the first three years following initiation of therapy, dependent on their treatment (Table 1). eGFR scores are then used to determine whether a patient has stage III chronic kidney disease (CKD) (eGFR of ≥ 30 to < 60 ml/min) or end-stage renal disease (ESRD; eGFR of < 30 ml/min). Patients with ESRD have an associated incremental cost, utility decrement and increased risk of mortality.

Mortality

Background mortality was derived from the gender-specific life tables for the general Greek population [37] and were adjusted to exclude deaths caused by viral hepatitis infection. In addition to background mortality, excess mortality due to active CHB was obtained from Iloeje *et al.* [31]. It is assumed that virally suppressed patients and patients with low viral loads (i.e., 300–9999 IU/ml) are not subject to excess mortality. Excess mortality due to treatment-related complications (i.e., stage III CKD, ESRD and MOF), as well as mortality due to liver-related complications, were obtained from the literature (Table 1).

Health utilities

Health state utility values in the model for liver disease health states were taken from a global standard gamble utility study among infected CHB patients (Table 2) [38]. Patients with hepatic flare were assigned a utility decrement equivalent to 1 month of DCC compared with the active CHB condition. It is assumed that the viral suppression and

Table 1. Clinical model inputs.

Parameter	Value	Distribution	Source	Ref.
Annual transition probabilities for disease progression				
HBeAg seroconversion to HBeAg negative	2.8%	Beta	Hsu (2002)	[25]
HBeAg seroconversion to HBeAg positive	3.0%	Beta	Shepherd (2006)	[26]
HBeAg seroconversion to HCC	0.2%	Beta	Hsu (2002)	[25]
HBeAg seroconversion to HBsAg seroclearance	0.7%	Beta	Dakin (2010)	[27]
HBsAg seroconversion to HCC	0.01%	Beta	Dakin (2010)	[27]
HBV DNA <300 to HBsAg seroclearance	0.2%	Beta	Chen (2009)	[28]
CC (on treatment) to DCC	1.4%	Beta	Dakin (2010)	[27]
CC (off treatment) to DCC	5.0%	Beta	Fattovich (2003)	[29]
DCC (off treatment) to CC	0.0%	N/A	Dakin (2010)	[27]
DCC (year 1) to CC	13.6%	Beta	Fattovich (2003) Bermingham (2015)	[29]
DCC (year 2) to CC	0.0%	N/A		
DCC to HCC	2.9%	Beta		
DCC to LTx	1.6%	Beta		
HCC to LTx	1.6%	Beta		
MOF risk over 10 years for TDF-based therapies				
Low risk (<10%)	5%	Beta/Cholesky	University of Sheffield	[23]
Medium risk (≥10%–≤20%)	15%	Beta/Cholesky		
High risk (≥21%)	25%	Beta/Cholesky		
MOF hazard ratio vs TDF				
TAF (vs TDF)	0.956	Lognormal	320–0108 and 320-0110 trials	[6,7]
ETV (vs TDF)	0.956	Lognormal	Assumed equivalent to TAF vs TDF	
Mean change in eGFR from baseline				
TAF				
Year 1	-3.1	Normal	320–0108 and 320-0110 trials	[6,7]
Year 2	-2.5			
Year 3	-2.5			
ETV				
Year 1	-2.7	Normal	Wu (2017)	[30]
Year 2	-3.7			
Year 3	-4.4			
TDF				
Year 1	-6.1	Normal	Wu (2017)	[30]
Year 2	-5.0			
Year 3	-4.9			
Excess mortality (hazard ratio) due to active CHB by HBV DNA levels (IU/ml)				
<300 (undetectable) – 99,999	1.0	Lognormal	Iloeje (2007)	[31]
100,000–999,999	2.0			
≥1 million	2.1			
Excess mortality (hazard ratio) due to treatment-related complications				
Stage III CKD	1.36	Lognormal	Neuhaus (2010)	[32]
ESRD	16.80	Lognormal	USRDS (2014)	[33]
MOF	1.26	Lognorma	Bliuc (2013)	[34]
Annual mortality risk due to liver-related complications				
CC	3.7%	Beta	Fattovich (2003)	[29]
DCC	15.6%	Beta		
HCC	56.0%	Beta	Dakin (2010)	[27]
LTx (first year)	21.0%	Beta	Veenstra (2007)	[35]
Post LTx (subsequent years)	5.75%	Beta		
ALT: Alanine aminotransferase; BSC: Best supportive care; CC: Compensated cirrhosis; CKD: Chronic kidney disease; DCC: Decompensated cirrhosis; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; ETV: Entecavir; HBeAG: Hepatitis B e-antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; LTx: Liver transplantation; MOF: Major osteoporotic fracture; N/A: Not applicable; Post-LTx: Post-liver transplantation; PSA: Probabilistic sensitivity analysis; TAF: Tenofovir alafenamide fumarate; TDF: Tenofovir diphosphate fumarate.				

ALT: Alanine aminotransferase; BSC: Best supportive care; CC: Compensated cirrhosis; CKD: Chronic kidney disease; DCC: Decompensated cirrhosis; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; ETV: Entecavir; HBeAg: Hepatitis B e-antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; LTx: Liver transplantation; MOF: Major osteoporotic fracture; N/A: Not applicable; Post-LTx: Post-liver transplantation; PSA: Probabilistic sensitivity analysis; TAF: Tenofovir alafenamide fumarate; TDF: Tenofovir diphosphate fumarate.

Table 2. Health utilities.

Health state		Health utility	Distribution	Source	Ref.
Liver disease health states					
No cirrhosis – viremic		0.68	Beta/Cholesky	Levy (2008)	[38]
No cirrhosis – viral suppression		0.77	Beta/Cholesky		
Compensated cirrhosis – viremic		0.68	Beta/Cholesky		
Compensated cirrhosis – viral suppression		0.69	Beta/Cholesky		
Decompensated cirrhosis		0.35	Beta/Cholesky		
Hepatocellular carcinoma		0.38	Beta/Cholesky		
Liver transplantation		0.57	Beta/Cholesky		
Post-liver transplantation		0.67	Beta/Cholesky		
Flare		0.03	Beta/Cholesky	Assumption	
HBeAg seroconverted, by age (years)	18–29	0.97	Beta/Cholesky	Assumption of 1% lower than HBsAg seroclearance	
	30–39	0.96	Beta/Cholesky		
	40–49	0.95	Beta/Cholesky		
	50–59	0.91	Beta/Cholesky		
	60–69	0.81	Beta/Cholesky		
	70–79	0.79	Beta/Cholesky		
	≥80	0.73	Beta/Cholesky		
HBsAg seroclearance, by age (years)	18–29	0.98	Beta/Cholesky	Levy (2008)	[38]
	30–39	0.97	Beta/Cholesky		
	40–49	0.96	Beta/Cholesky		
	50–59	0.92	Beta/Cholesky		
	60–69	0.82	Beta/Cholesky		
	70–79	0.79	Beta/Cholesky		
	≥80	0.74	Beta/Cholesky		
Major osteoporotic fracture states					
Year 1 (average utility multiplier)		0.729	Beta/Cholesky	Calculated based on Talevski (2021)	[40]
Year 2+ (average utility multiplier)		0.729	Beta/Cholesky		
Renal disease states					
Annual stage III CKD		0.80	Beta	Calculated based Cooper (2020)	[41]
Average ESRD utility multiplier		0.76	Beta		
CKD: Chronic kidney disease; ESRD: End-stage renal disease; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.					

CKD: Chronic kidney disease; ESRD: End-stage renal disease; HBsAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.

viral failure (without CC) states have the same utility score as active CHB. Utility values for HBsAg seroconverted patients are assumed to have the same quality of life as the general Greek population [39]. Utility values for HBsAg seroconverted patients are assumed to be 1% lower than that of the general population.

Patients with either an MOF or who progress to ESRD had an average utility multiplier applied to their health state utility (Table 2). The average utility multiplier for MOFs was calculated based on the proportion of fractures occurring at the hip, vertebral, forearm/wrist, weighted for the first year after a fracture and the years following [40]. The average utility multiplier for ESRD was calculated based on the proportion of patients who are treated with dialysis versus kidney transplant [41].

Costing inputs

All cost estimates are reported in 2021 Euros (€). Cost inputs from previous years were inflated to 2021 costs using the inflation rates from the Greek Consumer Price Index [42]. Costs from other jurisdictions were converted using purchasing power parity [43].

Treatment acquisition costs for all therapies are based on the indicated dosing information from the prescribing information and unit drug costs, obtained from the Greek price bulletin in 2022, with a blended cost of generic and brand name (Table 3). Health state costs were obtained from the literature and were included in the model as either per year or per event (Table 3). MOF costs were incorporated as a weighted average based on the cost of fractures at the hip (34.5% of fractures), vertebral (31.3% of fractures) and forearm/wrist (34.2% of fractures) [44]. Renal disease costs were accounted for stage III CKD and ESRD, separately. Given that patients with ESRD can

Table 3. Cost inputs.

Parameter	Cost	Distribution	Source	Ref.
Annual treatment acquisition costs				
TAF	€2936	N/A	Hellenic Association of Pharmaceutical Companies (2021)	[45]
TDF (88% generic)	€1431	N/A		
ETV (74% generic)	€2990	N/A		
TAF + ETV	€5926	N/A		
TDV + ETV	€4421	N/A		
Annual liver-related costs				
No cirrhosis	€635	Gamma/Cholesky	Athanasakis (2015) and Athanasakis (2013)	[46,47]
Compensated cirrhosis	€1330	Gamma/Cholesky	Gountas (2017)	[48]
Decompensated cirrhosis	€4426	Gamma/Cholesky		
Hepatocellular carcinoma	€21,621	Gamma/Cholesky	Athanasakis (2015) and Athanasakis (2013)	[46,47]
Liver transplantation	€34,620	Gamma/Cholesky	Veenstra (2007)	[35]
Post-liver transplantation	€3952	Gamma/Cholesky		
HBeAg seroconversion	€635	Gamma/Cholesky	Assumed same as no cirrhosis	
HBsAg seroconversion	0	N/A	Assumed to be 0	
Per event major osteoporotic fracture costs				
Hip	€12,111	Gamma	Hernlund (2013)	[49]
Vertebral	€2679			
Forearm/wrist	€740			
Weighted average cost [†]	€5268			
Annual renal disease costs				
Stage III CKD	€866	Gamma	Cicchetti 2011	[50]
Dialysis	€33,594	Gamma/Cholesky	Kaitelidou (2005), Kontodimopoulos (2007), Naoum (2016)	[51–53]
Transplant	€33,617	Gamma/Cholesky		
Weighted average cost ESRD year 1	€33,600	Gamma/Cholesky	Calculation [‡]	
Weighted average cost ESRD year 2	€24,859			
Per event CHB-related costs				
Resistance	€635	Gamma	Assumption same as no cirrhosis	
Flare	€369	Gamma	Assumption equal to one month cost of decompensated cirrhosis	
Treatment switch	€59	Gamma	Assumption 16% of flare	
Death	€6952	Gamma	Oyaguez (2017)	[54]

[†]Weighted average cost that 34.5% of fractures will be hip, 31.3% will be vertebral and the remaining 34.2% will be forearm/wrist [53].

[‡]Weighted average cost that 74.0% of ESRD patients are on dialysis and 26.0% receive a transplant.

CHB: Chronic hepatitis B; CKD: Chronic kidney disease; ESRD: End-stage renal disease; ETV: Entecavir; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; N/A: Not applicable; NHl: National Health Insurance; PSA: Probabilistic sensitivity analysis; TAF: Tenofovir alafenamide fumarate; TDF: Tenofovir disoproxil fumarate.

[†]Weighted average cost that 34.5% of fractures will be hip, 31.3% will be vertebral and the remaining 34.2% will be forearm/wrist [53].

[‡]Weighted average cost that 74.0% of ESRD patients are on dialysis and 26.0% receive a transplant.

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be treated with either dialysis or transplant, a weighted average was calculated. The cost of death was taken from a Spanish study [30].

Analyses

The proportion of patients experiencing a health event associated with advanced liver disease, and liver-related deaths, along with bone and renal events per 100 person-years, were determined for each treatment sequence. Total costs, life years (LYs) and quality-adjusted life years (QALYs) were also calculated. The incremental cost-effectiveness ratio (ICER) of switching from TDF to TAF versus TDF to ETV was determined. Deterministic sensitivity analyses where parameters were varied individually by +/- 10% along probabilistic sensitivity analyses, where all inputs are varied simultaneously over 1000 simulations, are presented for both treatment sequences. All efficacy variables were varied using a Dirichlet distribution.

Table 4. Health outcomes, base case analysis.

	TDF → TAF	TDF → ETV
Liver disease incidence		
Compensated cirrhosis	27.26%	27.66%
Decompensated cirrhosis	1.20%	1.24%
Hepatocellular carcinoma	7.07%	7.32%
Liver transplants	0.15%	0.15%
Adverse events (cases per 100 person-year)		
Chronic kidney disease (stage III)	1.53	1.56
End-stage renal disease	0.35	0.36
Major osteoporotic fractures	1.27	1.27

ETV: Entecavir; TAF: Tenofovir alafenamide fumarate; TDF: Tenofovir disoproxil fumarate.

Table 5. Costs and cost-effectiveness, base case analysis.

	TDF → TAF	TDF → ETV	Incremental
Total costs	€33,023	€32,666	€357
Treatment costs	€15,663	€15,236	€427
Health state costs	€13,086	€13,125	-€39
Adverse event costs	€4273	€4305	-€32
Total LYs	10.91	10.89	0.02
Total QALYs	7.69	7.67	0.02
Incremental cost per QALY			€17,113

ETV: Entecavir; LY: Life-year; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; TE: Treatment-experienced; TN: Treatment-naive; QALY: Quality-adjusted life-year.

Two scenario analyses were considered. The first was an alternative approach to the risk of developing HCC via ALT normalization, where HCC risk was determined based on time of ALT normalization. In comparing TAF to ETV, it was found that early ALT normalization was independently associated with lower HCC risk [55]. Therefore, in this approach, patients who achieved earlier ALT normalization had a lower risk of HCC. The risk of HCC by ALT normalization at a given time is summarized in [Supplementary Table 1](#). The proportion of patients who achieved ALT normalization for TDF and TAF was calculated from clinical trials using the central lab normal range [20]. ETV ALT normalization data was sourced from literature for available timepoints and populations [56–58]. Any data gaps were filled by assuming a relationship between TDF/TAF between the timepoints and/or populations and applied to ETV. The probability of achieving ALT normalization, by treatment and population and time point, is presented in [Supplementary Table 2](#). The second scenario analysis considered only a TE population, where all baseline clinical characteristics were identical with the exception that all patients had previously received treatment for CHB.

Results

Health outcomes

Over the course of a lifetime, patients who switched from TDF to TAF compared with patients who switched from TDF to ETV had lower incidence of compensated cirrhosis (27.26 vs 27.6%), decompensated cirrhosis (1.20 vs 1.24%) and HCC (7.07 vs 7.32%) ([Table 4](#)). CKD and ESRD events per 100 person-years were slightly lower in the TDF to TAF treatment scenario (CKD: 1.53; ESRD: 0.35) versus TDF to ETV (CKD: 1.56; ESRD 0.36); MOFs were similar for both (1.27).

Cost & cost-effectiveness outcomes

Total costs were higher for switching from TDF to TAF versus switching from TDF to ETV due to the higher cost of TAF ([Table 5](#)). Higher total LYs and QALYs were also observed when switching from TDF to TAF versus ETV. The resulting ICER for TDF to TAF versus TDF to ETV was €17,113 per QALY. At a willingness to pay (WTP) of €36,000/QALY, this ICER is considered cost effective.

Table 6. Scenario analyses: ALT normalization approach to hepatocellular carcinoma risk.

	ALT normalization approach to HCC risk		Only treatment experienced patients	
	TDF → TAF	TDF → ETV	TDF → TAF	TDF → ETV
Liver disease incidence				
Compensated cirrhosis	26.99%	27.39%	27.29%	27.92%
Decompensated cirrhosis	1.16%	1.20%	1.21%	1.27%
Hepatocellular carcinoma	11.69%	11.77%	7.07%	7.43%
Liver transplants	0.21%	0.22%	0.16%	0.17%
Adverse events per 100 person-years				
Chronic kidney disease (stage III)	1.57	1.60	1.65	1.70
End-stage renal disease	0.36	0.36	0.39	0.40
Major osteoporotic fractures	1.27	1.27	1.42	1.42
Total costs	€33,023	€32,847	€34,134	€33,613
Total LYs	10.63	10.62	11.05	11.02
Total QALYs	7.49	7.47	7.73	7.70
Incremental cost per QALY	€22,710		€17,324	

ALT: Alanine transaminase; ETV: Entecavir; HCC: Hepatocellular carcinoma; LY: Life-year; QALY: Quality-adjusted life-year; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate.

Sensitivity analyses

Results were robust across sensitivity analyses. In the one-way sensitivity analysis, the proportion at high risk of osteoporosis fracture, DNA and the hazard ratio for MOFS of ETV versus TDF were key drivers of QALY results (Supplementary Figure 2, left) while HBV DNA efficacy, the proportion at high risk of osteoporosis fracture and drug costs were key drivers of cost results (Supplementary Figure 2, right).

Scenario analyses

When considering the ALT normalization approach to determining risk of HCC, results were similar to the base case, resulting in an ICER of €22,710; this ICER remains below the accepted WTP threshold of €36,000/QALY (Table 6). Results were also similar to the base case in the scenario where all patients were assumed to have received prior treatment to CHB resulting in a cost effective ICER of €17,324.

Discussion

This study assessed the cost-effectiveness of switching patients from TDF to TAF versus TDF to ETV and found that the former resulted in better long-term health outcomes with a lower incidence of adverse liver disease events. While treatment with TAF resulted in higher incremental costs, the switch from TDF to TAF versus TDF to ETV was cost effective and well below the acceptable WTP threshold for the Greek national healthcare system of €36,000 per QALY gained. Further, results were similar across scenario analyses. Given the improved bone and renal outcomes associated with treatment with TAF, along with the reduction of viremia to undetectable levels, the results of this analysis provide further evidence that switching from TDF to TAF over ETV may be a preferred treatment sequence for patients with CHB.

HBV is a costly disease for Greece, with per patient average annual direct costs estimated at over €1800, placing estimates of total expenditure attributable to HBV in Greece at over €200 million annually [59]. In Greece, the mean age of CHB patients is reported to be 50 years. The increasing proportion of CHB patients with advanced age further carries the associated increased risk in both bone and renal diseases with their associated costs and impacts to quality of life. A prospective 2-year cohort study in patients with CHB in Greece with renal and/or bone disorders or risks found improvements in eGFR after 12–24 months of TAF treatment among switched patients, while maintaining or inducing virological suppression [60]. Given that risk of bone or renal disease increases with older age, switching from TDF to TAF may particularly reduce the unmet need related to chronic treatments with improved safety in Greek CHB patients.

Timely diagnosis along with effective treatments are critical to reducing the risk of advanced liver diseases for patients living with CHB. However, despite the efficacy of TDF as a first-line treatment, current guidelines recommend that patients at high-risk for bone and renal disease switch to TAF or ETV [8]. Multiple clinical studies have shown that switching to TAF from either TDF or other nucleoside analogues maintained or improved

virological and biochemical response, while improving bone- and renal-related safety outcomes [8]. Compared with a treatment sequence of TDF to ETV, improvements in liver disease outcomes and adverse bone and renal outcomes were observed with switching from TDF to TAF. These benefits in clinical outcomes in switching to TAF help drive the cost-effectiveness of this treatment sequence due to reduced costs in treating negative health outcomes such as HCC and ESRD.

This analysis should be interpreted in the context of its limitations. This model assumed that the probabilities of viral suppression over time are similar to those for the first year. However, patients who are virally suppressed are likely to remain suppressed for some time. Not all clinical and cost model inputs were available for a Greek reference population and data may not have been confirmed in Caucasians; however, given that the same inputs were used for both treatment sequences in the model, any potential differences would not incrementally affect the results. This model assumes that all patients who develop resistance discontinue active therapy and receive best supportive care. In clinical reality, a patient who fails a given therapy is likely to switch to an alternative therapy. Given the lack of data available for bone disease outcomes with ETV treatment, the same fracture risk was used as TAF; however, this is a conservative assumption that TAF would not confer additional benefit in prevention bone mineral loss.

Conclusion

Patients living with CHB who are unable to achieve undetectable viremia are at a high risk for adverse liver outcomes in relation to disease progression (i.e., HCC). While effective treatments for CHB exist, managing adverse events is important in select populations. The results from this analysis found that switching from TDF to TAF versus ETV was cost effective and reduced adverse liver disease outcomes while improving bone- and renal-related safety outcomes.

Summary points

- Chronic hepatitis B (CHB) is a major public health issue in Greece and can lead to serious adverse liver disease outcomes or death.
- Despite vaccination against HBV, between 20 and 30% of patients who become infected develop complications of cirrhosis and hepatocellular carcinoma.
- While multiple treatments exist, tenofovir alafenamide (TAF) demonstrated an added benefit of improved bone and renal outcomes over tenofovir disoproxil fumarate (TDF).
- This study assessed the cost-effectiveness of switching from TDF to TAF or entecavir (ETV) for the treatment of CHB in Greece to account for advanced liver disease.
- Switching from TDF to TAF had an overall lower incidence of liver disease events, chronic kidney disease and end-stage renal disease; switching from TDF to TAF versus TDF to ETV was cost effective while improving bone- and renal-related safety outcomes.
- Switching from TDF to TAF in patients living with CHB should be considered for patients at risk of bone and renal disease.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0090>

Author contributions

N Kachru, C Tsoulas, A Yehoshua, E Sinakos and E Cholongitas were responsible for the conception and design of the study. N Kachru, C Tsoulas and A Yehoshua were responsible for the data acquisition. NJ Smith and S Jeyakumar were responsible for the data analysis. NJ Smith was responsible for drafting the manuscript; all authors contributed to the revision of the manuscript.

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Competing interests disclosure

E Sinakos has received consulting fees and reimbursement of travel expenses from Gilead Sciences, Elpen, Vocate and Faran. N Kachru, C Tsoulas and A Yehoshua are employees and stockholders of Gilead Sciences. E Cholongitas has acted as an advisor and/or lecturer and/or received grants from Abbvie, Bristol-Meyers Squibb, Ipsen, GENESIS Pharma, Gilead, MSD, Novartis, Roche and WinMedica. S Jeyakumar and NJ Smith were employees of Maple Health Group at the time of the development and writing of the manuscript, and received consulting fees for this work. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Data sharing statement

The authors certify that this manuscript does not report original clinical trial data.

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