Cost-Effectiveness of Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide vs Entecavir for Chronic Hepatitis B Patients in Greece

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Key Findings

TDF→TAF is cost-effective vs TDF→ETV across treatment-naïve and -experienced CHB patients ≥60 years of age when considering a WTP threshold of €36,000/QALY (1× Greek GDP)

Conclusions

While effective treatments for CHB exist, managing adverse events is important in select populations

The estimates from this model found that switching from TDF to TAF vs ETV was cost-effective and reduced adverse liver disease outcomes while improving bone- and renal-related safety outcomes

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Introduction

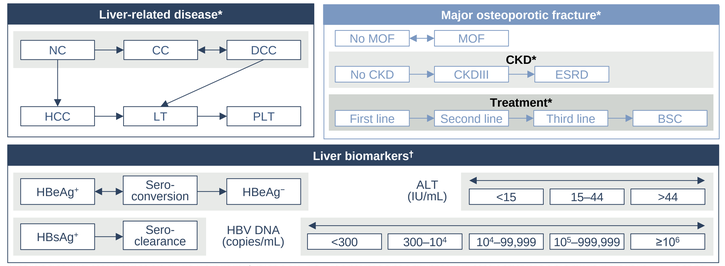
- Clinical and economic burden of chronic hepatitis B (CHB):
  - Less than 5% of infected adults develop CHB, which is defined as persistent hepatitis B virus (HBV) infection (the presence of detectable hepatitis B surface antigen [HBsAg] in the blood or serum for longer than 6 months), with or without associated active viral replication and evidence of hepatocellular injury and inflammation[1]
  - While the prevalence of HBV has decreased in many parts of the world, infection with HBV is a major public health concern in Greece
  - Surveillance data estimate the prevalence of HBV in Greece to be between 1.9% and 3.5%[2,3]
- Current CHB treatment strategies:
  - The goals of CHB management include viral suppression and normalization of serum alanine aminotransferase (ALT)[4]
  - 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 profiles and high barrier for developing treatment resistance[5]
  - Based on two head-to-head noninferiority Phase 3 trials, where TAF demonstrated an added benefit of improved bone and renal outcomes,[6,7] guidelines recommend switching patients who are at high risk for bone and renal disease from TDF to either TAF or ETV[8]
- As the mean age of Greek patients with CHB is reported to be 50 years, reducing the incidence of bone and renal complications is an important consideration when deciding treatment options[2]

Objective

- To assess the cost-effectiveness of switching from TDF to TAF (TDF→TAF) vs switching to ETV (TDF→ETV) in the treatment of Greek patients with CHB ≥60 years of age

Methods

Model Design



*Health states with these modules are mutually exclusive; †Patients are in all 4 biomarker states simultaneously; each biomarker state is mutually exclusive. ALT, alanine aminotransferase; BSC, best supportive care; CC, compensated cirrhosis; CKD, chronic kidney disease; CKDIII, stage 3 CKD; DCC, decompensated cirrhosis; ESRD, end-stage renal disease; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LT, liver transplant; MOF, major osteoporotic fracture; NC, noncirrhotic; PLT, post-liver transplant.

- An individual patient simulation model was developed to assess the impact of CHB treatment on liver-related outcomes over a lifetime time horizon (50 years)
- Within the model, patients could experience:
  - Spontaneous or treatment-induced responses (eg, hepatitis B e antigen [HBeAg]/HBsAg seroconversion and/or viral suppression)
  - Disease reactivation (eg, viral resistance)
  - Long-term liver complications
  - Treatment-related renal or bone complications
- Two patient profiles (virally suppressed or viremic) were created with corresponding HBV DNA and ALT level profiles sampled from clinical trial data (TAF/TDF)[6,7] with ETV assumed to have the same profile as TDF
- Following treatment initiation, HBV DNA and ALT levels shifted based on clinical trial data (TAF/TDF) and published literature values (ETV)
  - Responders (ie, those achieving viral suppression with undetectable HBV DNA levels by week 48) were able to achieve HBsAg or HBeAg seroconversion
- If treatment resistance occurred, it was assumed that HBV DNA and ALT levels remained at their corresponding highest level (ie, HBV DNA viral load >1,000,000 IU/mL and ALT level >44 IU/mL) for 3 months
- A proportion of patients who developed resistance could experience acute flare, some of whom developed decompensated cirrhosis (DCC)

Model Analyses

- Results were based on a simulated cohort of 100,000 patients
- Scenario analyses considered a disease progression approach based on time until ALT normalization and based on a treatment experienced (TE)-only subpopulation
- Costs and outcomes were discounted at 3.5%

Patients and Treatments

Patients

- Patient population profiles were based on clinical data and published literature[6,7,9]
- The population in the model included patients aged ≥60 years with CHB, of whom 1.6% were HBeAg positive,[2] 21% had cirrhosis,[9] and 57% had previously undergone some treatment for CHB (TE)[9]
- Based on the treatment outcome (ie, virally suppressed or viremic), a corresponding HBV DNA and ALT levels profile was sampled based on clinical trials comparing TAF and TDF for the treatment of HBV (320-0108 and 320-0110 trials)[6,7]
- HBV DNA and ALT profiles for ETV were assumed the same as for TDF

Treatments

- The model considered a strategy of switching from TDF to TAF (TDF→TAF) vs TDF to ETV (TDF→ETV)

Model Inputs

Clinical Inputs (see supplementary data for detailed clinical inputs)

- The impact of treatment on liver outcomes was determined by a risk score for progression to liver cirrhosis and a rate of progression to hepatocellular carcinoma (HCC) based on treatment strategy informed by available clinical data[10,11]
- Risk scores were calculated based on a patient's profile, and included sex, age, family history of HCC, alcohol consumption, serum ALT levels, and HBeAg/HBV DNA genotype[12]
  - The risk score was evaluated at each time step to account for changes in the variable parameters
- Disease progression rates, excluding transitions to compensated cirrhosis (CC) and HCC (which are dependent on the risk score), were sourced from published literature and converted to annual transition probabilities
- Increased risk of major osteoporotic fractures (MOFs)[13] and adverse renal events,[14] compared with the general population, were included
- Background mortality, along with excess mortality due to treatment-related complications, was obtained from the literature

Health Utilities (see supplementary data for detailed health utility inputs)

- Utility values for active CHB, CC, DCC, HCC, and liver transplant (LT)/post-LT were sourced from published literature[15-18]

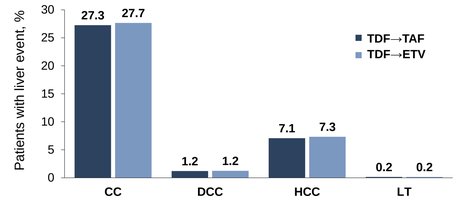
Cost Inputs

- Annual liver disease costs, adverse event–associated costs, and annual treatment costs were included; health state costs were based on published literature or internal research
- 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[19]
- 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[20]

Results

Health Outcomes (Base Case)

Liver Events



CC, compensated cirrhosis; DCC, decompensated cirrhosis; ETV, entecavir; HCC, hepatocellular carcinoma; LT, liver transplant; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Adverse Events

Per 100 patient-years	TDF→TAF	TDF→ETV
CKDIII	1.53	1.56
ESRD	0.35	0.36
MOF	1.27	1.27

CDKIII, stage 3 chronic kidney disease; ESRD, end-stage renal disease; ETV, entecavir; MOF, major osteoporotic fracture; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Over the course of a lifetime, patients who switch from TDF to TAF have an overall lower incidence of liver disease events compared with patients who switch from TDF to ETV
- Chronic kidney disease and end-stage renal disease events were slightly lower in the TDF to TAF treatment scenario vs TDF to ETV; MOF were similar for both

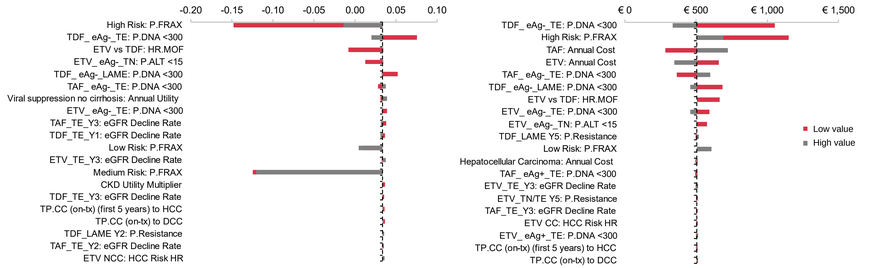
Costs and Cost-effectiveness (Base Case Analysis)

	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	€4,273	€4,305	−€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; QALY, quality-adjusted LY; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Total costs were higher for switching from TDF to TAF vs switching from TDF to ETV due to the higher cost of TAF. Higher total life-years (LYs) and quality-adjusted LYs (QALYs) were also observed when switching from TDF to TAF vs ETV. The resulting incremental cost-effectiveness ratio (ICER) for TDF to TAF vs TDF to ETV was €17,113 per QALY. At a willingness to pay (WTP) of €36,000/QALY, this ICER is considered cost-effective
- Results were robust across sensitivity analyses. In the one-way sensitivity analysis, the proportion at high risk of osteoporosis fracture, HBV DNA efficacy, and the hazard ratio for MOF of ETV vs TDF were key drivers of QALY results, while HBV DNA efficacy, the proportion at high risk of osteoporosis fracture, and drug costs were key drivers of cost results

One-way Deterministic Sensitivity Analysis for Base Case: QALYs (Left) and Costs (Right)



- 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. Results were also similar to the base case in the scenario where all patients were assumed to have received prior treatment for CHB, resulting in a cost-effective ICER of €17,324

Scenario Analysis Findings

	ALT normalization approach to HCC risk		Only TE 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 3)	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 aminotransferase; ETV, entecavir; HCC, hepatocellular carcinoma; LY, life-year; QALY, quality-adjusted LY; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, treatment experienced.

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