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REVIEW

A cost-effectiveness analysis of different therapies in patients with chronic hepatitis B in Italy

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Giorgio L Colombo[1,2]
Giovanni B Gaeta[3]
Mauro Viganò[4]
Sergio Di Matteo[2]

[1]University of Pavia, School of Pharmacy, Italy; [2]S.A.V.E. Studi Analisi Valutazioni Economiche, Milan, Italy; [3]Viral Hepatitis Unit, Second University, Naples, Italy; [4]Liver Unit, Ospedale San Giuseppe, Università degli Studi di Milano, Milan, Italy

Introduction: Chronic hepatitis B (CHB) is a prevalent disease associated with high morbidity, mortality, and impact on health care costs. Antiviral therapy is aimed at reducing hepatitis B virus replication in order to limit progressive liver disease and improve the natural history of the disease. This study estimates the cost-effectiveness of lamivudine, adefovir, telbivudine, entecavir, tenofovir, and pegylated interferon in patients with CHB.

Methods: A Markov model was developed to evaluate the costs and benefits of antivirals in a cohort of patients with CHB (hepatitis B e antigen [HBeAg]-positive and HBeAg-negative) and cirrhosis over a period of 10 years. Different rescue therapies were considered, according to current guidelines. Data on efficacy and changes in quality of life were derived from clinical trials and epidemiological Italian data. Direct costs were assessed from the perspective of the Italian National Health Service.

Results: Tenofovir was associated with lower costs and higher efficacy compared with entecavir, telbivudine, and adefovir, as shown by their incremental cost-effectiveness ratios (ICER) per quality-adjusted life-year (QALY) gained: tenofovir €30,959, entecavir €45,971, telbivudine €62,051, and adefovir €82,824. Even following 1 year of pegylated interferon therapy, tenofovir had a more favourable ICER per QALY gained compared with the other rescue options. The analysis of patients with cirrhosis confirms the results obtained with the CHB cohort though with higher ICERs. Sensitivity analyses on the main variables confirm the results of the base case scenario.

Conclusion: Within the Italian health care system, in patients with CHB, tenofovir is a cost-effective strategy compared with other available therapies. Public health care authorities would benefit from mathematical models designed to estimate the future burden of CHB infection together with the impact of treatment and drug resistance.

Keywords: chronic hepatitis B, Markov model, cost-effectiveness, lamivudine, adefovir, telbivudine, entecavir, tenofovir, pegylated interferon

Introduction

Chronic infection with hepatitis B virus (HBV) is a common cause of death associated with liver failure, cirrhosis, and hepatocellular carcinoma (HCC).[1] Despite the implementation of vaccination programs in various countries, the condition is still widespread, affecting 350 million to 400 million people worldwide.[2]

Morbidity and mortality in chronic hepatitis B (CHB) are related to persistence of viral replication and evolution to cirrhosis or HCC.[1] Treatment for CHB is therefore aimed at suppressing HBV replication to prevent progression of the disease. The current therapeutic options available in Italy and Europe include interferon α, conventional

Correspondence: Giorgio L Colombo
S.A.V.E. Studi Analisi Valutazioni Economiche, Via Previati, 74 – 20149 Milan, Italy
Tel +39 0248519231
Fax +39 0248198430
Email giorgio.colombo@unipv.it

or pegylated, and nucleoside/nucleotide analogs (NUCs). Interferon is administered subcutaneously, and its main advantage is the absence of resistance. Nonetheless, its use is limited by frequent side effects and the fact that it is considered a moderate antiviral agent.[1] NUCs vary greatly in terms of efficacy, induced viral resistance, and tolerance. Lamivudine and adefovir are early-generation oral agents whose main disadvantage is the high viral resistance they engender.[3] Telbivudine is a potent inhibitor of HBV but with a high rate of viral resistance.[2] Conversely, the latest-generation NUCs entecavir and tenofovir are both potent HBV inhibitors with an optimal resistance profile.[4–6]

The relevant role of entecavir and tenofovir has recently been highlighted by the European Association for the Study of the Liver (EASL), whose guidelines recommend pegylated interferon, entecavir, or tenofovir as first-line treatment for both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients.[1]

Considering the complexity of the disease, the EASL's recommendations are invaluable in assisting physicians in selecting the most favourable therapies. However, because CHB is a prolonged illness, the treatment of which may continue for many years, the need for drugs with potent antiviral activity, proven long-term safety, and a low rate of HBV antiviral resistance[1] should also be evaluated in terms of lifetime costs.

In a global context of limited health care resources, pharmacoeconomic considerations are a central factor to help policy makers make the most appropriate decisions on resource allocation. We therefore performed an economic analysis to estimate the cost-effectiveness of the treatments licensed in Italy for managing HBV infection in patients with chronic hepatitis and cirrhosis. We also estimated the impact of the disease on the quality of life of patients.

Patients and method

Model overview

We built a Markov model and evaluated the clinical and economic outcomes of a hypothetical cohort of 100 subjects (aged ≥18 years) with chronic HBV (92.70%) or cirrhosis (7.30%) over a 10-year horizon. The proportions of the two subpopulations were obtained from a study by Giannini et al.[7]

To mirror the case mix in clinical practice in Italy, we assumed that 20% of them were HBeAg-positive and 80% were HBeAg-negative.[8] The terms "HBeAg-positive" and "HBeAg-negative" define two categories of the CHB status, the first typically represents the early phase of chronic HBV infection, whereas the second represents a later phase.[1]

In the model, the individual's possible prognosis is divided into distinct health states. Costs and benefits are assigned to each health state and the movement of an individual between these health states over a given amount of time (each cycle of 1 year) is defined by transition probabilities. The costs and benefits of comparative treatments are then estimated according to the time spent in each state.

Because HBeAg-negative and HBeAg-positive populations present a different clinical course, prognosis, and response to therapy, separate transition probabilities were assigned to each group.

The model, which is represented in Figure 1, was structured with the following assumptions:

- On entering the model, previously untreated subjects start to receive one of the following competing options: i) no treatment, ii) tenofovir monotherapy, iii) lamivudine monotherapy, iv) adefovir monotherapy, v) entecavir monotherapy, vi) telbivudine monotherapy, and vii) pegylated interferon monotherapy.

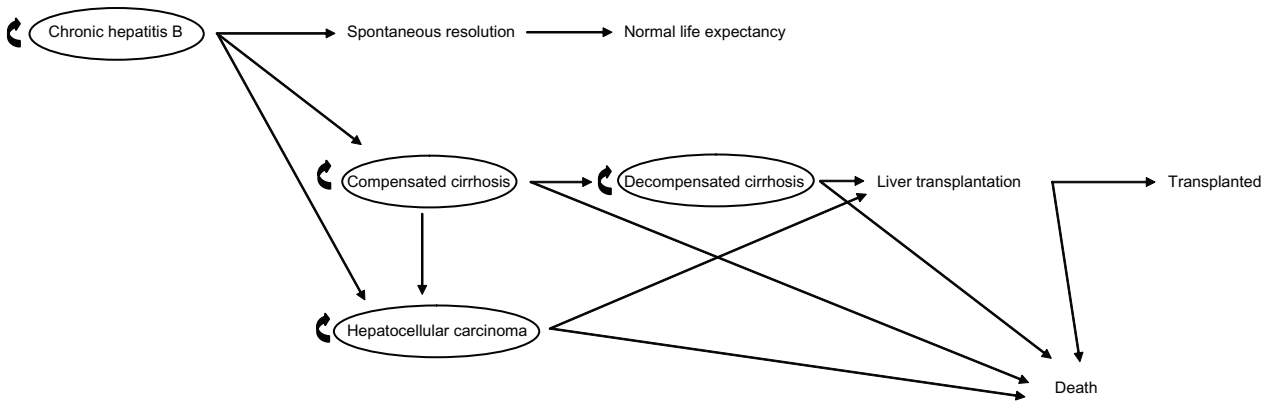

Figure 1 Structure of the Markov model for chronic hepatitis B.

- At the end of each cycle (1 year), the subjects with virologic response remain in the same state, whereas nonresponders move to the subsequent health states.
- Subjects who do not respond or who develop resistance to treatment receive a rescue therapy, ie, a second drug, according to the following scheme:

Initial treatment		Rescue therapy
tenofovir	→	add-on entecavir
lamivudine	→	add-on tenofovir
adefovir	→	add-on entecavir
entecavir	→	add-on tenofovir
telbivudine	→	add-on tenofovir
pegylated interferon	→	switch to entecavir or tenofovir

- In case of resistance, subjects with CHB remain in the state "chronic hepatitis B", whereas subjects with cirrhosis move to the subsequent states.
- Subjects who achieve HBeAg seroconversion discontinue therapy 12 months later; patients who achieve hepatitis B surface antigen (HBsAg) seroconversion discontinue therapy definitely.

According to the EASL guidelines, virologic response is achieved when HBV DNA level is reduced below the lower limit of detection of real-time polymerase chain reaction assays (10–15 IU/mL), resulting in biochemical remission, histological improvement, and prevention of complications.[1]

Seroconversion from HBeAg to anti-HBe antibodies with normal transaminases, leading to the "inactive HBV carrier state", represents the immunological control of the infection and reflects a favorable long-term outcome with a very low risk of cirrhosis or HCC in most subjects.[1] HBsAg loss or seroconversion is more rarely achieved and represents serologic recovery.[2] Both these possibilities were considered in the model.

A discount rate was applied to costs and utilities (range 0%–3%). Modeling was undertaken using Microsoft Excel 2003 (Microsoft Corporation, Redmond, Washington, USA).

Transition probabilities

Subjects who received no treatment followed the natural history of CHB according to their HBeAg status. The corresponding transition probabilities were derived from a study by Idris et al.[9] Subjects who received one of the six available therapeutic options progressed to virologic response, nonresponse, and resistance according to the drug they were given. The transition probabilities were derived from literature data (Tables 1 and 2). When data were not available, it was assumed that the response remained constant at the last observed value by applying the last value carried forward technique.

Outcomes

To evaluate cost-effectiveness, the incremental cost-effectiveness ratio (ICER) was used. When the value of a new therapeutic option needs to be assessed, the ICER provides the additional resources that have to be used to achieve the additional benefit. ICER is the difference in cost (ΔC) divided by the difference in effect (ΔE) between two alternatives. In this analysis, the direct costs

Table 1 Input data of the base case scenario

Variable		Value		Reference
HBeAg-positive		20.00%		8
Chronic infection		92.70%		7
Cirrhosis		7.30%		
Transition probabilities	**Annual rates of events according to HBeAg**			
		Positive	**Negative**	
Chronic hepatitis B	Spontaneous resolution	6.90%	1.60%	9
	Compensated cirrhosis	3.00%	4.60%	
	Hepatocellular carcinoma	1.50%	1.50%	
Compensated cirrhosis	Decompensated cirrhosis	7.30%	7.30%	9
	Hepatocellular carcinoma	3.40%	3.40%	
	Death	4.90%	4.90%	
Decompensated cirrhosis	Liver transplantation	21.00%	21.00%	9
	Death	19.00%	19.00%	
Hepatocellular carcinoma	Liver transplantation	25.00%	25.00%	9
	Death	43.30%	43.30%	
Liver transplantation	Death	6.90%	6.90%	9

Abbreviation: HBeAg, hepatitis B e antigen.

Table 2 Virologic response, HBV resistance, and seroconversion rates for each antiviral drug for both HBeAg-positive and -negative patients

List of variable	Value					Reference
	Years					
	1	2	3	4	5	
Undetectable HBV DNA						
HBeAg-positive						
Tenofovir	76.00%	78.00%	72.00%			5,10,11
Lamivudine	36.00%					12,13
Adefovir	21.00%	40.00%	48.00%			13,14
Entecavir[1]	67.00%	80.00%	82.00%			12,13
Telbivudine	60.00%	56.00%				15,16
Peginterferon	25.00%					1,13
HBeAg-negative						
Tenofovir	93.00%	91.00%	88.00%			5,17,18
Lamivudine	89.00%	63.00%	48.00%	39.00%		19
Adefovir	72.00%	80.00%	77.00%	73.00%	67.00%	20
Entecavir[a]	90.00%	94.00%	93.00%	91.00%	95.00%	13,21–24
Telbivudine	88.00%	82.00%		84.00%		16,25
Peginterferon	63.00%					1,13
Development of resistance						
HBeAg-positive						
Tenofovir	0.00%	0.00%	0.00%			1,11,26
Lamivudine	23.00%	46.00%	55.00%	71.00%	65.00%	27
Adefovir			20.00%			28
Entecavir	0.20%	0.50%	1.20%	1.20%	1.20%	29
Telbivudine	5.00%	25.10%				15,30
Peginterferon	na					
HBeAg-negative						
Tenofovir	0.00%	0.00%	0.00%			1,18,26
Lamivudine	20.00%	44.00%			60.00%	19,31
Adefovir	0.00%	3.00%	11.00%	18.00%	29.00%	20
Entecavir						
Telbivudine	2.20%	11.00%				15,30
Peginterferon	na					
HBsAg clearance/seroconversion						
HBeAg-positive						
Tenofovir	3.00%	6.00%	8.00%			5,10,11
Lamivudine	0.00%					
Adefovir	0.00%					
Entecavir	2.00%					4
Telbivudine	0.00%					
Peginterferon	4.00%	6.00%	8.00%			32,33
HBeAg-negative						
Tenofovir	0.00%	0.00%	0.00%			5,17,18
Lamivudine	0.00%	0.00%	0.00%			
Adefovir	0.00%	0.00%	0.00%			
Entecavir	0.00%					
Telbivudine	0.00%					
Peginterferon	3.00%	6.00%	8.00%			34,35
HBeAg seroconversion						
HBeAg-positive						
Tenofovir	21.00%	26.00%	26.00%			1,5,10,11,36
Lamivudine	22.00%	22.50%				1,15,36
Adefovir	12.00%	29.00%	43.00%			1,36–38
Entecavir	21.00%	24.00%		16.00%		1,36,38–40
Telbivudine	23.00%	30.00%				1,36,41
Peginterferon	30.00%	41.00%				1,36,42

Note: [a]Data beyond 1 year need to be interpreted with caution due to regimen intensification, including doubling of dose.
Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

Table 3 Cost data: average cost of different stages of the disease (€, year 2009 values) and annual drug costs

Antiviral	Annual cost (€)	Reference
Tenofovir	3062.35	48
Lamivudine	1153.40	48
Adefovir	4595.35	48
Entecavir	4595.35	48
Telbivudine	4595.35	48
Peginterferon	8356.55	48
Disease state	**Annual cost (€)[a]**	
Chronic hepatitis B	1977.02	49
Compensated cirrhosis	3384.56	49
Decompensated cirrhosis	3384.56	49
Hepatocellular carcinoma	6808.71	49
Liver transplantation	82867.40	49
Follow-up post-transplantation	6358.04	50
Monitoring for nephrotoxic effects	23.50	51
		52

Note: [a]Costs of drugs are excluded.

and effectiveness of each drug were compared with the direct costs and effectiveness of the disease natural history (absence of treatment).

$$\text{ICER} = \frac{\left(\text{Cost}_{\text{drug}} - \text{Cost}_{\text{absence of treatment}}\right)}{\left(\text{Effectiveness}_{\text{drug}} - \text{Effectiveness}_{\text{absence of treatment}}\right)}$$

Utilities

The analysis conducted is a cost–utility analysis, ie, an economic evaluation that estimates the cost per quality-adjusted life-year (QALY) gained from undertaking one intervention instead of another.[43] The QALY is a potential measure of health and is obtained by multiplying the duration of a health state (in years) by a factor representing the quality ("utility") of that health state. A QALY value of 1 is equivalent to a year of "perfect health", whereas a value of zero corresponds to "death". Utilities were considered for the following states: virologic response (1.000), inactive HBV carrier (0.960), CHB (0.910), compensated cirrhosis (0.800), decompensated cirrhosis (0.600), HCC (0.730), and liver transplantation (0.860).[44–46] These values were calculated using the Health Utility Index (HUI).[47]

Costs

Only direct health care costs (ie, health service costs) were considered in the analysis, which were calculated from the Italian National Health Service's perspective. These costs pertained to annual costs per person and included expenditures related to the diagnosis of the disease, laboratory testing, drugs, follow-up, and disease complication costs. In the case of tenofovir, costs also included periodic monitoring of renal functioning, which was performed monthly during the first year and every 3 months for the following years (Table 3).

Results

The model was built using epidemiological data of CHB prevalence in Italy. Our results show that the mean annual cost per patient with CHB or cirrhosis receiving antiviral therapy was between €2573 and €7639 compared with subjects who received no treatment. The ICER per QALY gained for a) tenofovir monotherapy, b) pegylated interferon (first year) followed by tenofovir, c) pegylated interferon (first year) followed by entecavir, d) lamivudine with early add-on tenofovir, and e) entecavir monotherapy were all favorable at a threshold of €50,000 per QALY compared with the natural history of the disease and varied between €30,959 and €45,971 (Table 4). Conversely, telbivudine and adefovir did not have a favourable ICER compared with the natural history of the disease, as their range was between €62,051 and €82,824 per QALY gained (Table 4). Of note, because of the optimal combination of cost and effectiveness, tenofovir was the strategy with the best ICER.

Table 4 Results: costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER) of the base case scenario (10-year horizon)

Treatment	Mean annual cost per patient (€)	Mean annual QALY per patient	Mean cost per QALY (€)	Delta cost (€)	Delta QALY	ICER per QALY (€) 12 months
	a	b	a/b	Δa	Δb	Δa/Δb
Natural history of disease	2572.84	0.815	3158.74			
Tenofovir	5116.00	0.896	5711.00	2543.00	0.081	31,291
Peginterferon (first year) → tenofovir	5276.00	0.897	5883.00	2703.00	0.082	32,863
Peginterferon (first year) → entecavir	6206.00	0.897	6922.00	3633.00	0.082	44,243
Lamivudine (→ add-on tenofovir)	4737.00	0.862	5495.00	2164.00	0.048	45,513
Entecavir	6302.00	0.895	7043.00	3729.00	0.080	46,498
Telbivudine	6970.00	0.885	7878.00	4397.00	0.070	62,642
Adefovir	7679.00	0.876	8769.00	5106.00	0.061	83,475

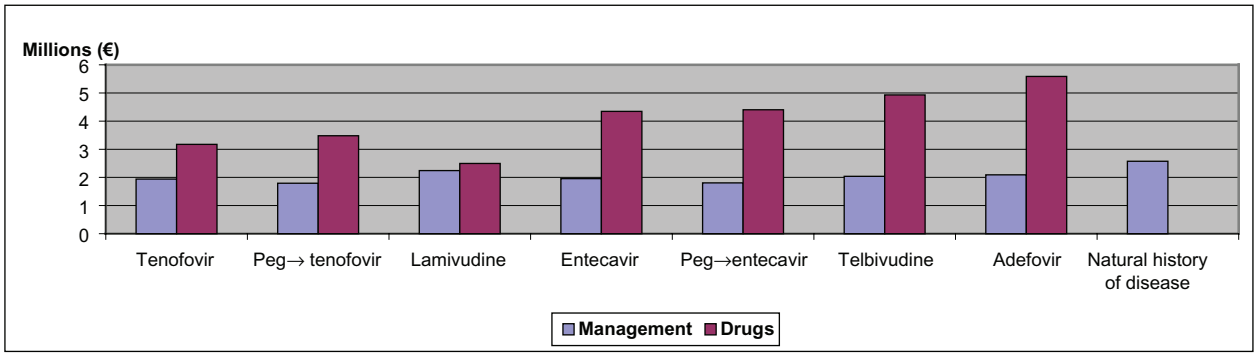

Figure 2 Total costs at 10 years for drugs and other health costs calculated for a cohort of 100 patients.

By estimating the cost of the different strategies at 5 and 10 years, we showed that tenofovir alone or following pegylated interferon in a group of HBeAg-positive patients contributed to reducing the costs of disease management over time.

In our simulation, HBeAg-positive subjects showed more favorable ICERs compared with HBeAg-negative subjects, whereas, as assessed in the sensitivity analyses, treatment of subjects with cirrhosis resulted in higher ICERs, which often exceeded the international threshold of cost-effectiveness of €25,000–35,000 (about £20,000–30,000) indicated, for example, by the National Institute for Health and Clinical Excellence (NICE).[53]

To test the robustness of our evaluations, sensitivity analyses were carried out by varying parameters such as the proportion of HBeAg-positive and HBeAg-negative subjects, the proportion of subjects with cirrhosis, the cost of tenofovir and entecavir, and the overall cost of patient management. Other sensitivity analyses were carried out for the inclusion of bone mineral densitometry for subjects on tenofovir and discounting for costs and QALYs. In all cases, the results of the base case scenario were confirmed (Table 5 and Figure 4).

Discussion

Chronic HBV infection is a prevalent disease, the management of which is associated with high costs due to treating complications, antiviral drug therapy, and monitoring of HBV drug resistance.[9] Current guidelines have provided physicians with clear recommendations on how to select the most effective treatments for each patient.[1] However, their indications have failed to include pharmacoeconomics considerations to address the financial burden of CHB and its consequences on the limited health care budgets of many countries.

To contribute to a better understanding of the impact of managing subjects with CHB in Italy, we have developed a cost-effectiveness analysis on the six treatments that are currently available. Our results have shown that tenofovir is the most cost-effective oral antiviral compared with the other agents for HBeAg-positive and HBeAg-negative subjects and for patients with cirrhosis. In the case of drug failure, the use of tenofovir and entecavir as rescue therapies has a more favorable ICER than the use of adefovir and lamivudine. Furthermore, tenofovir assessment has included costs for renal monitoring and bone mineral densitometry, which were not considered in the most recent published studies.[6,54,55]

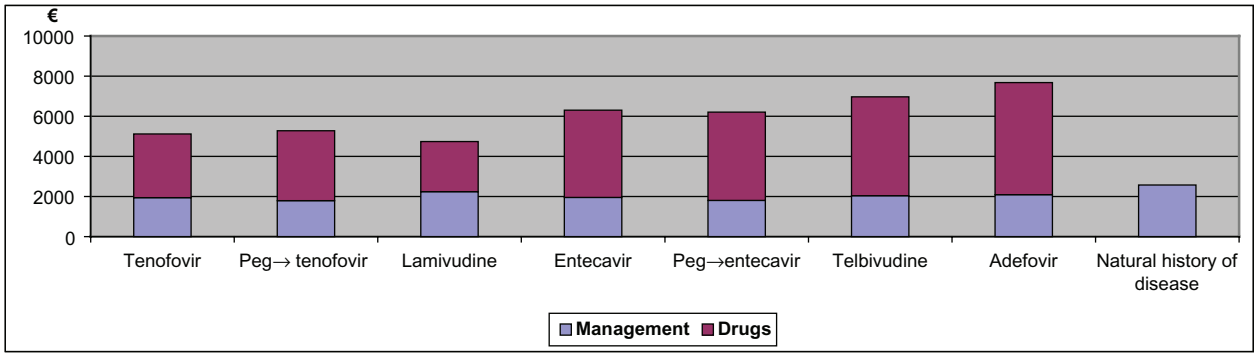

Figure 3 Mean cost per patient per year.

Table 5 Results of one-way sensitivity analyses

Treatment	HBeAg + 100% patients (€)	HBeAg – 100% patients (€)	Chronic infection (HBeAg+ and HBeAg–) (€)	All cirrhosis 100% (€)	Bone mineral densitometry (once yearly)[a] (€)	Cost of tenofovir + 25% (€)	Cost of tenofovir – 25% (€)	Cost of entecavir + 25% (€)	Cost of entecavir – 25% (€)	Cost of patient managment + 25% (€)	Cost of patient managment – 25% (€)
Tenofovir	22,529.88	35,735.55	30,142.25	68,833.82	34,158.69	39,509.61	23,072.13	32,836.13	29,745.61	29,068.21	33,513.53
Peginterferon (first year) → tenofovir	14,567.56	42,201.14	30,120.86	763,518.21	32,863.49	39,254.41	26,472.56	34,023.92	31,703.06	30,291.63	35,435.35
Peginterferon (first year) → entecavir	22,955.75	52,229.84	40,927.54	926,281.56	44,243.49	44,705.92	43,781.06	54,128.98	34,357.99	41,754.22	46,732.76
Lamivudine (→ add-on tenofovir)	37,925.19	49,035.21	43,316.39	120,302.03	45,512.86	51,488.20	39,537.51	45,512.86	45,512.86	43,437.54	47,588.18
Entecavir	42,334.29	48,232.72	45,090.30	89,758.12	46,498.01	47,201.28	45,794.73	59,339.67	33,656.34	44,368.64	48,627.37
Telbivudine	64,859.53	61,262.65	60,468.32	131,144.93	62,642.20	64,406.33	60,878.06	62,642.20	62,642.20	60,505.18	64,779.21
Adefovir	80,301.41	86,021.84	80,029.43	198,460.85	83,475.21	83,475.21	83,475.21	85,827.10	81,123.31	81,244.14	85,706.27

Note: [a]According to clinical practice and expert opinion.
Abbreviation: HBeAg, hepatitis B e antigen.

The ICER per QALY gained was below the threshold of €23,000–34,000 (about £20,000–30,000) set by NICE only in the case of tenofovir as first-line treatment or as rescue therapy following pegylated interferon. In all other cases, ICER per QALY gained exceeded NICE's threshold. Though no officially established threshold is available for Italy, it is worth noting that recent guidelines by the Italian Health Economics Association (AIES)[56] recommend that a threshold of €25,000–40,000 be adopted. Other acceptable references of cost-effectiveness for the Italian context are €36,500 and €60,000 and have been calculated by two different authors.[57,58]

Our results are in line with other recent pharmacoeconomics analyses, in particular with the study of Buti et al[54] and with the more recent cost–utility analysis of Dakin et al.[55] Unlike these two studies, though, which assessed only the cost-effectiveness of NUCs, we were also able to model the treatment with pegylated interferon and show that the strategy of using pegylated interferon (first year) followed by tenofovir may represent a good cost-effectiveness solution for HBeAg-positive subjects, although this approach is not as cost-effective as starting with tenofovir for HBeAg-negative subjects. Conversely, peginterferon usage as first-line therapy in cirrhotic patients seems to not be cost-effective. Furthermore, health care authorities would benefit from treating patients before they develop cirrhosis, as shown by lower ICERs. In this way, as all available treatment strategies for CHB were evaluated, the model can be employed to make projections of health care spending within the National Health Service.

Based on all these findings, it appears that the "economic" profile of tenofovir is in line with its optimal clinical profile, as outlined in the EASL's guidelines, where, together with pegylated interferon and entecavir, tenofovir is recommended as first-line treatment for both HBeAg-positive and HBeAg-negative subjects with CHB.[1]

The study has a few limitations, the most important of which concerns the quality of data entered into the model. Parameters such as efficacy, for example, are based on studies with a limited timeframe and hence may be inadequate for modeling the treatment of a chronic disease for a longer time. Another important limitation is with regard to the assumptions on which the analysis is based, which may be necessary to simplify the model or in cases of incomplete data. Specifically, this was with regard to the transition probabilities, which were lacking in some cases and thus assumed to remain constant over time, and the utilities, which were derived from different literature sources and considered to be acceptable for an Italian population.

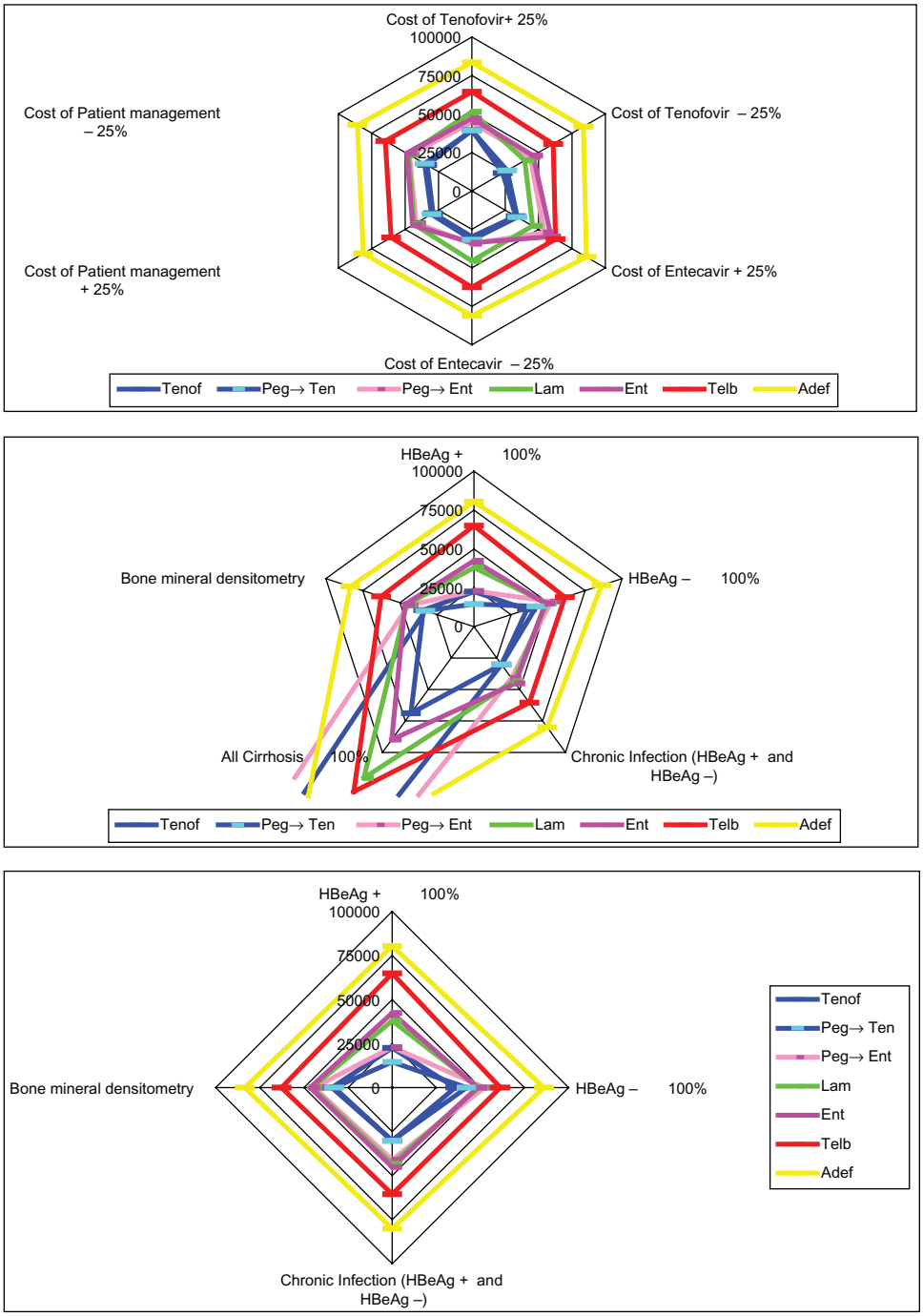

Figure 4 Results of one-way sensitivity analyses.

Despite these drawbacks, which are typical of most model-based economic evaluations, our study contributes to confirming the cost-effectiveness of some drugs, and in particular of tenofovir, also in the Italian context.

To conclude, it is worth noting that the developed model is a dynamic instrument that can be adapted to various health care settings, in that it can be run using different input data (ie, efficacy, cost, and epidemiological). By allowing simulations of different scenarios, it represents an invaluable tool for policy makers and health care professionals to make short- and long-term cost projections and thus evaluate their impact on the available budgets.

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Declaration

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