

# Cost-effectiveness comparison of lamivudine plus adefovir combination treatment and nucleos(t)ide analog monotherapies in Chinese chronic hepatitis B patients

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**Background/aim:** Lamivudine (LAM) plus adefovir (ADV) combination therapy is clinically efficacious for treating chronic hepatitis B (CHB) patients in China, but no pharmacoeconomic evaluations of this strategy are available. The aim of this study was to examine the cost-effectiveness of LAM plus ADV combination treatment compared with five other nucleos(t)ide analog monotherapies (LAM, ADV, telbivudine [TBV], entecavir [ETV], and tenofovir [TDF]).

**Methods:** To simulate the lifetime (40-year time span) costs and quality-adjusted life-years (QALYs) for different therapy options, a Markov model that included five initial monotherapies and LAM plus ADV combination as an initial treatment was developed. Two kinds of rescue combination strategies (base-case: LAM + ADV then ETV + ADV; alternative: direct use of ETV + ADV) were considered separately for treating patients refractory to initial therapy. One-way and probabilistic sensitivity analyses were used to explore model uncertainties.

**Results:** In base-case analysis, ETV had the lowest lifetime cost and served as the reference therapy. Compared to the reference, LAM, ADV, and TBV had higher costs and lower efficacy, and were completely dominated by ETV. LAM plus ADV combination therapy or TDF was more efficacious than ETV, but also more expensive. Although the incremental cost-effectiveness ratios of combination therapy or TDF were both higher than the willingness-to-pay threshold of \$20,466/QALY gained for the reference treatment, in an alternative scenario analysis LAM plus ADV combination therapy would be the preferable treatment option.

**Conclusion:** ETV and LAM plus ADV combination therapy are both cost-effective strategies for treating Chinese CHB patients.

**Keywords:** cost-effectiveness, chronic hepatitis B, nucleos(t)ide analog, combination treatment

## Introduction

Chronic hepatitis B (CHB) is a serious public health problem that affects more than 240 million people worldwide. Each year, approximately 650,000 patients die from hepatic decompensation, cirrhosis, and hepatocellular carcinoma (HCC) caused by hepatitis B chronic infection.<sup>1</sup> According to a national seroepidemiological survey, there are an estimated 93 million chronic hepatitis B virus (HBV) carriers in China, and among them 30 million are CHB patients.<sup>2</sup> Recently, HBV DNA levels were found to be an important risk factor associated with the development of advanced liver diseases in CHB patients.<sup>3</sup> Thus, the current primary goal of antiviral therapy is to delay or prevent progression of liver diseases by suppressing HBV DNA replication to the lowest possible levels.<sup>2,4-6</sup>

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Current nucleos(t)ide analogs to treat CHB in China include lamivudine (LAM), adefovir (ADV), telbivudine (TBV), entecavir (ETV), and tenofovir (TDF), although high resistance rates to LAM, ADV, and TBV have hampered the therapeutic effectiveness of these drugs.<sup>7–10</sup> Because of superior efficacy and markedly low resistance, several guidelines have recommended ETV and TDF as first-line options for treating CHB.<sup>4–6</sup> However, despite their effectiveness, the high daily cost of ETV and TDF therapy may present a substantial economic burden for CHB patients in the long-term. Recent evidence from research suggested that in the absence of cross-resistance to LAM and ADV,<sup>11</sup> LAM plus ADV combination therapy could be used for treating CHB patients, and might in turn reduce drug-associated resistance,<sup>12</sup> especially for LAM-resistant or liver-transplant patients.<sup>13–16</sup> A meta-analysis comparing the efficacy of LAM plus ADV combination therapy and ETV monotherapy for CHB patients showed that combination therapy generates a much higher virologic response rate and lower drug resistance than ETV monotherapy for up to 96 weeks.<sup>17</sup> In addition, previous clinical experiences or studies demonstrated the excellent effectiveness of an initial combination strategy for treating CHB patients.<sup>18–24</sup> In China, initial use of LAM plus ADV combination therapy has been recommended for treating CHB patients with high viral loads<sup>25</sup> and appears to be a promising and superior option for CHB patients.

Considering the prolonged nature of CHB, the long-term cost of combination therapy should be taken into account. However, to our knowledge, there is no study that compares the cost-effectiveness of LAM plus ADV combination treatment with current available nucleos(t)ide monotherapies used to treat Chinese CHB patients. Therefore, the objective of this study was to evaluate the long-term cost-effectiveness of LAM plus ADV combination treatment compared with the five nucleos(t)ide monotherapies (LAM, ADV, TBV, ETV, and TDF) currently used for CHB patients.

## Methods

### Treatment options

Six different initial strategies for CHB patients were considered: LAM monotherapy (100 mg/d), ADV monotherapy (10 mg/d), TBV monotherapy (600 mg/d), ETV monotherapy (0.5 mg/d), TDF monotherapy (300 mg/d), and combination therapy using LAM (100 mg/d) plus ADV (10 mg/d).<sup>2</sup> After a 1-year cycle of treatment, patients with detectable serum HBV DNA (>300–400 copies/mL) were considered as nonresponders, and these patients, along with HBV drug-resistant patients, received rescue therapies. In order to simplify the model, two

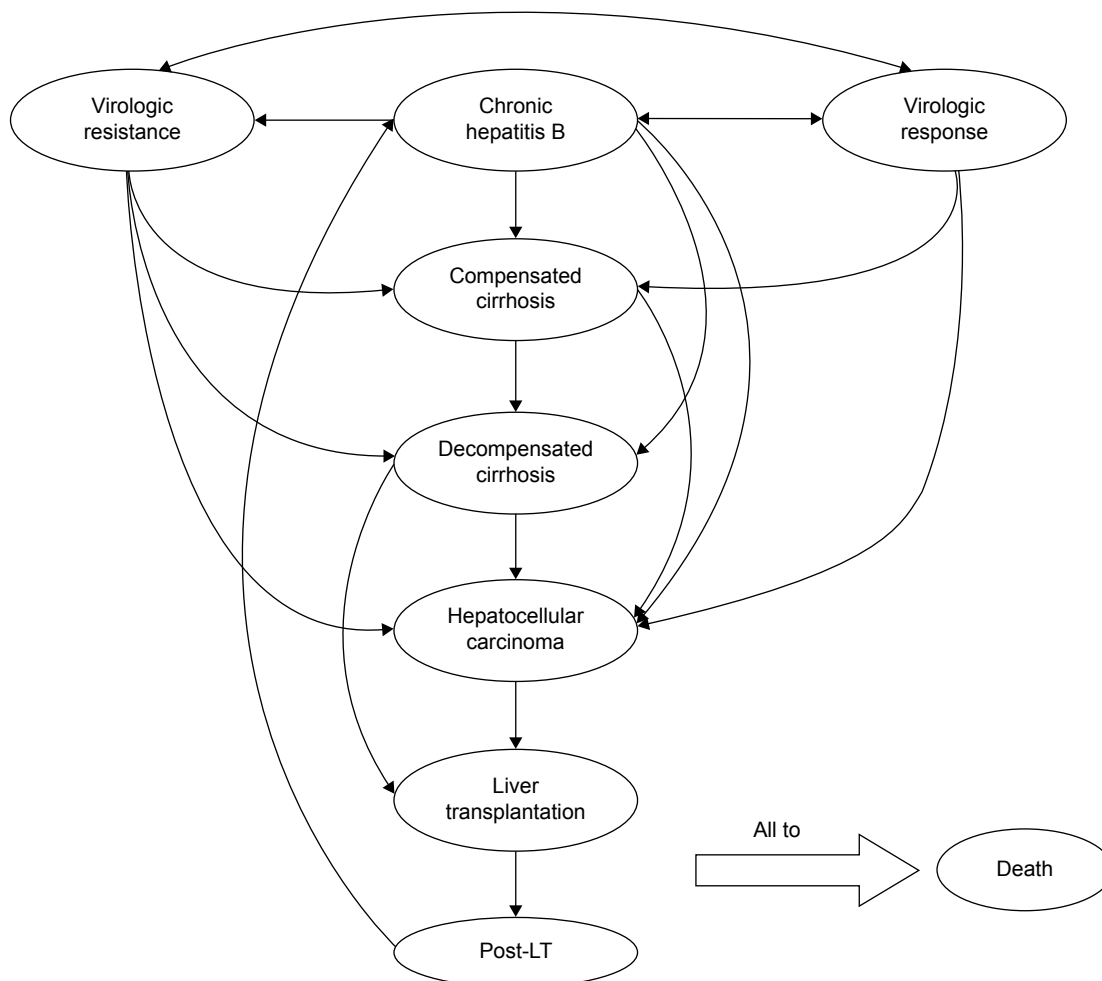
rescue combination strategies were considered separately. In base-case analysis, the most common rescue strategy of LAM (100 mg/d) plus ADV (10 mg/d) combination treatment was first used for patients whose initial therapy failed, and then the more potent combination of ETV (1 mg/d) and ADV (10 mg/d) was administered to patients who developed drug resistance or showed no response to prior rescue strategies. The direct combination of ETV (1 mg/d) and ADV (10 mg/d) was considered in an alternative scenario analysis.<sup>15</sup>

### Markov model

A Markov model (compiled using TreeAge Pro Suite 2014 Program Software; TreeAge Software, Inc., Williamstown, MA, USA) was used to simulate the disease progression of CHB patients and to evaluate lifetime costs, life years saved (LYS), and quality-adjusted life years (QALYs) that were associated with LAM plus ADV combination treatment and the five nucleos(t)ide analogs. A Chinese cohort of 35-year-old hepatitis B e antigen (HBeAg)-positive or -negative patients with CHB was entered into the model. Patients were HBV DNA positive, and alanine transaminase level was elevated, but there were no related liver diseases. The life expectancy of Chinese people is 75 years, and thus the lifetime horizons of this model were set at 40 years.<sup>26</sup> Based on previous studies,<sup>27,28</sup> the model consisted of nine mutually-exclusive disease states, including CHB, virologic response, virologic resistance, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation, post-liver transplantation, and death (Figure 1). Patients entered the model from the CHB state and could enter into the next state or remain in the same state after each 1-year cycle. Previous studies showed a significant association between serum HBV DNA levels and disease progression,<sup>3</sup> and thus patients who had HBV DNA levels as low as 300–400 copies/mL might have a decreased risk of progressing to advanced liver disease.<sup>2,29</sup> Similarly, in our model, the annual transition rates between disease states were mostly dependent on HBV DNA level.<sup>30</sup> Compared with nonvirologic responders (HBV DNA load >300–400 copies/mL) and virologic-resistant patients, patients categorized as being in a virologic response state (HBV DNA load <300–400 copies/mL) were less likely to progress to cirrhosis and HCC.<sup>3,27</sup> Beyond the first year, a discount rate of 5% was applied to adjust costs and effectiveness.

### Clinical data

The disease transition rates, treatment-induced virologic response, and resistance rates were all derived from studies



**Figure 1** Diagram of CHB patient transition states in the Markov model.  
**Abbreviations:** post-LT, post-liver transplantation; CHB, chronic hepatitis B.

based on Chinese patients (Tables 1 and 2). Cumulative rates from original research were converted to an annual average rate based on the following formula:

$$P = 1 - (1 - P_t)^{1/t}, \quad (1)$$

where  $P$  is the annual transition rate for each cycle of the model, and  $P_t$  is the cumulative rate for  $t$  years.<sup>31</sup> Meta-analysis was conducted to adjust for large variances in data extracted from the original literature.

### Cost and utility data

Direct health-care costs related to CHB included costs arising from examinations, physician visits, laboratory testing, and disease complications (Table 3).<sup>32</sup> Drug costs were taken from National Development and Reform Commission information.<sup>33</sup> All costs were adjusted to 2014 prices using the China health-care consumer price index and then converted

to 2014 values in US dollars (USD) using an exchange rate of 1 USD = 6.1429 Chinese Yuan.<sup>26</sup>

Each disease state in the model was assigned a utility score between 0 (death) and 1 (perfect health) to quantify patient utilities for different disease states (Table 3). Utility estimates were derived from results for the Chinese population included in a multinational study conducted by Levy et al,<sup>34</sup> which evaluated the utilities of CHB-related disease states using a standard gamble technique.

### Cost-effectiveness analysis

Cumulative lifetime cost, LYS, and QALYs were used as outcome measures. A cost-effectiveness ratio (CER) was used to calculate the mean cost per one QALY for each treatment strategy. The therapy that generated the lowest lifetime cost was considered as the reference treatment. When a treatment had a greater efficacy and a greater cost in relation to the reference, an incremental cost-effectiveness

**Table 1** Annual transition rates of disease states used in the model (%)

Initial state	Entered state	Model input (range)	Reference numbers
CHB	Compensated cirrhosis	1.0 (0.8, 1.2)	Adjusted based on 43, 44
	Decompensated cirrhosis	0.5 (0.3, 0.7)	Adjusted based on 44, 45
	Hepatocellular carcinoma	0.4 (0.3, 0.5)	Adjusted based on 43, 45
	Death	0.9 (0.8, 1.0)	Adjusted based on 43, 45
Virologic response	Compensated cirrhosis	0.4 (0.2, 0.6)	3
	Hepatocellular carcinoma	0.2 (0.1, 0.3)	3
	Death	Natural cause of death	59
Virologic resistance	Compensated cirrhosis	1.0 (0.8, 1.2)	Assumed equal to CHB
	Decompensated cirrhosis	0.5 (0.3, 0.7)	Assumed equal to CHB
	Hepatocellular carcinoma	0.4 (0.3, 0.6)	Assumed equal to CHB
	Death	0.9 (0.8, 1.0)	Assumed equal to CHB
Compensated cirrhosis	Decompensated cirrhosis	2.6 (1.5, 3.7)	Adjusted based on 45, 46
	Hepatocellular carcinoma	1.8 (0.8, 2.8)	Adjusted based on 45, 46
	Death	2.5 (1.5, 3.5)	Adjusted based on 45, 46
Decompensated cirrhosis	Hepatocellular carcinoma	9.1 (8.2, 10.0)	47
	Liver transplantation	5.5 (1.0, 10.0)	27
	Death	10.4 (9.4, 11.4)	48
Hepatocellular carcinoma	Liver transplantation	5.5 (1.0, 10.0)	27
	Death	52.0 (46.8, 57.2)	48
Liver transplantation	Death	12.0 (10.8, 13.2)	49
Post-liver transplantation	HBV relapse	4.8 (4.3, 5.3)	50
	Death	8.1 (7.3, 8.9)	50

**Abbreviations:** CHB, chronic hepatitis B; HBV, hepatitis B virus.

ratio (ICER) was determined. An ICER was not calculated if a strategy had a greater cost but lower efficacy. In addition, according to the recommendation of the World Health Organization, the treatment strategy was acceptable for patients when the ICER was below the 3× Gross Domestic Product (GDP) ceiling ratio,<sup>32</sup> and thus to identify the most cost-effective strategy, the willingness-to-pay (WTP)

threshold was set as \$20,466/QALY gained (3× GDP per capita of China, 2014).

## Sensitivity analysis

One-way sensitivity analysis was conducted to evaluate the uncertainty of each parameter, and the results were expressed as tornado charts. A probabilistic sensitivity analysis

**Table 2** Treatment-related annual rates used in the model

Treatment	Virologic response (%)		Resistance rate (%)	
	Probability (range)	Reference numbers	Probability (range)	Reference numbers
<b>HBeAg-positive</b>				
LAM	35 (27, 43)	9, 51	17.0 (12.1, 21.9)	9, 51
ADV	23 (14, 32)	8, 52	3.1 (1.3, 4.9)	8
TBV	64 (61, 67)	9, 17	8.1 (7.5, 8.7)	9, 10
ETV	69 (62, 76)	17, 51, 52	0.9 (0.6, 1.2)	51, 53
TDF	75 (73, 77)	17, 54, 55	0.5 (0.1, 0.9)	54, 56
LAM + ADV	77 (66, 88)	18–20	0.8 (0.1, 1.5)	18, 22, 23
<b>HBeAg-negative</b>				
LAM	75 (73, 77)	9, 60	17.0 (12.1, 21.9)	9, 51
ADV	61 (59, 63)	52	3.1 (1.3, 4.9)	8
TBV	85 (80, 90)	9	8.1 (7.5, 8.7)	9, 10
ETV	90 (86, 94)	17, 51, 60	0.8 (0.6, 1.2)	51, 53
TDF	94 (92, 96)	17, 54, 55	0.5 (0.1, 0.9)	54, 56
LAM + ADV	91 (87, 95)	18, 24	0.8 (0.1, 1.5)	18, 22, 23
<b>Rescue strategies</b>				
LAM + ADV	63 (52, 74)	15	6.9 (6.2, 7.6)	15
ETV + ADV	73 (65, 81)	15	0.0	15

**Abbreviations:** HBeAg, hepatitis B e antigen; LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ETV, entecavir; TDF, tenofovir.

**Table 3** Annual costs (US dollars, 2014 values) and disease-state utilities

Average disease costs (per patient/year)	Base case (range)	Reference numbers
<b>Drug costs</b>		
LAM	913 (822, 1,004)	33
ADV	1,059 (953, 1,165)	33
TBV	1,314 (1,183, 1,445)	33
ETV	2,044 (1,840, 2,248)	33
TDF	3,176 (2,858, 3,494)	Local pharmacy
<b>Disease-state costs</b>		
CHB	1,876 (1,688, 2,064)	57
Virologic response	1,876 (1,688, 2,064)	Assumed equal to CHB
Virologic resistance	1,876 (1,688, 2,064)	Assumed equal to CHB
Compensated cirrhosis	2,853 (2,568, 3,138)	57
Decompensated cirrhosis	5,274 (4,747, 5,801)	57
Hepatocellular carcinoma	7,930 (7,137, 8,723)	57
Liver transplantation	62,001 (55,801, 68,201)	58
Post-liver transplantation	9,391 (8,452, 10,330)	58
<b>Disease-state utilities (QALYs)</b>		
CHB	0.52 (0.47, 0.57)	34
Virologic response	0.71 (0.64, 0.78)	34
Virologic resistance	0.52 (0.47, 0.57)	Assumed equal to CHB
Compensated cirrhosis	0.57 (0.51, 0.63)	34
Decompensated cirrhosis	0.26 (0.23, 0.29)	34
Hepatocellular carcinoma	0.31 (0.28, 0.34)	34
Liver transplantation	0.41 (0.37, 0.45)	34
Post-liver transplantation	0.55 (0.49, 0.61)	34

**Notes:** All drug costs and direct disease-state costs are expressed in 2014 US dollars (\$, USD) per patient/year.

**Abbreviations:** LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ETV, entecavir; TDF, tenofovir; CHB, chronic hepatitis B; QALYs, quality-adjusted life years.

(PSA) based on a second-order Monte Carlo simulation of 1,000 patients was also performed,<sup>35</sup> and cost-effectiveness acceptability curves or scatter plots of pairwise coupling were generated. Appropriate distributions were correspondingly assigned to the input parameters in the model, wherein  $\beta$  distributions were assumed for probability and utility values, and  $\gamma$  distributions were used for cost variables.

## Results

### Base-case analysis

The model simulated the lifetime of CHB patients and calculated the cumulative costs, LYS, QALYs, CER, and ICER (Table 4). Health outcomes (such as 10-year cumulative incidence of compensated cirrhosis, decompensated cirrhosis, and HCC of six drug therapy options) are shown in Figure 2. In the HBeAg-positive cohort, LAM plus ADV combination therapy was the most efficacious, achieving 15.90 LYS and 10.98 QALYs. In the HBeAg-negative cohort, TDF generated the highest number of LYS and QALYs, with 15.87 and 10.93 years, respectively. In the HBeAg-positive cohort, the 10-year cumulative incidences of compensated cirrhosis, decompensated cirrhosis, HCC, and death for LAM plus ADV combination therapy were 4.58%, 1.17%, 2.82%, and 5.50%, respectively. Meanwhile, the incidences of advanced liver diseases for TDF were 4.46%, 1.04%, 2.73%, and 5.18%, respectively, in the HBeAg-negative cohort.

In both patient groups, the least expensive strategy over a lifetime was ETV, which served as the reference therapy.

**Table 4** Base-case cost and effectiveness of treatment strategies

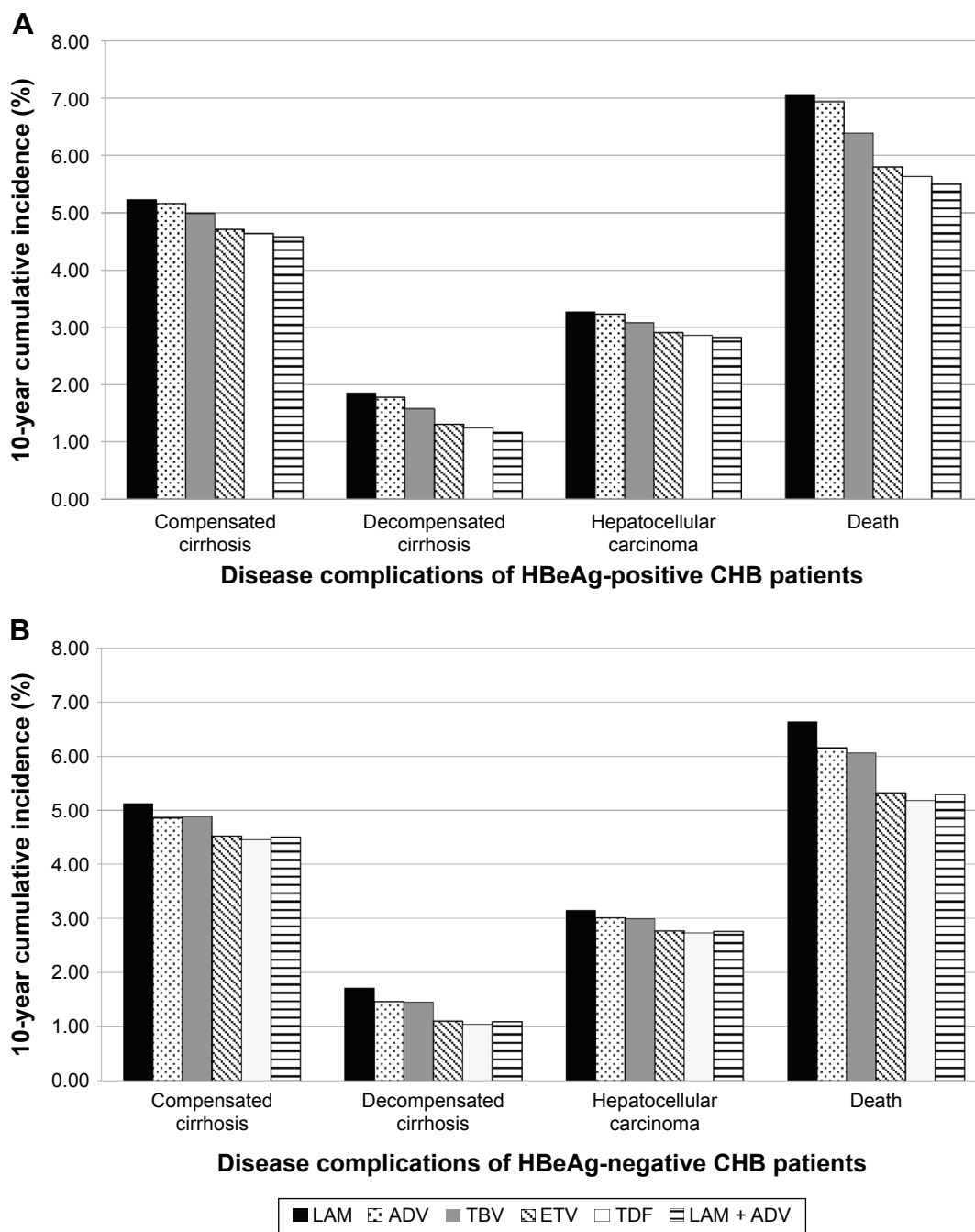
Drug	ETV <sup>a</sup>	LAM	ADV	TBV	TDF	LAM + ADV
<b>HBeAg-positive patients</b>						
Cost (×\$1,000)	72.15	83.48	81.24	76.63	82.64	74.45
QALYs	10.88	10.55	10.59	10.68	10.93	10.98
LYS	15.84	15.64	15.66	15.73	15.87	15.90
Incremental cost (×\$1,000)	–	–11.33	–9.09	–4.48	–10.49	–2.30
Incremental LYS	–	0.20	0.18	0.11	–0.03	–0.06
Incremental QALYs	–	0.33	0.29	0.20	–0.05	–0.10
CER (×\$1,000/QALYs)	6.63	7.91	7.67	7.18	7.56	6.78
ICER (×\$1,000/QALYs)	–	Dominated	Dominated	Dominated	209.80	23.00
<b>HBeAg-negative patients</b>						
Cost (×\$1,000)	67.15	78.30	69.92	72.82	80.99	69.84
QALYs	11.00	10.62	10.76	10.74	11.05	11.02
LYS	15.92	15.70	15.78	15.77	15.94	15.93
Incremental cost (×\$1,000)	–	–11.15	–2.77	–5.67	–13.84	2.69
Incremental LYS	–	0.22	0.14	0.15	–0.02	–0.01
Incremental QALYs	–	0.38	0.24	0.26	–0.05	–0.02
CER (×\$1,000/QALYs)	6.10	7.37	6.50	6.78	7.33	6.34
ICER (×\$1,000/QALYs)	–	Dominated	Dominated	Dominated	276.80	134.50

**Notes:** <sup>a</sup>The therapy used as a reference treatment. All costs are expressed in 2014 US dollars (\$). Dominated: The therapy has higher cost and lower efficacy in comparison with the reference treatment. ICER is calculated by using the formula ICER = Incremental cost/Incremental QALYs. “–” ETV was the baseline comparator.

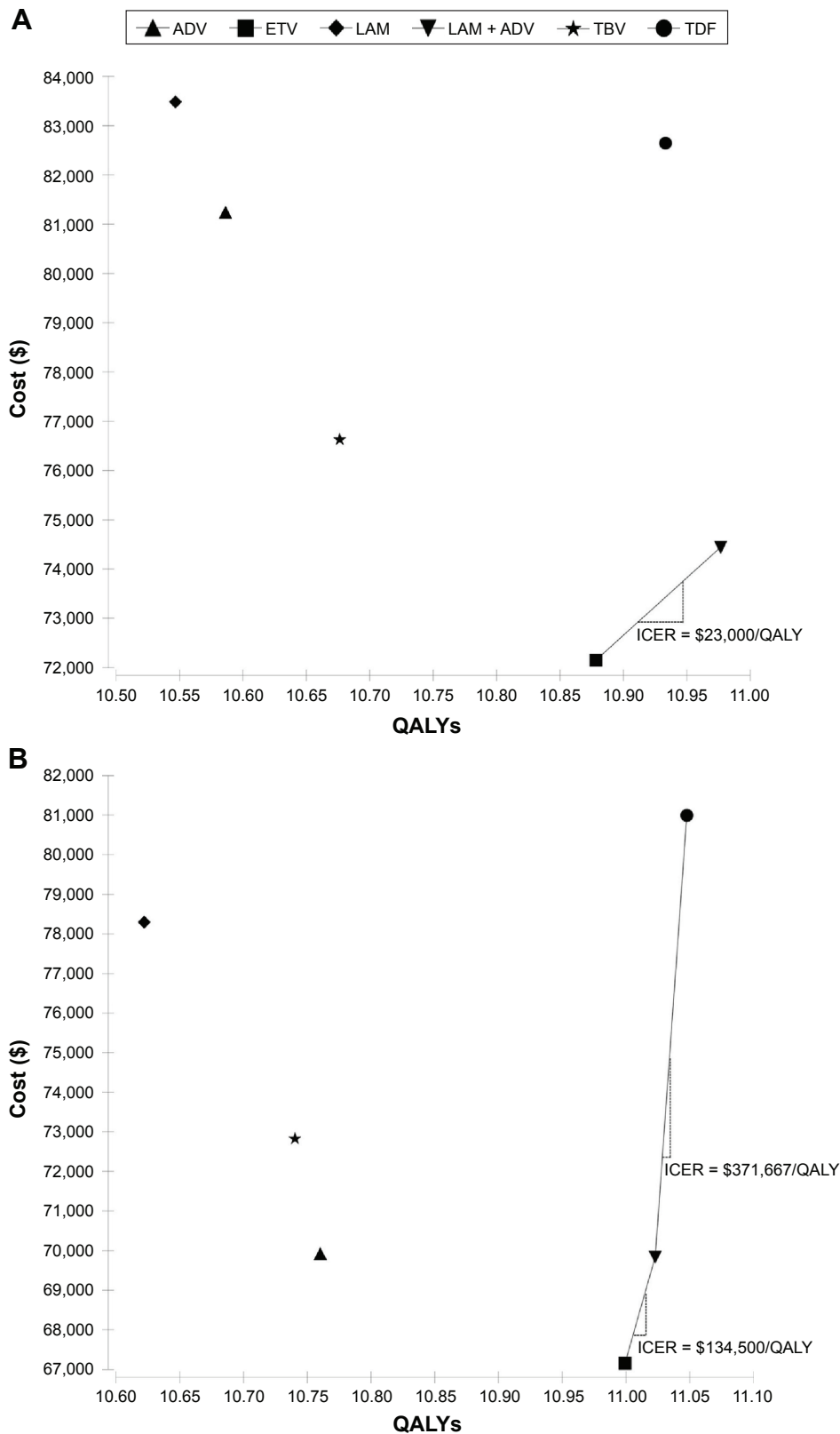
**Abbreviations:** ETV, entecavir; LAM, lamivudine; ADV, adefovir; TBV, telbivudine; TDF, tenofovir; HBeAg, hepatitis B e antigen; QALYs, quality-adjusted life years; LYS, life years saved; ICER, incremental cost-effectiveness rate.

Compared with other treatment options, ETV also achieved an excellent CER, indicating that ETV had the lowest cost per one QALY (HBeAg-positive: \$6,630/QALY, HBeAg-negative: \$6,100/QALY). LAM, ADV, and TBV were more cost-effective, but less efficacious than ETV. With respect to ETV, TDF had the highest lifetime cost, and the ICER of TDF (HBeAg-positive: \$209,800/QALY gained; HBeAg-negative: \$276,800/QALY gained) was far

higher than the WTP threshold of \$20,466/QALY gained. The LAM plus ADV combination therapy achieved more LYS and QALY than ETV, but was also more expensive. The ICER of LAM plus ADV combination therapy compared with ETV was \$23,000/QALY gained for HBeAg-positive and \$134,500/QALY gained for HBeAg-negative cohorts, which was also higher than the WTP threshold (Figure 3).



**Figure 2** Ten-year cumulative incidence of advanced liver diseases for HBeAg-positive (A) and -negative (B) CHB patients after different therapy strategies. **Abbreviations:** LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ETV, entecavir; TDF, tenofovir; HBeAg, hepatitis B e antigen; CHB, chronic hepatitis B.



**Figure 3** Cost-effectiveness of different treatment strategies for HBeAg-positive (A) and -negative (B) chronic hepatitis B patients. **Notes:** The x-axis represents the life-time QALYs for each treatment, and the y-axis indicates the life-time costs (US dollars). The straight lines represent the cost-effectiveness frontier, which joins the treatments that are not dominated by any other treatment. The slope of this line at any point represents the ICER for the comparison between the treatments at either end of the line. **Abbreviations:** LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ETV, entecavir; TDF, tenofovir; QALYs, quality-adjusted life years; HBeAg, hepatitis B e antigen; ICER, incremental cost-effectiveness ratio.

## Alternative scenario analysis

Table 5 shows the results of alternative rescue treatment strategies (direct use of ETV plus ADV combination rescue therapy). In contrast to base-case analysis, the lowest life-time cost and best CER (HBeAg-positive: \$6,780/QALY; HBeAg-negative: \$6,340/QALY) were obtained with LAM plus ADV combination treatment, and thus this combination was used as the reference therapy. As LAM, ADV, and TBV had higher cost and lower efficacy than LAM plus ADV combination therapy, they were directly dominated by the combination therapy in both cohorts. ETV and TDF were also dominated by LAM plus ADV combination therapy, except in the HBeAg-negative cohort. However, the ICER of ETV and TDF versus LAM plus ADV combination treatment was far higher than the WTP threshold of \$20,466/QALY gained in the HBeAg-negative group.

## One-way sensitivity analysis

One-way sensitivity analysis for ETV was conducted by varying all model parameters based on their range of values. The ten most influential parameters are presented as a tornado diagram (Figure 4). In both cohorts, the most influential parameter was found to be the utility of virologic response. However, none of the variations would change the finding that ETV was the most cost-effective treatment, except for the virologic response and resistance rate of LAM plus ADV combination treatment. By using the threshold analysis, LAM

plus ADV combination therapy would become the optimal therapy when the response rate was above 78% or the resistance rate was below 0.8% in the HBeAg-positive cohort, and for the HBeAg-negative cohort response and resistance rates had to be above 93% and below 0.4%, respectively.

## Probabilistic sensitivity analysis

The PSA showed that at the WTP threshold of \$20,466/QALY gained, ETV was the most cost-effective treatment in 46.3% and 55.7% of the simulations for HBeAg-positive and HBeAg-negative groups, respectively (Figure 5). LAM plus ADV combination therapy would be the preferable option when the threshold was beyond \$24,000/QALY gained for the HBeAg-positive cohort, or \$83,000/QALY gained for the HBeAg-negative cohort.

Scatter plots indicated that in the HBeAg-positive cohort, ETV dominated LAM, ADV, TBV, TDF, and LAM and ADV combination therapy in 100.0%, 99.8%, 84.0%, 97.2%, and 54.0% simulations, respectively, that were under the \$20,466/QALY gained threshold (Figure 6). Among HBeAg-negative patients, the percentages of simulations where ETV dominated were 100.0%, 93.6%, 95.0%, 99.4%, and 60.1%, respectively (Figure 6).

## Discussion

Hepatitis B is a major global public health concern, especially in China. Persistent HBV infection has been a critical

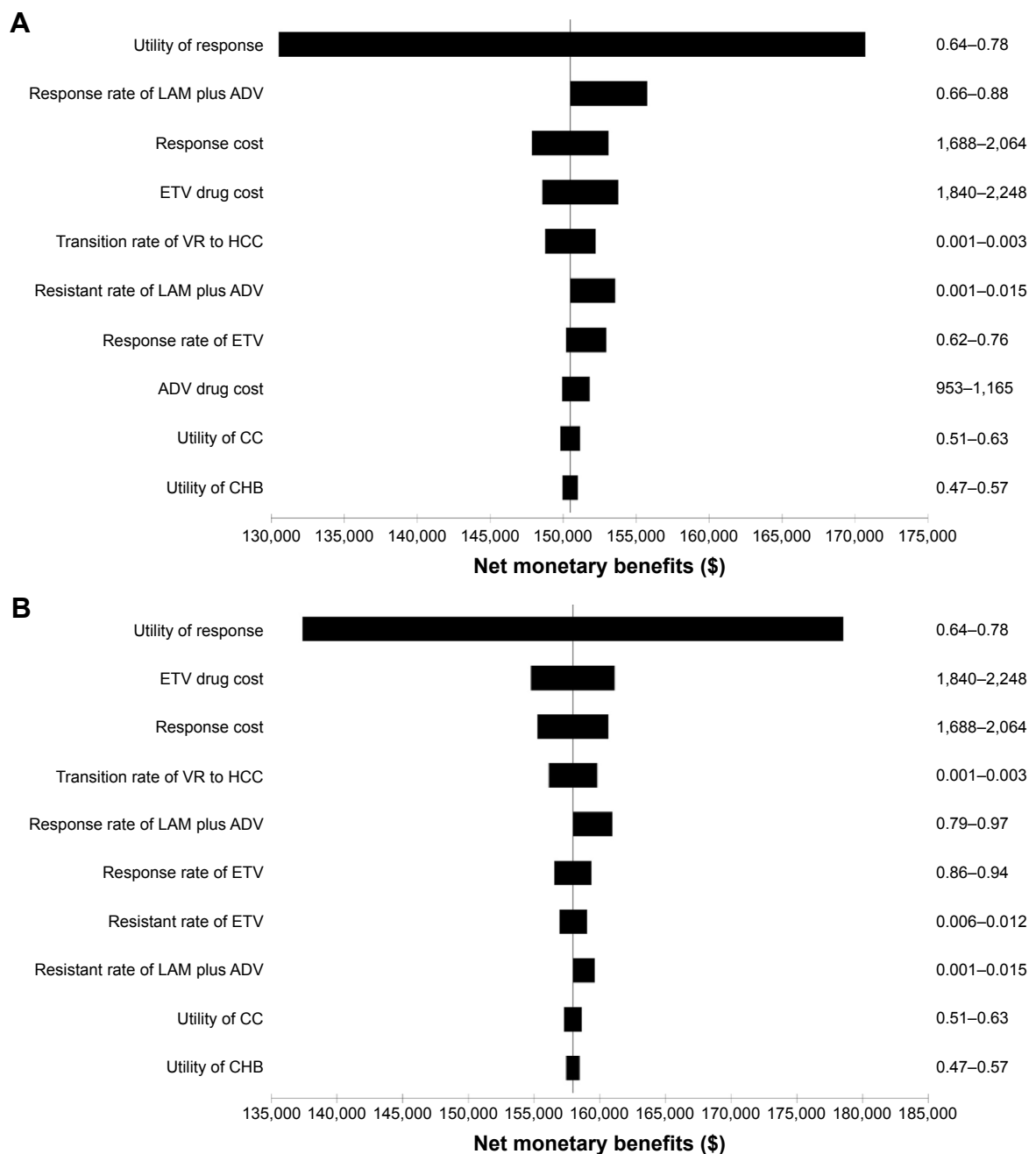
**Table 5** Alternative cost and effectiveness of five treatment strategies

Drug	LAM + ADV <sup>a</sup>	LAM	ADV	TBV	ETV	TDF
<b>HBeAg-positive patients</b>						
Cost (×\$1,000)	74.45	99.88	96.42	89.47	78.84	87.68
QALYs	10.98	10.70	10.73	10.79	10.94	10.98
LYS	15.90	15.72	15.74	15.79	15.87	15.90
Incremental cost (×\$1,000)	–	–25.43	–21.97	–15.02	–4.39	–13.23
Incremental LYS	–	0.18	0.16	0.11	0.03	<0.01
Incremental QALYs	–	0.28	0.25	0.19	0.04	<0.01
CER (×\$1,000/QALYs)	6.78	9.33	8.99	8.29	7.21	7.99
ICER (×\$1,000/QALYs)	–	Dominated	Dominated	Dominated	Dominated	Dominated
<b>HBeAg-negative patients</b>						
Cost (×\$1,000)	69.84	92.69	80.21	83.93	70.36	82.72
QALYs	11.02	10.75	10.85	10.84	11.03	11.06
LYS	15.93	15.76	15.82	15.81	15.93	15.95
Incremental cost (×\$1,000)	–	–22.85	–10.37	–14.09	–0.52	–12.88
Incremental LYS	–	0.17	0.11	0.12	<0.01	–0.02
Incremental QALYs	–	0.27	0.17	0.18	–0.01	–0.04
CER (×\$1,000/QALYs)	6.34	8.62	7.39	7.74	6.38	7.48
ICER (×\$1,000/QALYs)	–	Dominated	Dominated	Dominated	52.00	322.00

**Notes:** <sup>a</sup>The therapy used as a reference treatment. All costs are expressed in 2014 US dollars (\$). Dominated: The therapy has higher cost and lower efficacy in comparison with the reference treatment. ICER is calculated by using the formula ICER = Incremental cost/Incremental QALYs. “–” LAM+ADV is the baseline comparator.

**Abbreviations:** LAM, lamivudine; ADV, adefovir; TBV, telbivudine; ETV, entecavir; TDF, tenofovir; HBeAg, hepatitis B e antigen; QALYs, quality-adjusted life years; LYS, life years saved; ICER, incremental cost-effectiveness rate.





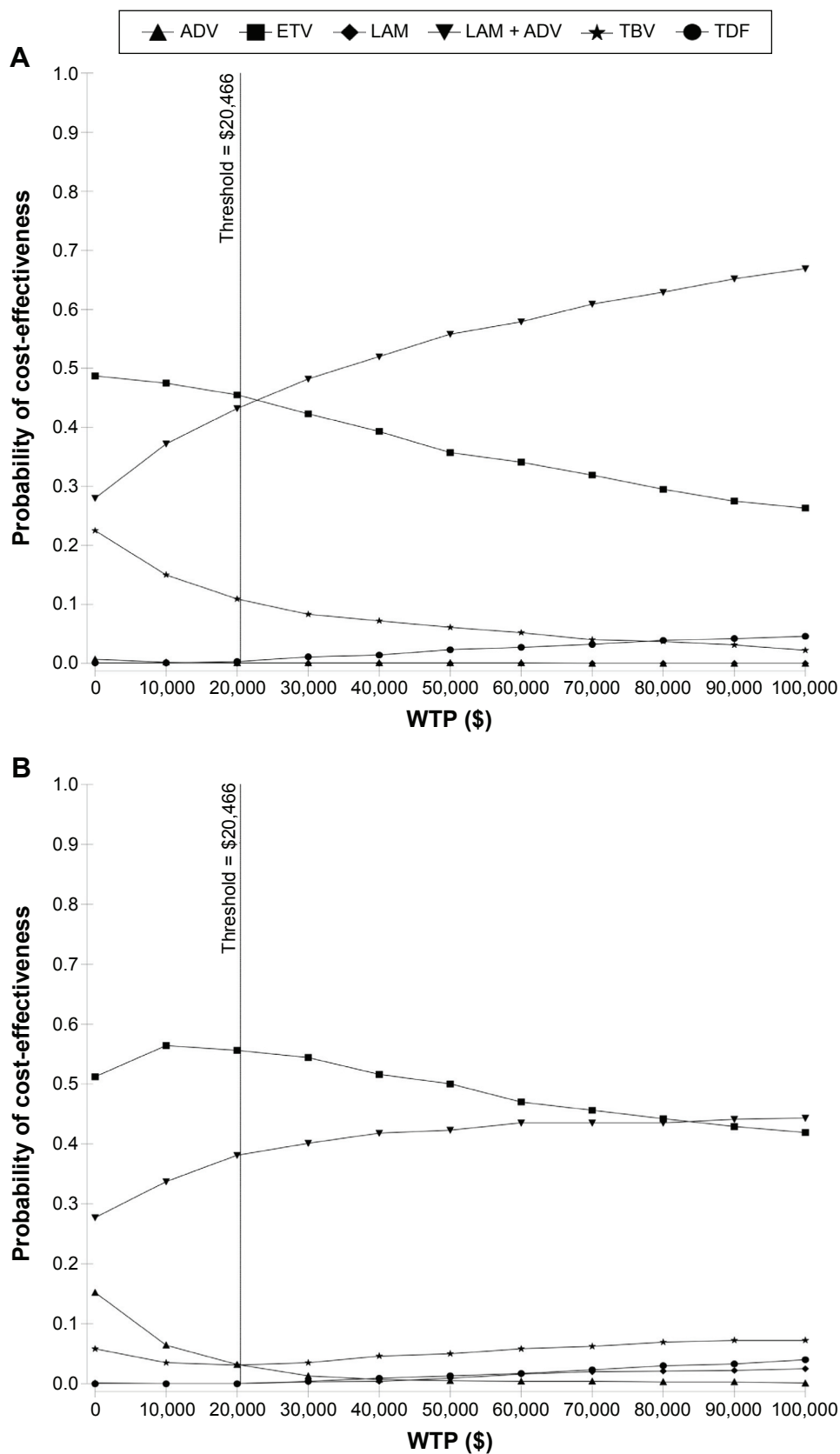
**Figure 4** Results of one-way sensitivity analysis for HBeAg-positive (A) and -negative (B) CHB patients at a threshold of \$20,466/QALY gained.

**Note:** The vertical dotted line represents the base-case results where ETV was the most cost-effective strategy.

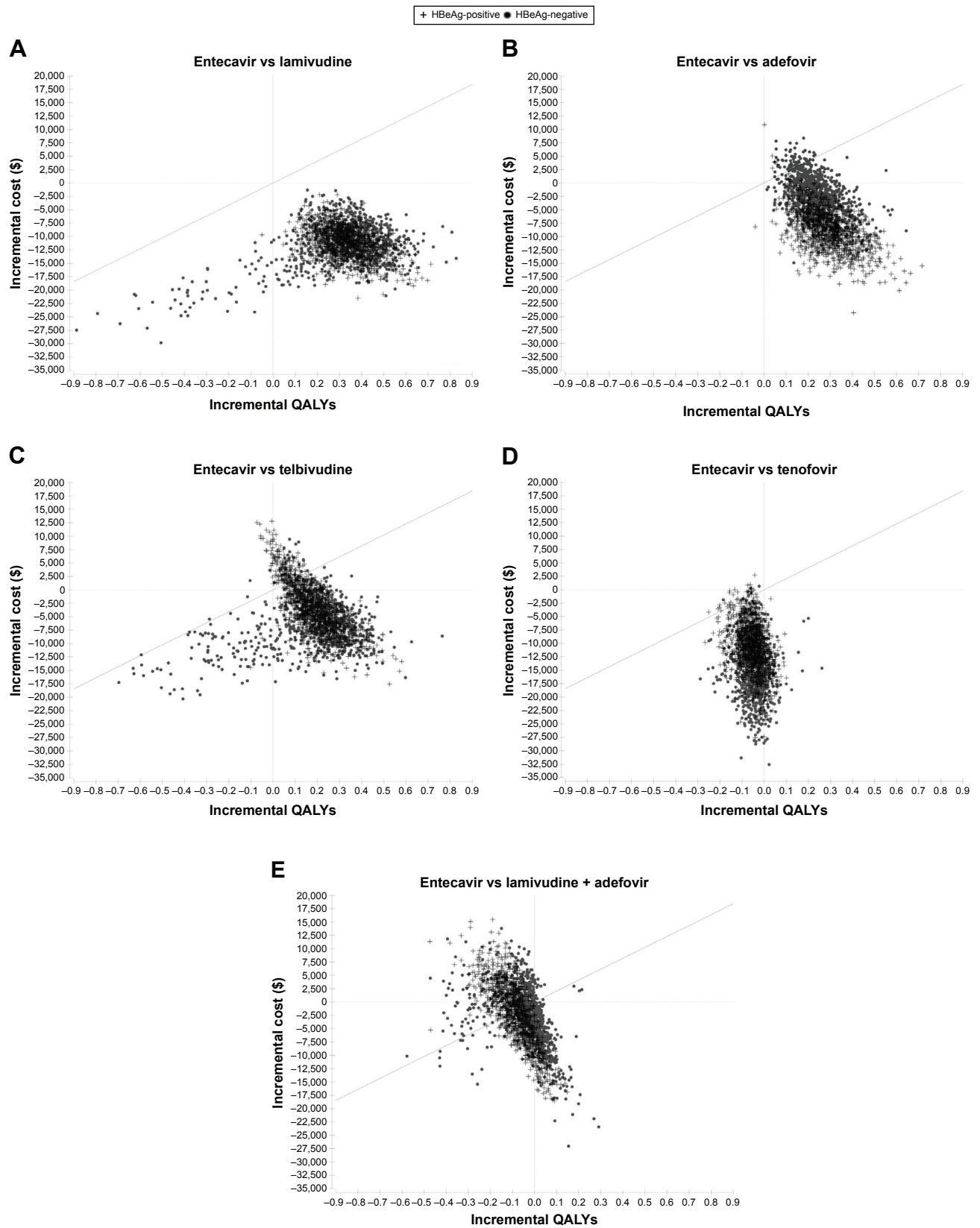
**Abbreviations:** LAM, lamivudine; ADV, adefovir; ETV, entecavir; VR, virologic response; HCC, hepatocellular carcinoma; CC, compensated cirrhosis; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; QALYs, quality-adjusted life years.

risk factor in CHB patients who, in the absence of timely and effective therapy, ultimately progress to cirrhosis and HCC.<sup>3,36</sup> CHB-related complications can lead to significant mortality and substantial economic consequences.<sup>37</sup> For CHB patients in China, LAM remains a promising option because its price is the lowest of the five currently available nucleos(t)ide analogs. However, due to the high resistance rate of LAM, patients will eventually have to switch or combine with other

antiviral drugs for continuous therapy, which ultimately results in higher costs for long-term treatment.<sup>9</sup> Recently, ADV was found to have no cross-resistance with LAM, TBV, and ETV, and thus this drug is used as a basic agent for combination therapy.<sup>11,38,39</sup> In 2011, LAM plus ADV combination therapy was recommended for initial treatment of CHB patients.<sup>25</sup> Nonetheless, this recommendation does not take into account cost-effectiveness as a factor for selecting



**Figure 5** Cost-effectiveness acceptability curves of different strategies for HBeAg-positive (A) and -negative (B) chronic hepatitis B patients. **Notes:** The y-axis indicates the probability that the therapy is a cost-effective strategy. The x-axis represents the WTP threshold to pay one additional QALY. **Abbreviations:** ADV, adefovir; ETV, entecavir; LAM, lamivudine; TBV, telbivudine; TDF, tenofovir; HBeAg, hepatitis B e antigen; WTP, willingness-to-pay; QALY, quality-adjusted life year.



**Figure 6** Probabilistic results for incremental cost-effectiveness comparisons between treatment with entecavir and (A) lamivudine monotherapy, (B) adefovir monotherapy, (C) telbivudine monotherapy, (D) tenofovir monotherapy, and (E) lamivudine plus adefovir combination therapy for a simulation involving 1,000 patients.

**Notes:** The y- and x-axes represent the incremental costs and incremental QALYs gained, respectively. Dots below the ICER threshold reflect simulations in which cost per QALYs gained with entecavir are below the Chinese threshold of \$20,466/QALY gained.

**Abbreviations:** QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

suitable therapies. As such, a current economic analysis was performed to evaluate the long-term cost-effectiveness of LAM plus ADV combination therapy versus other nucleos(t)ide analogs for the treatment of Chinese CHB patients.

Our study showed three key findings. First, in a base-case analysis the use of first-line treatment with ETV was the most cost-effective treatment for both HBeAg-positive and HBeAg-negative patients relative to other strategies. ETV directly dominated LAM, ADV, and TBV due to its lower cost and higher efficacy in both cohorts. Although TDF and LAM plus ADV combination therapy generated higher LYS and QALYs than ETV monotherapy, the ICER of these approaches compared with ETV was beyond the WTP threshold of \$20,466/QALY gained. Second, we found that LAM monotherapy was never a cost-effective option for CHB patients because of its high viral resistance and nonresponse in long-term treatment, which might result in higher costs over the course of a lifetime. Another finding of our study was that basic rescue strategies had much better CER than alternative rescue treatments. Although potent combination rescue therapy was beneficial to improve health efficacy (LYS and QALYs), these strategies also presented greater economic burdens for Chinese patients. Hence, the basic rescue strategy would be the better option from an economic perspective. In addition, since the potent rescue strategy largely increased the lifetime costs of the other five nucleos(t)ide monotherapies considered, they were totally dominated by LAM plus ADV combination therapy, except for ETV and TDF in the HBeAg-negative group. However, the ICERs of ETV and TDF versus combination therapy were far higher than the WTP threshold of \$20,466/QALY gained, which indicated that the LAM plus ADV combination therapy would become the most cost-effective treatment, or even a cost-saving strategy for both HBeAg-positive and HBeAg-negative groups when patients directly used a potent rescue strategy.

This study is the first economic evaluation to assess the cost-effectiveness of LAM plus ADV combination therapy compared with other nucleos(t)ide analog monotherapies for treating CHB infections in Chinese patients. Since LAM plus ADV combination therapy was recommended for CHB patients in 2011,<sup>25</sup> a meta-analysis conducted in China showed that LAM plus ADV combination therapy can enhance anti-HBV agents and reduce viral resistance, which could permit long-term use.<sup>17</sup> In addition, a clinical study conducted in India suggested that LAM plus ADV combination therapy was not inferior to ETV and TDF monotherapies, especially when treatment costs were taken

into consideration,<sup>40</sup> although this strategy remains controversial. A global multicenter, randomized and double-blind study found that LAM plus ADV combination therapy could not significantly suppress HBV DNA levels and reduce viral resistance,<sup>41</sup> and thus some treatment guidelines do not recommend this strategy.<sup>4,5</sup> The parameters of our study were derived from clinical trials based on Chinese populations, and the results of base-case analysis showed that LAM plus ADV combination therapy would not be the most cost-effective treatment for CHB patients compared with other nucleos(t)ide analog monotherapies. These results are consistent with a previous study, which evaluated the cost-effectiveness of initial LAM plus ADV combination therapy and ETV in a scenario analysis and found that ETV monotherapy is a better option than combination therapy.<sup>42</sup> Although LAM plus ADV combination therapy has greater clinical effectiveness, it also presents a greater economic burden for CHB patients. Moreover, the annual cost of LAM combined with ADV is higher than some nucleos(t)ide analog monotherapies, but unlike antiviral monotherapies, patients treated with drug combinations can develop multidrug resistance that requires more potent rescue strategies, such as ETV plus ADV or TDF combinations, to overcome initial combination therapy failure. Thus, even if the LAM plus ADV combination strategy is a cost-effective treatment for patients who directly received the potent rescue treatment (ETV plus ADV) after developing resistance to nucleos(t)ide analog monotherapies, its CER was still below that of ETV monotherapy followed by basic rescue therapy.

Several limitations of this analysis must be considered. First, due to the lack of long-term experience with different treatment strategies, the parameters in our model were mainly obtained from clinical trials conducted over 2–5 years, and this was particularly the case for LAM plus ADV combination therapy data. In China, there are no clinical trials of initial LAM plus ADV combination strategy that lasted for more than 3 years. Thus, a long-term randomized controlled trial (RCT) is needed to demonstrate the efficacy and safety of LAM plus ADV combination therapy. Moreover, future economic studies can incorporate results from long-term RCT or empirical data to further validate the model. Second, the annual costs of CHB and disease complications in China were obtained from a study published in 2009, which required the use of China health-care consumer price indices to adjust the costs to current levels.

In conclusion, the results of this analysis reveal that the long-term use of ETV remains a cost-effective strategy in Chinese CHB patients. However, LAM plus ADV combination

therapy would be the optimal strategy in a scenario where potent rescue treatment is directly administered for patients with prior nucleos(t)ide analog monotherapy failure.

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## Disclosure

The authors report no conflicts of interest in this work.

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