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First line nucleos(t)ide analog monotherapy is more cost-effective than combination strategies in hepatitis B e antigen-positive chronic hepatitis B patients in China

Xue-Ru Yin[1], Zhi-Hong Liu[1], Jing Liu[2], Yuan-Yuan Liu[1], Li Xie[3], Li-Bo Tao[2], Ji-Dong Jia[4], Fu-Qiang Cui[5], Gui-Hua Zhuang[6], Jin-Lin Hou[1]

[1]Hepatology Unit, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China;
[2]Health Economics Research Institute, Sun Yat-Sen University, Guangzhou, Guangdong 510085, China;
[3]Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiao Tong University Health Science Center, Xi'an, Shaanxi 710061, China;
[4]Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China;
[5]School of Public Health, Peking University, Beijing 100191, China;
[6]School of Public Health, Xi'an Jiao Tong University Health Science Center, Xi'an, Shaanxi 710061, China.

Abstract

Background: Nucleos(t)ide analog (NA) in combination with peginterferon (PegIFN) therapy in patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) shows better effectiveness than NA monotherapy in hepatitis B surface antigen loss, termed "functional cure," based on previous published studies. However, it is not known which strategy is more cost-effective on functional cure. The aim of this study was to analyze the cost-effectiveness of first-line monotherapies and combination strategies in HBeAg-positive CHB patients in China from a social perspective.

Methods: A Markov model was developed with functional cure and other five states including CHB, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and death to assess the cost-effectiveness of seven representative treatment strategies. Entecavir (ETV) monotherapy and tenofovir disoproxil fumarate (TDF) monotherapy served as comparators, respectively.

Results: In the two base-case analysis, compared with ETV, ETV generated the highest costs with $44,210 and the highest quality-adjusted life-years (QALYs) with 16.78 years. Compared with TDF, treating CHB patients with ETV and NA – PegIFN strategies increased costs by $7639 and $6129, respectively, gaining incremental QALYs by 2.20 years and 1.66 years, respectively. The incremental cost-effectiveness ratios were $3472/QALY and $3692/QALY, respectively, which were less than one-time gross domestic product per capita. One-way sensitivity analysis and probabilistic sensitivity analyses showed the robustness of the results.

Conclusion: Among seven treatment strategies, first-line NA monotherapy may be more cost-effective than combination strategies in HBeAg-positive CHB patients in China.

Keywords: Hepatitis B; Functional cure; Quality-adjusted life-year; Cost-effectiveness

Introduction

Hepatitis B virus (HBV) infection continues to be a major global public health issue that is associated with an increased risk of cirrhosis and hepatocellular carcinoma (HCC). In 2016, approximately 292 million lives were affected by HBV infections worldwide with China, India, Nigeria, Indonesia, and the Philippines accounting for over 57%.[1] Notably, China was estimated to have 86 million individuals with HBV infections.[1]

In May 2016, the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate the viral hepatitis threat by 2030. Anti-viral treatment will be needed to meet the strategy targets of treating 80% of eligible chronic HBV infections. The global target of anti-viral treatment is largely influenced by China because China accounts for 29.5% of all HBV infections globally, while only an estimated 11% of eligible individuals were treated.[1]

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are recommended as first-line anti-viral drugs by international guidelines.[2-4] In addition, peginterferon (PegIFN) is also recommended by Chinese guideline.[4] However, there exist obvious limitations of the currently available HBV therapies. Although long-term suppression of HBV DNA

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Correspondence to: Dr. Jin-Lin Hou, Hepatology Unit, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China
E-Mail: jlhousmu@163.com

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with alanine aminotransferase normalization is available to a large extent with first-line regimens in clinical practice, sustained viral suppression does not completely prohibit the progression to cirrhosis or HCC. In addition, high costs and adverse effects resulting from long duration or even lifelong treatment cannot be ignored. Hence, achieving hepatitis B surface antigen (HBsAg) loss, termed "functional cure," is the optimal therapeutic endpoint. Chinese guidelines mention that during treatment, functional cure should be pursued to the greatest extent possible for eligible patients.[4] However, the rates of HBsAg loss in patients receiving first-line regimens are very low.

The mechanism of HBsAg loss remains largely unknown; however, it has been suggested that the role of an unknown immune-related mechanism is crucial.[5] Previous studies suggested that the decline of HBsAg levels is more pronounced in hepatitis B e antigen (HBeAg)-positive patients compared with HBeAg-negative patients.[6] Theoretically, a combined nucleos(t)ide analog (NA) and PegIFN approach may provide advantages by combining the potent anti-viral effect of NA plus the immune modulation of PegIFN. Therefore, in recent years, some important studies of combination therapeutic strategies of NA and PegIFN have been conducted, including *de novo* combination strategy, "add-on" strategy and "switch-to" strategy. And the results of combination strategies showed superiority in functional cure in selected individuals.[7-11] However, the costs of the combination strategies are relatively high and unfavorable safety profile makes many patients unwilling for such kinds of treatments. Few cost-effectiveness analyses focused on functional cure in HBeAg-positive chronic hepatitis B (CHB) patients with combination therapies, although cost-effectiveness analysis is quite important to inform policy and decision making. Thus, we aimed to analyze the cost-effectiveness of current treatment approaches in a Chinese setting.

Methods

Description of anti-viral treatment strategies

We compared seven representative treatment strategies in HBeAg-positive CHB patients in China: (1) TDF monotherapy (300 mg/d) for life (strategy TDF); (2) ETV monotherapy (0.5 mg/d) for life (strategy ETV); (3) ETV in addition to PegIFN (strategy ETV + PegIFN). Patients received 180 μg/week PegIFN for 48 weeks, with a 24-week add-on course of ETV 0.5 mg once daily starting at week 13 of PegIFN therapy[11]; (4) TDF adding on PegIFN (strategy TDF + PegIFN). Patients received 180 μg/week PegIFN plus TDF 300 mg/d for 48 weeks[7]; (5) ETV adding on then switching to PegIFN (strategy ETV - PegIFN). After 1 to 3 years of ETV treatment, patients with HBV DNA <1000 copies/mL along with HBeAg <100 PE IU/mL received additional ETV for 8 weeks and PegIFN 180 μg/week therapy for 48 weeks,[10] while the other patients continued receiving ETV therapy; (6) PegIFN addition on adefovir (ADV) (strategy PegIFN + ADV). After 24 weeks of PegIFN treatment, patients with HBsAg <1500 IU/mL and HBV DNA $<10^5$ copies/mL received PegIFN for a further 24 weeks of treatment and the other patients received PegIFN for another 72 weeks plus ADV for 36 weeks[9]; and (7) NA (lamivudine, ETV or telbivudine) switching to PegIFN (strategy NA – PegIFN). After 1 to 3 years of NA treatment, patients with HBeAg seroconversion and HBV DNA <200 IU/mL switched to PegIFN 180 μg/week therapy for 96 weeks, and the other patients continued NA therapy.[8] Strategy (1) and (2) served as comparators respectively. The combination strategies above have different patterns of patient selection, timing, and the duration of adding on or switching to a treatment. The initiation of treatment followed Chinese guideline recommendations. These strategies are presented in Figure 1.

Base-case simulation and Markov model

A cost-effectiveness analysis was based on a Markov model simulating a hypothetical cohort of 1000 cases of Chinese CHB patients aged 35 years fulfilling Chinese guidelines criteria for treatment of hepatitis B [Figure 2]. Excel spreadsheet software (Microsoft, Redmond, WA, USA) was used. Patients were tracked as they moved between the following health states: functional cure, and other five states including CHB, compensated cirrhosis, decompensated cirrhosis, HCC, and death. The life expectancy of Chinese people is 76.7 years, and thus, the lifetime horizons of this model were set at 42 years.[12] The cycle length was 1 year. Details of the parameters used to derive transition probabilities between two states and related references are found in Table 1. Model input parameters were mainly derived from published studies based on the Chinese population, our long-term cohorts in China and government documents. Notably, some transition probabilities used in the ETV strategy analysis were based on the Realm cohort of HBeAg-positive Chinese CHB patients who received up to 10 years of monotherapy with ETV (ClinicalTrials.gov identifier: NCT00388674). The cumulative probabilities or rates from published original studies were all converted to annual probabilities by the formula:

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

where P is the annual transition rate for each model cycle and P_t is the cumulative rate for t years.[12]

Costs and utility scores

This study considered the direct costs of states within the span of 1 year from the social perspective, indirect and intangible costs were not included. Direct costs included medical and non-medical costs. The direct medical costs of disease states included outpatient expenditures, inpatient expenditures, and expenditures on medicines self-purchased in retail pharmacies derived from published reports. Furthermore, the direct medical costs of branded drugs used in the treatment strategies were calculated based on the current local market. The direct non-medical costs included the family's travel expenses to get treatment and the patient's extra health product expenses derived from published reports. Due to the differences in costs between various regions in China and between branded drugs and generic drugs, a wide range was used in the

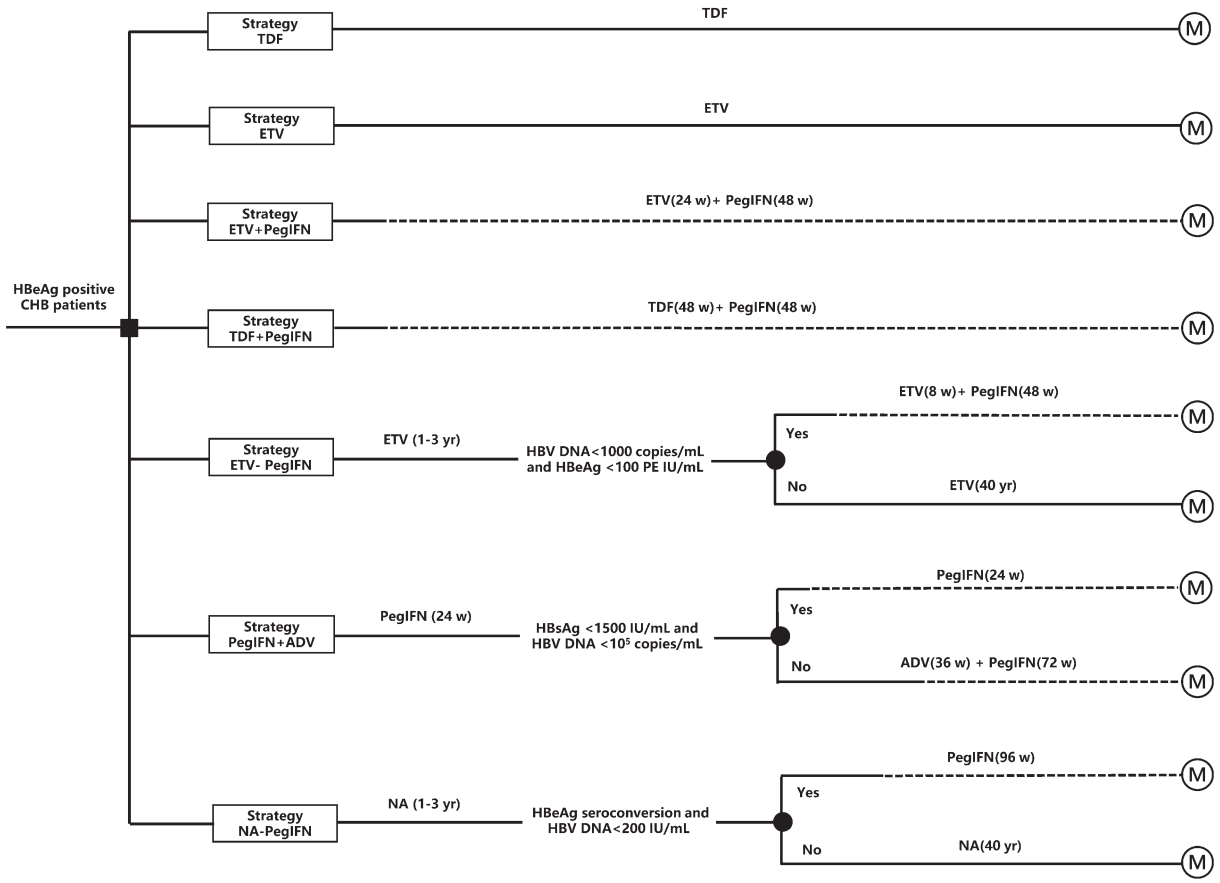

Figure 1: The treatment strategies included in this study. ADV: Adefovir; CHB: Chronic hepatitis B; ETV: Entecavir; HBeAg: Hepatitis B e antigen; M: Markov model; NA: Nucleos(t)ide analog; PegIFN: Peginterferon; TDF: Tenofovir; w: Weeks; yr: Years.

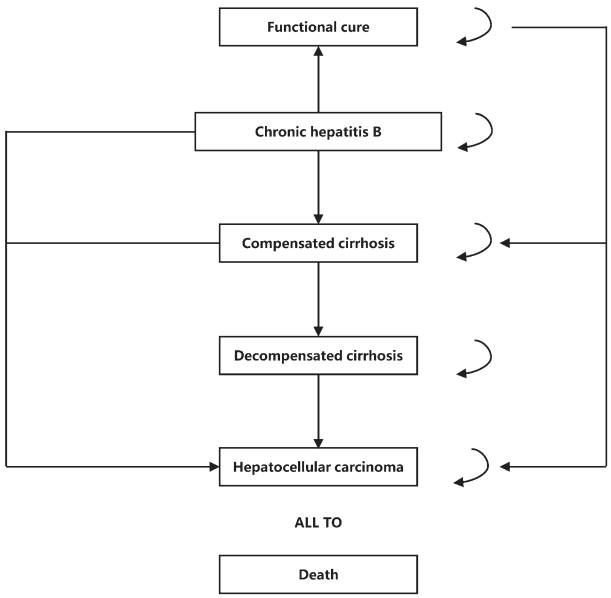

Figure 2: Markov model. Markov diagram of health states and possible transitions between them during each 1-year cycle. During each 1-year cycle, individual chronic hepatitis B patients either remained in their assigned health state (recursive arrow) or progressed to a new health state (straight arrow).

sensitivity analyses to account for uncertainties. All costs were converted from Chinese Yuan to US dollars at an average exchange rate of 6.75 in 2017. Both costs and quality-adjusted life-years (QALYs) were discounted at an annual rate of 5%, based on China Guidelines for Pharmacoeconomic Evaluations and were adjusted between 0% and 10%.[13] Constant utility scores were assigned to different disease states based on published reports, shown in Table 2.

Cost-effectiveness analysis

The outcomes measured were QALYs, life expectancy, incremental costs, incremental QALYs, and the incremental cost per QALY gained, defined as the incremental cost-effectiveness ratio (ICER). The cumulative numbers of patients in functional cure, compensated cirrhosis, decompensated cirrhosis, HCC, and death at 42 years are shown as clinical outcomes. Previous literature recommended that the cost-effectiveness threshold be set at either US $50,000 or three times the per-capita gross domestic product (GDP) of the studied population per one additional QALY gained.[14] The per-capita GDP reported by the Chinese government was US $8839 in 2017. In this study, we used US $26,517/QALY as the cost-effectiveness threshold.[15]

Table 1: Annual transition probabilities of disease states used in the study model (%).

Annual transition probabilities	Base-case		Reference
	Value (%)	Range (%)	
CHB to FC			
Strategy TDF	0.04	0.02–0.06	[17]
Strategy ETV	0.24	0.12–0.36	Realm cohort
Strategy ETV + PegIFN (1st year)	6.80	1.05–12.64	[11]
Strategy TDF + PegIFN (1st year)	4.00	1.05–12.64	[7]
Strategy ETV – PegIFN (1st year)	8.50	3.80–16.10	[10]
Strategy PegIFN + ADV (1st and 2nd year)	0.02	0.01–0.03	[9]
Strategy NA – PegIFN (1st and 2nd year)	10.90	8.35–12.88	[8]
Strategy NA – PegIFN (NA)	0.32	0.16–0.48	Realm cohort
CHB to CC			
Strategy TDF	1.00	0.80–1.20	[18]
Strategy ETV	0.20	0.10–0.30	Realm cohort
Strategy NA – PegIFN (NA)	0.20	0.10–0.30	Realm cohort
CHB to HCC			
Strategy TDF	0.70	0.40–1.00	[19]
Strategy ETV	0.30	0.15–0.45	Realm cohort
Strategy NA – PegIFN (NA)	0.40	0.20–0.60	Realm cohort
CHB to death			
Strategy TDF	0.84	0.75–0.93	[20]
Strategy ETV	0.30	0.15–0.45	Realm cohort
Strategy NA – PegIFN (NA)	0.30	0.15–0.45	Realm cohort
FC to CC	0.02	0.01–0.03	[21]
FC to HCC	0.02	0.01–0.03	[21]
FC to death			
35–39 years	0.12	0.06–0.18	[21]
40–44 years	0.18	0.09–0.27	[21]
45–49 years	0.26	0.13–0.39	[21]
50–54 years	0.42	0.21–0.63	[21]
55–59 years	0.62	0.31–0.93	[21]
60–64 years	1.03	0.52–1.55	[21]
65–69 years	1.72	0.86–2.58	[21]
70–74 years	3.06	1.53–4.59	[21]
75–77 years	4.95	2.48–7.43	[21]
CC to DC	2.60	1.50–3.70	[22,23]
CC to HCC	1.80	0.80–2.80	[22-24]
CC to death	2.50	1.50–3.50	[22-24]
DC to HCC	3.40	1.00–10.00	[25]
DC to death	10.40	9.40–11.40	[26]
HCC to death	23.30	20.00–30.00	[27]

CHB: Chronic hepatitis B; FC: Functional cure; TDF: Tenofovir; ETV: Entecavir; PegIFN: Peginterferon; ADV: Adefovir; NA: Nucleos(t)ide analog; CC: Compensated cirrhosis; HCC: Hepatocellular carcinoma; DC: Decompensated cirrhosis.

Sensitivity analysis

Sensitivity analyses were performed to evaluate the uncertainty of parameter estimates and the robustness of the model. One-way sensitivity analyses were performed for all parameters within their respective ranges, shown in Table 1, to show how each parameter impacted the results and to identify the main influential parameters. The results were expressed as tornado charts. A probabilistic sensitivity analysis (PSA) was further conducted to estimate the simultaneous impact of parameter uncertainty on the analysis. Appropriate distributions were correspondingly assigned to the input parameters in the model, wherein Gamma distributions were assumed for cost variables, and Beta distributions were assumed for utility and probability variables. The results of 400 iterations were plotted as cost-effectiveness acceptability curves.

Results

Base-case results

The QALYs, life expectancy, incremental costs, incremental QALYs and ICERs of the included strategies are shown in Table 3. Clinical outcomes are shown in Supplementary Table 1, http://links.lww.com/CM9/A92. Strategy ETV had the highest costs ($44,210) with the highest numbers for life expectancy and QALYs, at 17.05 and 16.78 years, respectively. Strategy ETV + PegIFN had the lowest costs $33,207. Strategy TDF + PegIFN had with the lowest years

Table 2: Costs, discount rate, and utility scores of disease states used in the study model.

Costs	Value	Range	Reference
Disease states (per year) (US$ 2017)			
HBeAg positive chronic hepatitis B	1177	589–1766	[28]
Compensated cirrhosis	2000	1000–3000	[28]
Decompensated cirrhosis	3601	1801–5402	[28]
Hepatocellular carcinoma	12,710	6355–19,065	[28]
Branded drugs (per year) (US$ 2017)			
TDF	881	32–1322	[29]
ETV	1352	34–2028	[29]
PegIFN	7076	3538–10,614	[29]
Strategy PegIFN + ADV (1st year)	7583	3792–11,375	[29]
Strategy NA – PegIFN (1st year)	7278	3639–10,917	[29]
Utility scores			
HBeAg positive chronic hepatitis B	0.99	0.90–1.00	[30]
Functional cure	1.00	0.95–1.00	[30]
Compensated cirrhosis	0.80	0.70–0.90	[30]
Decompensated cirrhosis	0.60	0.50–0.70	[30]
Hepatocellular carcinoma	0.73	0.50–0.80	[30]
PegIFN	0.70	0.60–0.80	[30]
Discount rate	0.05	0–0.10	[13]

HBeAg: Hepatitis B e antigen; TDF: Tenofovir; ETV: Entecavir; PegIFN: Peginterferon; ADV: Adefovir; NA: Nucleos(t)ide analog.

Table 3: Base-case cost and effectiveness results of alternative treatment strategies.

Items	Strategy TDF	Strategy ETV	Strategy ETV + PegIFN	Strategy TDF + PegIFN	Strategy ETV – PegIFN	Strategy PegIFN + ADV	Strategy NA – PegIFN
Cost ($)	36,571	44,210	33,207	34,311	43,009	38,276	42,700
QALYs	14.58	16.78	13.23	13.12	13.72	13.14	16.24
Life expectancy (years)	15.08	17.05	14.25	14.15	14.64	14.36	16.64
CER ($/QALY)	2508	2635	2509	2615	3134	2912	2629
TDF as the comparator							
Incremental Cost ($)	Comparator	7639	−3364	−2260	6438	1705	6129
Incremental QALYs	Comparator	2.2	−1.35	−1.46	−0.86	−1.44	1.66
ICER ($/QALY)	Comparator	3472	2492	1548	−7486	−1184	3692
ETV as the comparator							
Incremental Cost ($)	−7639	Comparator	−11,003	−9899	−1201	−5934	−1510
Incremental QALYs	−2.2	Comparator	−3.55	−3.66	−3.06	−3.64	−0.54
ICER ($/QALY)	3472	Comparator	3099	2705	392	1630	2796

"–" Represents negative value. TDF: Tenofovir; ETV: Entecavir; PegIFN: Peginterferon; ADV: Adefovir; NA: Nucleos(t)ide analog; QALYs: Quality-adjusted life years; CER: Cost-effectiveness ratios; ICER: incremental cost-effectiveness ratios.

for life expectancy and QALYs, at 14.15 and 13.12 years, respectively.

Compared with TDF, treating CHB patients with ETV, ETV – PegIFN, NA – PegIFN, PegIFN + ADV, TDF + PegIFN, and ETV + PegIFN strategies increased costs by $7639, $6438, $6129, $1705, –$2260, and –$3364, respectively, gaining incremental QALYs by 2.20, –0.86, 1.66, –1.44, –1.46, and –1.35 years, respectively [Figure 3]. The ICERs of ETV and NA – PegIFN strategies were $3472/QALY and $3692/QALY, respectively, which were less than one time GDP per capita.

Compared with ETV, treating CHB patients with ETV + PegIFN, TDF + PegIFN, TDF, PegIFN + ADV, NA – PegIFN, and ETV – PegIFN increased costs by –$11,003, –$9899, –$7639, –$5934, –$1510, and –$1201, respectively, gaining incremental QALYs by –3.55, –3.66, –2.20, –3.64, –0.54, and –3.06 years, respectively [Figure 3].

One-way sensitivity analysis

A series of one-way sensitivity analyses were performed in base-case scenario for all parameters to test robustness of the results. A tornado graph, presented by net benefits, illustrated the top 15 influential parameters in the ETV monotherapy model [Figure 4]. In the model, the cost-effectiveness of ETV monotherapy was most sensitive to the probability of CHB to CHB with ETV monotherapy, followed by the probability of CHB to CHB with TDF monotherapy. All parameters had little impact on the robustness of the models.

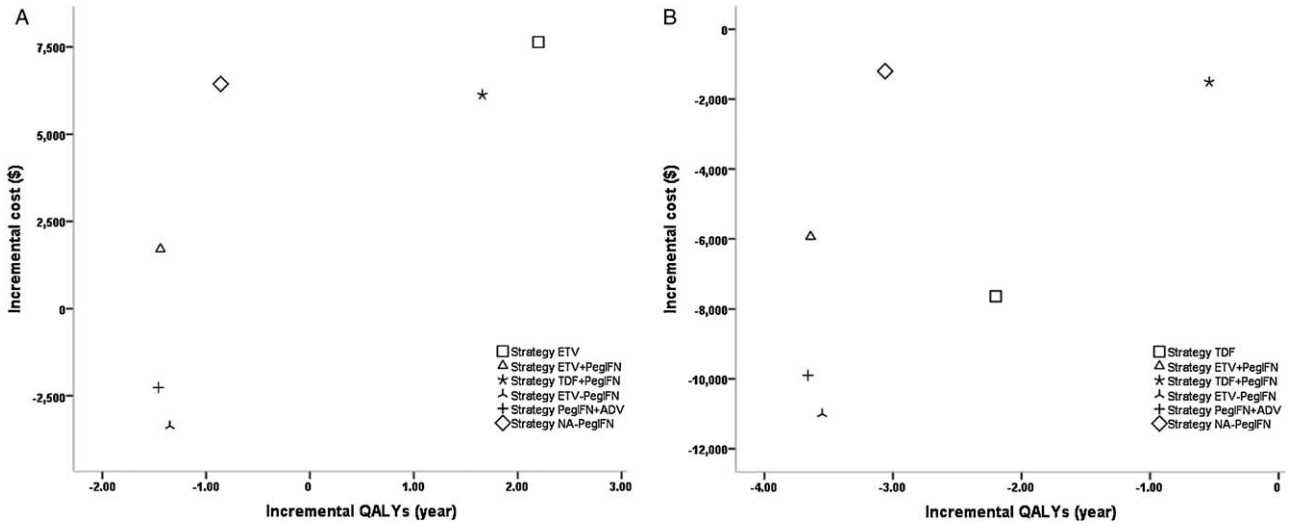

Figure 3: Cost-effectiveness of various treatments for HBeAg-positive chronic hepatitis B patients. The *x*-axis represents the life-time incremental quality-adjusted life years for each therapy, and the *y*-axis indicates the life-time incremental costs (US dollar). (A) TDF monotherapy served as a comparator; (B) ETV monotherapy served as a comparator. ADV: Adefovir; CHB: Chronic hepatitis B; ETV: Entecavir; HBeAg: Hepatitis B e antigen; NA: Nucleos(t)ide analog; PegIFN: Peginterferon; TDF: Tenofovir.

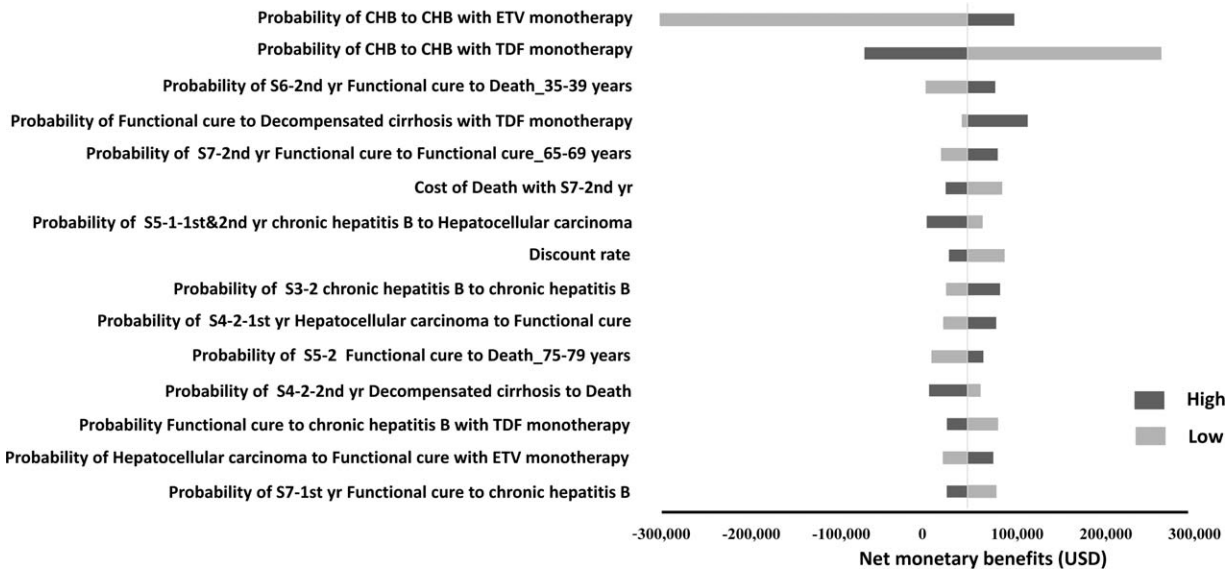

Figure 4: One-way sensitivity analyses (net benefit). Tornado diagram comparing one-way sensitivity analyses of the most influential parameters on the cost-effectiveness of ETV in the HBeAg-positive model at a threshold of US$26,517/quality-adjusted life-year gained. CHB: Chronic hepatitis B; ETV: Entecavir; HBeAg: Hepatitis B e antigen; S3: Strategy ETV – PegIFN; S4: Strategy ADV + PegIFN; S5: Strategy NA – PegIFN; S6: Strategy ETV + PegIFN; S7: Strategy TDF + PegIFN; TDF: Tenofovir; USD: US dollars; Yr: Year.

Probabilistic sensitivity analysis

PSA with 5000 Monte Carlo simulations was conducted to assess the impact of uncertain parameters varying simultaneously within defined distributions. The results are displayed in the cost-effectiveness plane [Figures 5 and 6] and the cost-effectiveness acceptability curves in Figure 7. PSA results demonstrated that the cost per QALY gained was lower than the three times of GDP per capita in China in 92.04% of simulations in the optimal strategy.

Discussion

In this study, we evaluated the cost-effectiveness of seven representative treatment strategies for HBeAg-positive CHB patients in China. Our analyses suggested that first-line NA monotherapy (ETV or TDF) was more cost-effective compared with combination approaches for HBeAg-positive CHB patients in China in terms of functional cure. Compared with ETV monotherapy, ETV generated the highest costs and the highest QALYs. Compared with TDF monotherapy, ETV monotherapy and NA – PegIFN strategy were cost-effective. A series of sensitivity analyses were performed to overcome the impact of the uncertainty of parameter estimates on the model results. The result of PSA confirmed that ETV monotherapy had the highest probability of cost-effectiveness.

It is universally acknowledged that the rates of HBsAg loss with current drugs are generally low but may largely differ

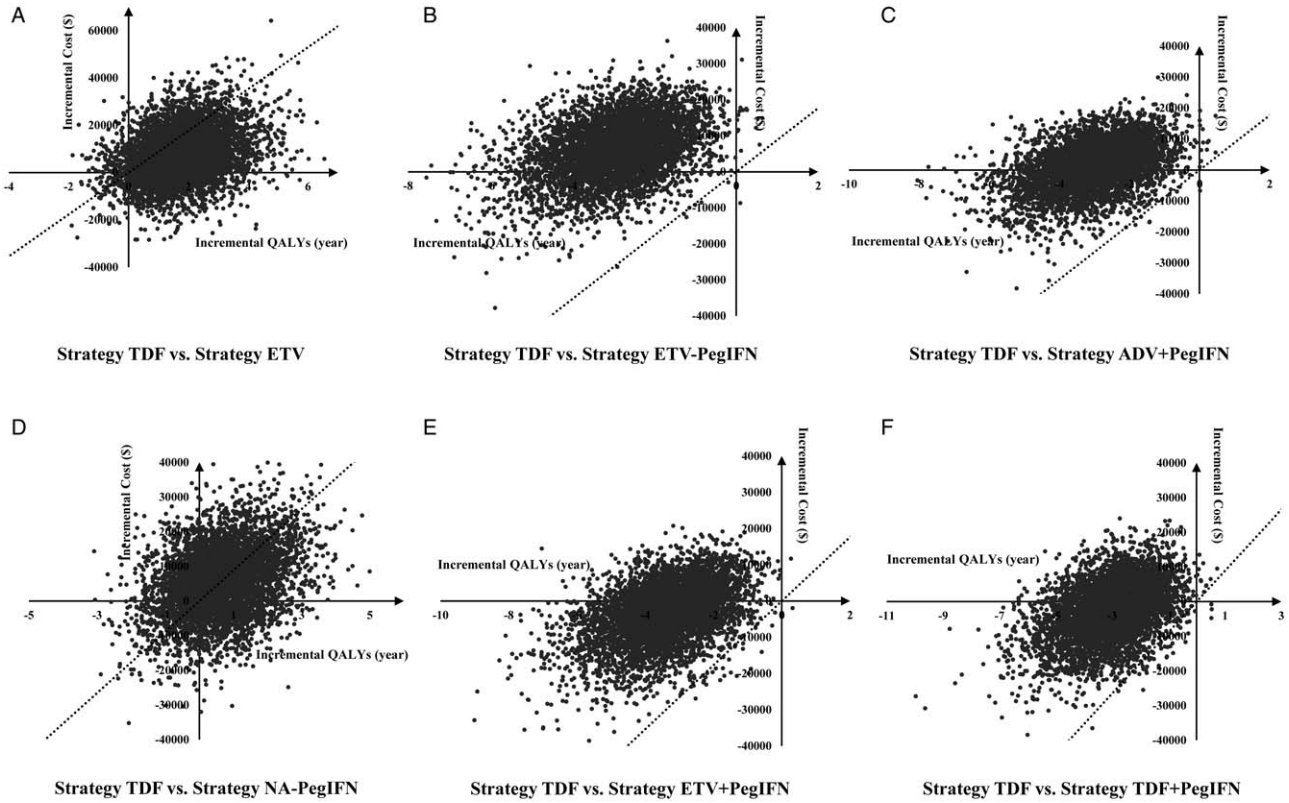

Figure 5: Probabilistic results of the incremental cost-effectiveness comparisons between TDF monotherapy and other strategies for a simulation of 1000 patients. The *y* axis represents the incremental costs. The *x* axis represents the incremental quality adjusted life years (QALYs) gained. ADV: adefovir; ETV: entecavir; NA: nucleos(t)ide analogue; PegIFN: peginterferon; TDF: tenofovir.

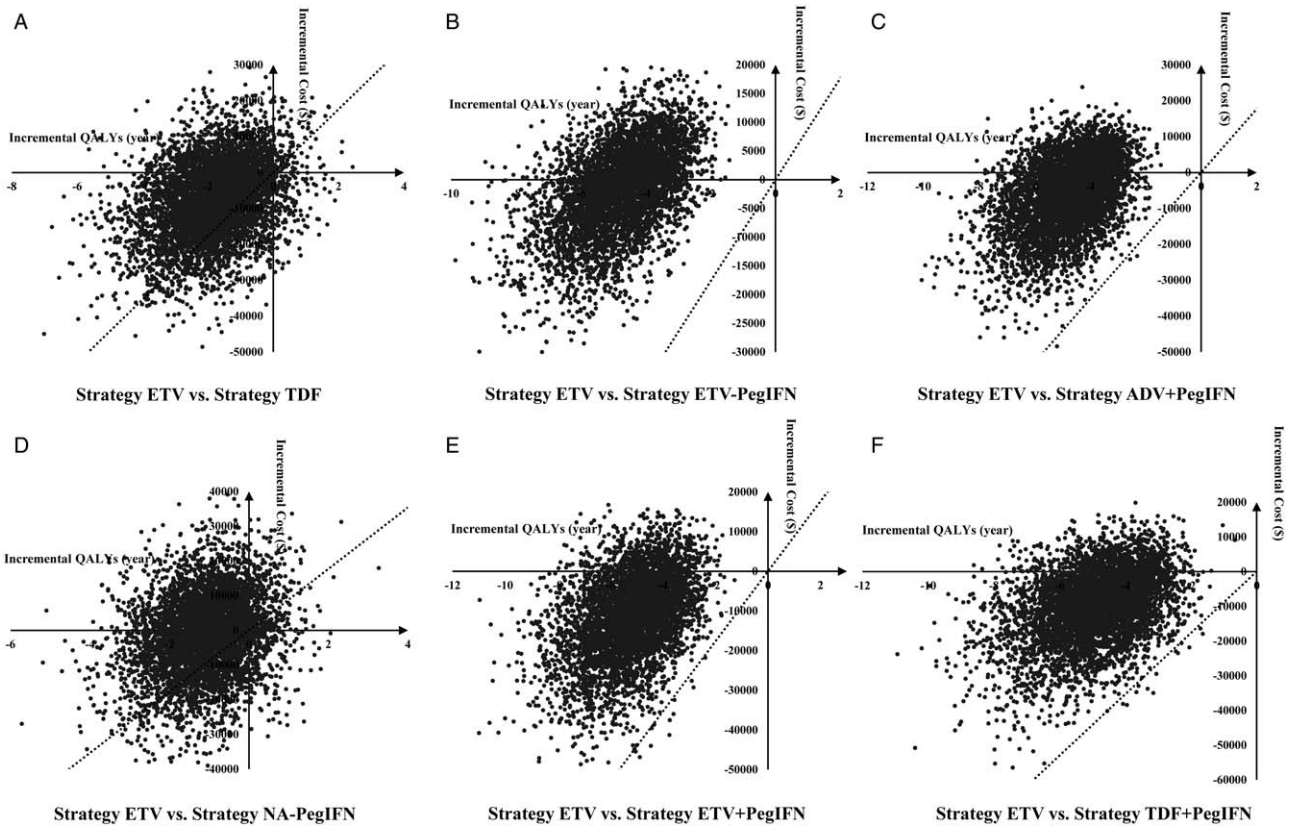

Figure 6: Probabilistic results of the incremental cost-effectiveness comparisons between ETV monotherapy and other strategies for a simulation of 1000 patients. The *y* axis represents the incremental costs. The *x* axis represents the incremental quality adjusted life years (QALYs) gained. ADV: adefovir; ETV: entecavir; NA: nucleos(t)ide analogue; PegIFN: peginterferon; TDF: tenofovir.

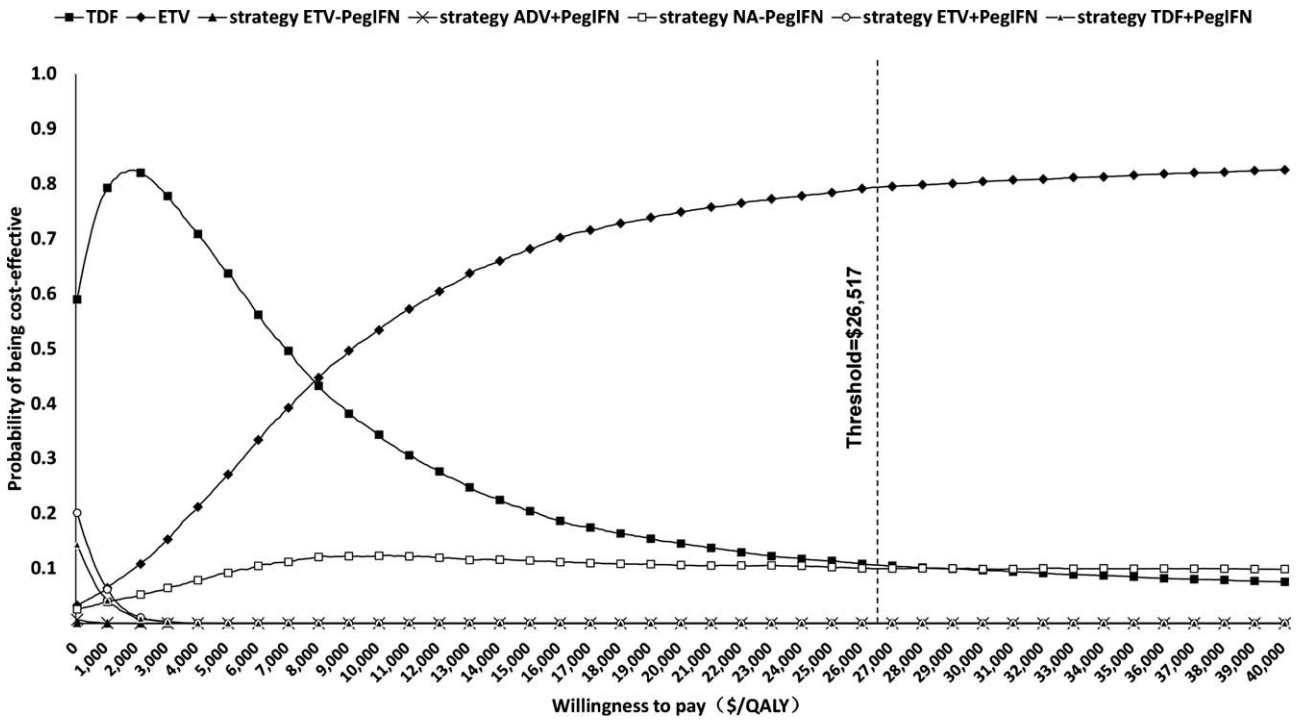

Figure 7: Cost-effectiveness acceptability curves of different treatment strategies for hepatitis B e-antigen-positive chronic hepatitis B patients. The *y*-axis indicates the probability that the therapy is cost-effective. The *x*-axis represents the willingness-to-pay threshold. ADV: Adefovir; CHB: Chronic hepatitis B; ETV: Entecavir; HBeAg: Hepatitis B e antigen; NA: Nucleos(t)ide analog; PegIFN: Peginterferon; TDF: Tenofovir.

in various approaches.[7-11] Many previous studies revealed that the combination therapies compared with monotherapies could increase the rate of HBsAg loss in selected patients.[7-11] Our analyses confirmed that the cumulative functional cure patient numbers for combination strategies were indeed greater than those for ETV or TDF monotherapy. However, even considering the superiority in achieving functional cure, combination strategies were still not cost-effective in our analyses compared with ETV or TDF monotherapy. In contrast, ETV and TDF monotherapy dominated QALYs relatively. Supplementary Table 1, http://links.lww.com/CM9/A92 showed that there would be less cumulative deaths in ETV and TDF monotherapies. Thus, from the lifelong perspective, ETV or TDF monotherapy was projected to have better performance of preventing disease progression.[16-24] Moreover, not all combination therapy approaches are valuable to the Chinese people. The study of strategy TDF + PegIFN suggested that a significant improvement in the rate of HBsAg loss was mainly observed in genotype A patients with TDF plus PegIFN treatment.[7] Meanwhile, genotypes B and C, which are the most prevalent genotypes in China, had limited potential benefit of this therapy strategy for HBsAg loss.[16] In addition, strategy NA – PegIFN seemed cost-effective compared with TDF monotherapy; however, due to PegIFN increases the risk of adverse effects, this strategy should be carefully assessed in each individual patient weighing all potential advantages and disadvantages. Furthermore, lamivudine or telbivudine was not recommended as the prior anti-viral treatment considering its relatively worse efficacy and higher resistance rate.[2,3] Besides that, the robustness of HBsAg loss after off-treatment of PegIFN should be considered. Whether the short-term benefits of combination approaches on HBsAg loss can be enhanced or translated into long-term benefits remains unknown. Further investigations are still needed to clarify this important issue. Thus, strategy NA – PegIFN has limited value.

Functional cure is indeed an ideal endpoint that we exert all our efforts to realize; however, considering the whole progression of the disease, not all approaches with superiority in functional cure are cost-effective. The patient selection, timing, and the duration of the combination strategy may be the key factors. However, those issues still need further investigation. We must recognize that the benefits of the current combination approaches are limited compared with ETV or TDF monotherapy. Recently, the prices of TDF and ETV fell sharply in China and become affordable and relatively low price in China which enhanced their superiority in cost-effectiveness. Therefore, the current combination approaches have limited value to promote in clinical practice.

In this study, considering the superiority of combination strategies in achieving HBsAg loss, we used functional cure as one of states with other five states including CHB, compensated cirrhosis, decompensated cirrhosis, HCC, and death. In addition, due to well-designed combination therapy studies in Chinese HBeAg-positive CHB patients were limited, we chose five high-quality combination studies, which were mentioned in international guidelines or expert consensus and mainly conducted in the Chinese

population, to represent different types of combination strategies.

There are several limitations to this study. First, due to the lack of long-term (more than 10 years) observational data in the Chinese population, including long-term oral regimens and PegIFN discontinuation follow-up, the parameters used in the model to represent more than 10 years of treatment were assumed to be equal to those for the previous 10 years; as a result, the model might not exactly reflect the real-world experience. Second, all patients in the model were assumed to receive life-long NA treatment without considering compliance with NA treatment, which might overestimate the effectiveness of TDF and ETV treatment.

In conclusion, the results from the present analyses suggest that first-line monotherapy may be more cost-effective than combination strategies for HBeAg-positive CHB patients in China.

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Conflicts of interest

Jin-Lin Hou is a consultant for AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson, and Roche and received grants from Bristol Myers Squibb and Johnson & Johnson. The remaining authors have nothing to disclose.

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