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Cost-Effectiveness Analysis of Alternative Antiviral Strategies for the Treatment of HBeAg-Positive and HBeAg-Negative Chronic Hepatitis B in the United Kingdom

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ABSTRACT

Background: Seven drugs are licensed for the treatment of chronic hepatitis B (CHB) in the United Kingdom. Which initial treatment, secondary therapy, and whether antivirals should be given alone or in combination are questions of considerable uncertainty. **Objective:** The aim of this model was to undertake a comprehensive economic evaluation of all antiviral treatments for CHB to recommend the most cost-effective therapeutic sequence. **Methods:** We developed a probabilistic Markov model to compare the cost-effectiveness of all clinically relevant antiviral treatment sequences for nucleos(t)ide-naive adults with hepatitis B e-antigen (HBeAg)-positive or HBeAg-negative CHB. Relative rates of HBeAg seroconversion and viral suppression were obtained from a network meta-analysis. Data on mortality, antiviral drug resistance, durability of response, adverse events, and costs were obtained from published literature. Results are reported in terms of lifetime costs, quality-adjusted life-years (QALYs), and expected net benefit. **Results:** In the base-case analysis, pegylated interferon alpha-2a (peg-IFN α-2a) followed by tenofovir disoproxil fumarate was most effective and cost-effective in HBeAg-positive patients, with a cost of £7488 per QALY gained compared with no treatment. In HBeAg-negative patients, peg-IFN α-2a followed by entecavir was most effective and cost-effective, with a cost of £6981 per QALY gained. The model was robust to a wide range of sensitivity analyses. **Conclusions:** Peg-IFN α-2a followed by tenofovir disoproxil fumarate or entecavir is the most effective antiviral treatment strategy for people with both variants of CHB. At a cost of less than £10,000 per QALY gained, these sequences are considered cost-effective in England and Wales. The results of this analysis were used to inform 2013 National Institute for Health and Care Excellence guideline recommendations.

Keywords: antiviral treatment, chronic hepatitis B, cost-effectiveness analysis, interferon-alpha, nucleosides, nucleotides.

Introduction

Chronic hepatitis B (CHB) is an infectious disease that affects approximately 400 million people worldwide [1]. The hepatitis B virus (HBV) infects liver cells and may lead to an immune response in which infected cells are killed but the virus is not eliminated. Over time, this can lead to cirrhosis, hepatocellular carcinoma (HCC), and death [1].

There are two molecular variants of HBV, which are defined according to the presence or absence of the hepatitis B "e" antigen (HBeAg). Over the course of infection, HBeAg-negative CHB may arise because of the selection of precore or other HBV mutant strains affecting the expression of HBeAg [2]. This variant is more frequently observed in older patients and is associated with worse outcomes than HBeAg-positive CHB [3].

Currently, seven drugs are licensed for the treatment of adults with CHB. Interferon-alpha (IFN-α) and pegylated interferon alpha-2a (peg-IFN α-2a) are injected subcutaneously, whereas nucleosides (lamivudine [LAM], entecavir [ETV], and telbivudine) and nucleotides (adefovir [ADV] and tenofovir [TDF]) are administered orally.

Interferon amplifies the immune response with the aim of achieving seroconversion and is administered over a 24- or 48-week course. Nucleos(t)ide analogues (NAs) inhibit viral

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replication and must be continued long-term. Although interferon may reduce the probability of requiring NA treatment, it is costly and associated with significant adverse effects. NAs are associated with relatively few adverse outcomes, but the effectiveness of some drugs is limited by high rates of antiviral resistance.

Patients may receive treatment of finite duration with IFN-α or peg-IFN α-2a before starting NA therapy, or they may initiate a long-term course of NA treatment de novo. If patients develop resistance to an NA, they may be switched to a complementary "rescue therapy" with a drug that does not share cross-resistance. Alternatively, they may receive "add-on" therapy as a means of controlling multidrug resistance.

The choice of initial therapy, rescue therapy, and whether rescue therapy should be given alone or in combination are issues of considerable uncertainty. Several economic evaluations have considered parts of this question in isolation, but none has simultaneously assessed all available alternatives in both HBeAg-positive and HBeAg-negative populations [4]. The aim of this model was to undertake a comprehensive economic evaluation of all antiviral treatments for CHB to recommend the most cost-effective therapeutic sequence. This model was developed by the guideline development group (GDG) of the 2013 National Institute for Health and Care Excellence (NICE) guideline Diagnosis and Management of Chronic Hepatitis B in Children, Young People and Adults [5]. The results of this analysis were used to inform recommendations within the guideline.

Methods

Model Overview

We developed a probabilistic Markov cohort model using TreeAge 2009 to estimate lifetime costs in 2011 British pounds and quality-adjusted life-years (QALYs) from a UK National Health Service (NHS) and personal social services perspective. Costs and QALYs were discounted at the standard annual rate of 3.5% [6]. Total net benefit (NB) was used to rank order the cost-effectiveness of each antiviral treatment strategy.

Figure 1 illustrates the key health states used to represent the natural history of CHB and possible transitions between them. Baseline population characteristics and baseline transition probabilities are reported in Table 1. The model structure and baseline transition probabilities were informed by our review of previously published CHB models [7–9]. Structural decisions and probability estimates were discussed with clinical experts from the GDG to ensure that the assumptions and choice of data were directly relevant to the United Kingdom (see Appendix Tables 4 and 5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.007). Relative estimates of effectiveness are reported in Table 1 and described below.

Patients entered the model as NA-naive adults with either HBeAg-positive or HBeAg-negative CHB. Approximately one-fifth of HBeAg-positive patients had evidence of active cirrhosis at baseline, compared with one-third of the HBeAg-negative population [12]; the remaining patients had active CHB that required treatment. *Active CHB* was defined as the presence of HB surface antigen (HBsAg) for at least 6 months and HBV DNA of more than 2000 IU/ml. Consistent with the epidemiological literature, the average age at the start of treatment was 31 years for HBeAg-positive and 40 years for HBeAg-negative patients [12]. Most of the patients in both populations were male [12]. People coinfected with HIV and treatment-experienced patients with LAM-resistant HBV were excluded from the model.

At the end of each cycle, patients could remain in each health state, achieve spontaneous or treatment-induced responses (HBeAg seroconversion or viral suppression), or experience a reactivation of the disease [17]. Patients could also develop

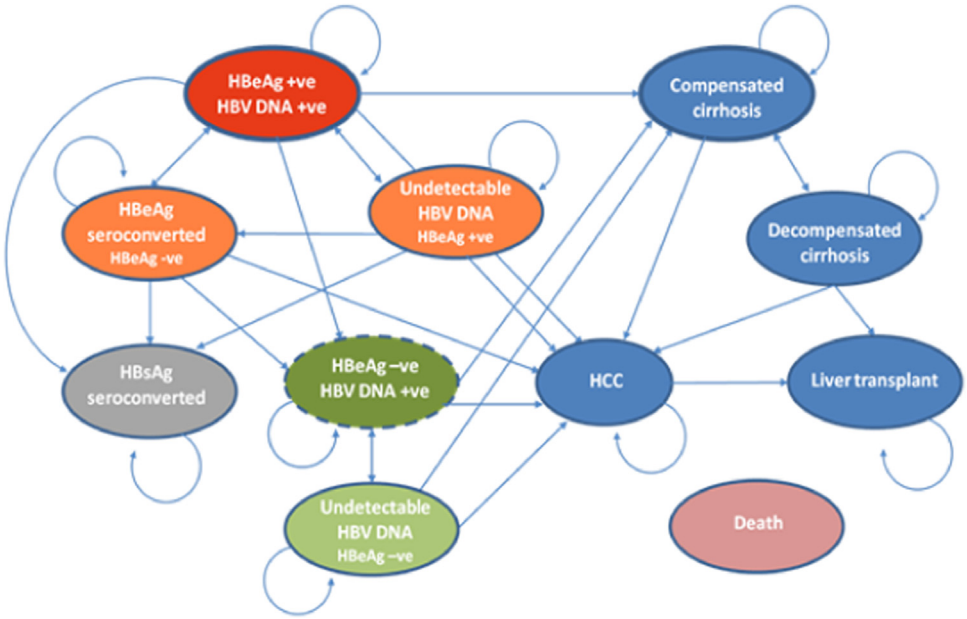

Fig. 1 – Natural history of CHB. A Markov model was developed to extrapolate the impact of short-term serologic and virologic changes on long-term outcomes in patients with either HBeAg-positive or HBeAg-negative CHB. Linear arrows indicate transitions between health states may occur at each cycle. Circular arrows indicate residual probabilities (i.e. one minus the sum of all other transition probabilities from that health state). All individuals were exposed to a background rate of mortality in each health state (not shown). (Color version of figure is available online.)

Table 1 – Baseline population characteristics, transition probabilities, and relative effectiveness.

Model parameter	Population					
	HBeAg-positive CHB			HBeAg-negative CHB		
	Point estimate	Range	Source	Point estimate	Range	Source*
Initial cohort characteristics						
Age (y)	31	24–36	[10]	40	36–45	[10]
Male:female ratio	3.2	1.5–4.9	[10]	10.5	3.9–17	[10]
Compensated cirrhosis	17%	10%–24%	[10]	35%	29%–38%	[10]
Median serum HBV DNA (log_{10} copies/mL)	9.2	1.7–905	[10]	7.6	5.8–1756.8	[10]
Median serum ALT (IU/L)	143.4	83.0– 252.5	[10]	145.5	69.0–229.5	[10]
Natural history of CHB*						
Active CHB to HBsAg seroconversion	1.8%	0.0%– 2.3%	[7]	0.4%	0.2%–0.9%	[10]
Active CHB to HBeAg seroconversion	10.7%	5.6%–17.7%	[7]	NA		
HBeAg seroconversion to active CHB	0.5%	0.3%–0.9%	[11]	NA		
HBeAg-positive CHB to HBeAg-negative CHB	5.0%	2.5%–7.5%	[12]	NA		
Active CHB to undetectable HBV DNA	5.3%	2.7%–8.8%	*	4.8%	1.2%–17.9%	[13]
Undetectable HBV DNA to active CHB	12.5%	0.0%–28.7%	[7]	12.5%	0.0%–28.7%	[7]
Active CHB to HCC	0.5%	0.4%–0.6%	[14]	0.5%	0.2%–1.5%	[11]
Active CHB to CC	5.3%	2.3%–11.8%	[12]	NA		
HBeAg seroconversion to HBsAg seroconversion	0.7%	0.3%–1.3%	[7]	NA		
HBeAg seroconversion to HBeAg-negative CHB	2.8%	2.2%–3.5%	[11]	NA		
HBeAg seroconversion to HCC	0.2%	0.1%–0.5%	[11]	NA		
Undetectable HBV DNA to HBeAg seroconverison	5.3%	2.7%–8.8%	*	NA		
Undetectable HBV DNA to HBsAg seroconversion	1.8%	0.0%–2.3%	[7]	NA		
Undetectable HBV DNA to HCC	0.1%	0.0%–0.2%	[14]	0.5%	0.2%–1.5%	[7]*
Undetectable HBV to CC	1.6%	0.5%–3.4%	[7]*	0.5%	0.0%–1.3%	[7]
CC to HCC	2.3%	1.0%–4.4%	*	2.3%	1.0%–4.4%	[7]*
CC to DC no treatment	5.0%	2.3%–9.5%	[7]	NA		
CC to DC on treatment	1.4%	0.8%–2.0%	[7]	NA		
DC to CC no treatment	0.0%	0.0%–0.0%	[7]	0.0%	0.0%–0.0%	[7]
DC to CC first year on treatment	13.6%	10.5%–16.6%	[7]	NA		
DC to HCC	2.9%	1.0%–6.3%	*	2.9%	1.0%–6.3%	[7]*
DC to liver transplant	1.6%	0.0%–20.0%	[15]*	1.6%	0.0%–20.0%	*
HCC to liver transplant	1.6%	0.0%–3.1%	[7]*	1.6%	0.0%–3.1%	*
CC mortality	3.7%	3.0%–4.4%	[10]	3.7%	3.0%–4.4%	[10]
DC mortality	15.6%	11.9%–20.3%	[10]	15.6%	11.9%–20.3%	[10]
HCC mortality	56.0%	43.0%–99.0%	[7]	56.0%	43.0%–99.0%	[7]
LT mortality first year	21.0%	6.0%–42.0%	[16]	21.0%	6.0%– 42.0%	[16]
LT mortality subsequent years	5.7%	2.0%– 11.0%	[16]	5.7%	2.0%– 11.0%	[16]
Relative risk of HBeAg seroconversion at 48 wk compared with placebo						
LAM	2.35	2.04–2.66	[5]	NA		
ETV	2.43	1.83–3.57	[5]	NA		
TDF	2.70	2.21–2.66	[5]	NA		
Peg-IFN α-2a + LAM	3.12	2.65–3.59	[5]	NA		
Peg-IFN α-2a	3.72	3.19–4.24	[5]	NA		
Relative risk of achieving undetectable HBV DNA at 48 wk compared with placebo						
LAM	25.60	25.53–25.67	[5]	10.12	9.92–10.32	[5]
ETV	42.85	42.46–43.24	[5]	13.63	12.96–14.30	[5]
TDF	61.02	60.67–61.37	[5]	13.85	13.54–14.16	[5]
Peg-IFN α-2a + LAM	79.09	76.06–82.12	[5]	30.97	29.97–31.97	[5]
Peg-IFN α-2a	84.72	81.50–87.94	[5]	29.45	26.63–32.27	[5]

ALT, alanine aminotransferase; CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; ETV, entecavir; HBV, hepatitis B virus; IU, international units; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; LAM, lamivudine; LT, liver transplant; NA, not applicable; Peg-IFN α-2a, pegylated interferon alpha-2a; TDF, tenofovir.

* See Supplemental Material files found at http://dx.doi.org/10.1016/j.jval.2015.05.007 for a detailed calculation of each transition probability.

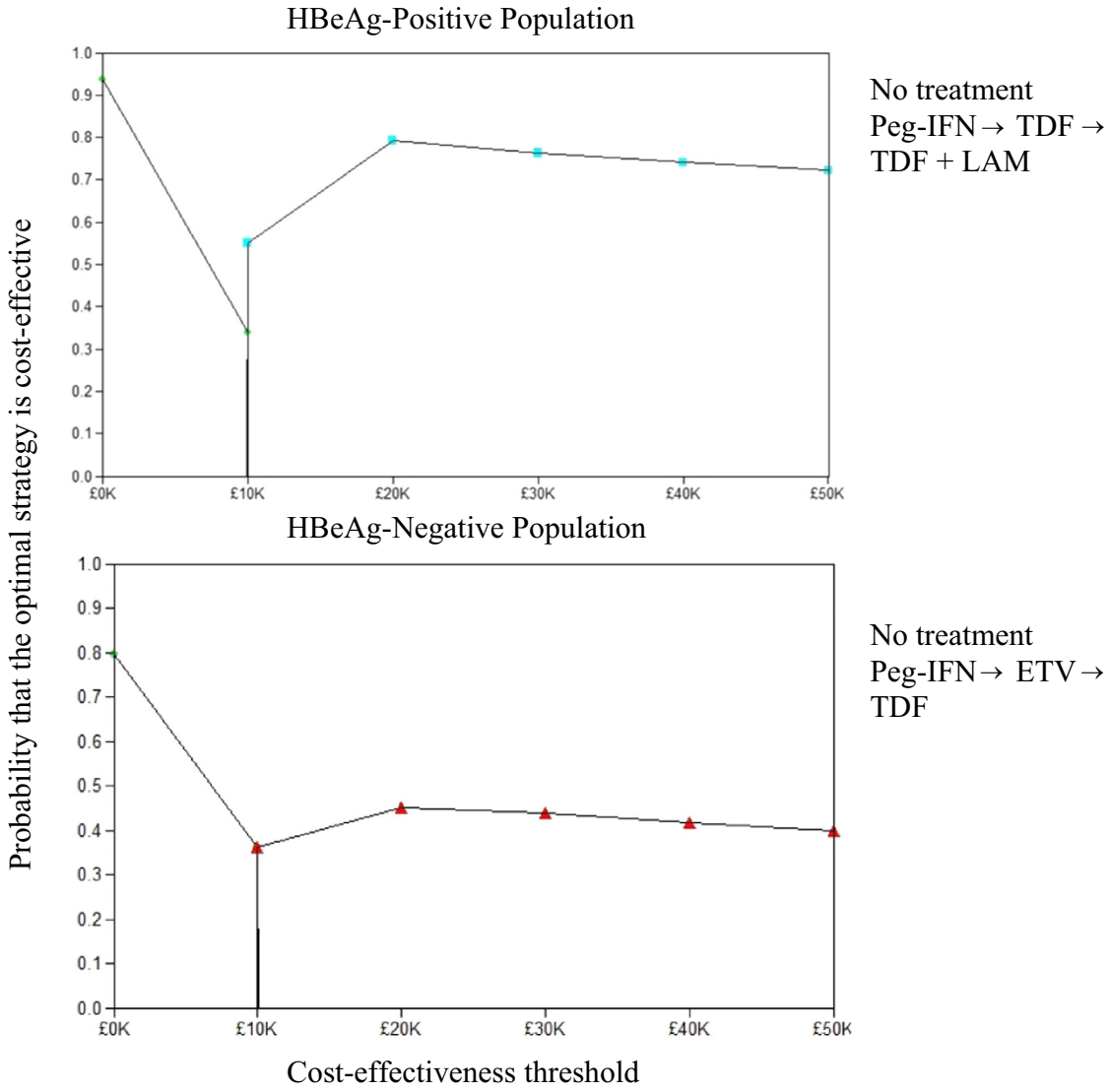

Fig. 2 – Cost-effectiveness acceptability frontier. Abbreviations: Peg-IFN, pegylated interferon alpha 2a; LAM, lamivudine; ETV, entecavir; TDF, tenofovir. (Color version of figure is available online.)

resistance to the active treatment, resulting in virologic breakthrough and a change in treatment (not illustrated). A proportion of patients with HBeAg-positive CHB could develop HBeAg-negative CHB or transition from HBeAg seroconversion to HBeAg-negative CHB. Patients who did not respond to treatment entered progressive stages of liver disease such as compensated or decompensated cirrhosis at rates that varied according to viral load. They may remain in the compensated stage or transition from decompensated to compensated cirrhosis spontaneously or as a result of treatment. People in both decompensated cirrhosis and HCC health states were considered eligible for liver transplant. Patients could develop HCC or die at any stage of the model (see Figs. 1 and 2 in Supplemental Materials found at: http://dx.doi.org/10.1016/j.jval.2015.05.007).

The baseline risk of all-cause mortality was based on UK life tables [18] multiplied by the standardized risk of mortality in people with CHB reported by the REVEAL trial [19]. A mortality risk in excess of baseline was applied to people with compensated cirrhosis [10], decompensated cirrhosis [10], HCC [7], and liver transplant [16].

Comparators

Three key considerations influenced the selection of clinically appropriate treatment alternatives:

1. In the United Kingdom, LAM alone is no longer considered an effective monotherapy based on extremely high rates of resistance; however, it may be used in combination with other NAs.
2. Resistance to LAM is known to confer cross-resistance to other nucleosides that share the same site of action and reduces sensitivity to ETV. When patients are treated sequentially with drugs that have overlapping resistance profiles, the second therapy is not only less effective but may also lead to multidrug resistance [20].
3. Certain combinations of drugs may cause renal toxicity when used in combination (e.g., ADV and TDF).

To improve the efficiency of the model, several additional factors were used to limit the number of included comparators:

1. On the basis of results of the network meta-analysis (NMA) conducted for this analysis, ADV was not considered a part of

any treatment sequence given that TDF was found to be both more effective and less costly [5,21].
2. Because of an absence of evidence, peg-IFN α-2a plus LAM was the only combination first-line therapy included in the NMA.
3. Peg-IFN α-2b was not included as a comparator in the model because there are currently no published randomized controlled trials of peg-IFN α-2b compared with other therapies included in the clinical review. Therefore, peg-IFN α-2b could not be included in the NMA.
4. Telbivudine was excluded from the model because it is not recommended for the treatment of CHB in the United Kingdom [22].
5. Emtricitabine was not included in the model because it is not licensed for the treatment of CHB in the United Kingdom.

Nineteen clinically relevant treatment sequences were determined on the basis of these criteria. Treatment options included peg-IFN α-2a, peg-IFN α-2a with LAM, TDF, and ETV. In those who failed to achieve HBeAg seroconversion or viral suppression, LAM, TDF, and ETV were included as second- and third-line treatments. All strategies assumed that resistance or withdrawal from third-line NA therapy was followed by best supportive care. A full list of included and excluded treatment sequences can be found in Appendix Tables 1 and 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.007.

Treatment Effectiveness

Treatment effectiveness was evaluated in terms of different rates of HBeAg seroconversion, undetectable HBV DNA, antiviral resistance, treatment durability, and withdrawal because of adverse events. It was conservatively assumed that antiviral treatment did not affect the probability of HBsAg seroconversion.

The probability of achieving undetectable HBV DNA and HBeAg seroconversion with each antiviral was based on the NMA conducted as part of the NICE clinical guideline [5]. Four NMAs (one per population per outcome) were conducted. Data within each NMA were obtained by a systematic review of MEDLINE, Embase, and the Cochrane Library from their date of inception to October 10, 2012. Only English-language randomized controlled trials that reported the proportion of patients who achieved undetectable HBV DNA or HBeAg seroconversion in treatment-naive adults were included. Undetectable HBV DNA was defined by a viral load of less than 300 copies per ml (approximately 54 IU/ml [23]). NAs were evaluated after 48 to 52 weeks of treatment and peg-IFN α-2a at 26-week follow-up. Treatment doses were within the therapeutic range indicated by the British National Formulary [24]. For full methods and results, refer to http://www.nice.org.uk/guidance/cg165/evidence/cg165-hepatitis-b-chronic-appendices-ho2.

Based on the results of this NMA, the risk of achieving undetectable HBV DNA and HBeAg seroconversion for each drug relative to placebo is reported in Table 1. The probability of achieving each outcome was calculated by applying each relative risk to the relevant baseline transition probability (Table 1). When two NAs were used in combination, the most effective component was used to inform each probability. People with cirrhosis were treated with TDF, which has been shown to be the most effective and cost-effective drug for this condition based on previous modeling [5]. It was assumed that previous exposure to peg-IFN α-2a had no impact on NA efficacy. In other words, NAs were assumed to have the same effectiveness if used following peg-IFN α-2a failure as if they were used in peg-IFN α-2a–naive patients.

The model allowed for patients to switch or add-on treatment after the development of resistance to NAs. Rates of resistance to each drug over 5 years were collected from published trials (Table 2). Few studies have evaluated rates of resistance over the longer term. In the absence of available data, resistance was assumed to occur at a constant rate beyond 5 years. This is consistent with assumptions made by other cost-effectiveness studies [7,25,26]. Resistance to third-line agents resulted in a switch to best supportive care.

In the absence of other data, estimates of serologic and virologic treatment durability (i.e., maintenance of response) were obtained from recent clinical practice guidelines [1,27] in which HBeAg seroconversion was reported to be less durable after discontinuation of NA compared with peg-IFN α-2a therapy in HBeAg-positive CHB. In contrast, viral suppression was reported to be more durable after discontinuing NAs than peg-IFN α-2a in people with HBeAg-negative CHB (Table 3). It was assumed that the probability of relapse was unrelated to the time spent in the inactive carrier state.

NAs are generally well tolerated, with adverse-effect profiles similar to that of placebo [45]. Rare instances of myopathy, neuropathy, and pancreatitis in LAM and ETV and nephrotoxicity to TDF have been reported. In contrast, interferons are associated with influenza-like symptoms, depression, and anxiety. The cost of monitoring for toxic adverse effects for each drug is described below. It was assumed that patients who experience these adverse effects would discontinue therapy; withdrawal rates for each therapy are described in Table 3.

Quality of Life

Most of the previously published economic evaluations of CHB [7,16,26,46] used utility estimates from Levy et al. [47], which were derived from 534 CHB-infected and 600 uninfected respondents across six countries. More than 60% of the infected respondents were from Hong Kong and China and expressed significantly different outcomes compared with the remaining countries.

More recently, Woo et al. [34] elicited utilities from 400 Canadians with CHB using the standard gamble technique to elicit values for six CHB-related health states: CHB, compensated and decompensated cirrhosis, HCC, and liver transplantation within and after the first year; utilities are reported in Table 2.

These values represent a greater sample size from a more applicable population. The impact of using utilities by Levey is explored in sensitivity analysis.

Because we assumed that patients would immediately discontinue or switch drugs (and therefore recover) if they experienced an adverse event, the potential impact of adverse events on quality of life was not included in the model. The effect of this assumption was explored in sensitivity analysis.

Costs

Drug acquisition costs were obtained from the British National Formulary [24]. Both resource use and unit costs associated with monitoring for toxicity and response to therapy were informed by expert opinion. Estimates of resource use associated with managing patients on each drug were solicited from clinical experts. Unit costs associated with each laboratory test, diagnostic test, and outpatient visit were based on 2011 NHS Reference Costs [48] and expert opinion.

If a patient received a combination of drugs, the more costly of the two monitoring strategies was applied to account for the maximum number of tests. The cost of managing progressive liver disease was based on a study by Brown et al. [49] and

Table 2 – Antiviral treatment durability, adverse events, quality of life, and costs.

Model parameter	Point estimate	Range	Source
Probability of HBeAg seroreversion in people with HBeAg-positive CHB*			
Peg INF α2a	3%	2%–4%	[27]
LAM and ETV	20%	15%–25%	[27]
TDF and ADV	25%	20%–30%	[27]
Probability of viral reactivation in people with HBeAg-negative CHB*			
Peg-IFN α-2a	95%	90%–100%	[1]
LAM and ETV	90%	85%–95%	[27]
TDF and ADV	92%	87%–97%	[27]
Withdrawal due to adverse events			
Peg INF α-2a	5%	3%–6%	[28–30]
LAM	5%	3%–7%	[31,32]
ETV	1.5%	1%–2%	[31,32]
TDF	3%	1%–5%	[33]
Health state utilities			
HBsAg seroconversion	0.87	0.85–0.88	[34]
Active noncirrhotic CHB	0.87	0.85–0.88	[34]
Viral suppression	0.87	0.85–0.88	Assumed equal to active CHB
Compensated cirrhosis	0.81	0.75–0.86	[34]
Decompensated cirrhosis	0.49	0.22–0.75	[34]
Hepatocellular carcinoma	0.85	0.76–0.95	[34]
Postliver transplant	0.72	0.60–0.83	[34]
Cost of antiviral drug treatment (£) (per year)			
Peg INF α-2a (135 μg injection)	5,971	4,862–7,204	[24]
LAM (100 mg/d)	1, 015	829–1,224	[24]
ADV (10 mg tablet/d)	3,610	2,939–4,344	[24]
ETV (0.5 mg and 1 mg tablet/d)	4,420	3,594–5,319	[24]
TDF (245 mg tablet/d)	2,925	2,382–3,527	[24]
Cost of monitoring for toxicity and response to therapy (£) (per year)			
Peg INF α-2a	832	679–1,000	See Appendix Table 1
LAM and ADV	871	871–1,057	See Appendix Table 1
TDF and ETV	876	711–1,057	See Appendix Table 1
Cost of managing liver disease due to CHB (£) (per year)			
Compensated cirrhosis	2,235	1,815–2,692	[34]
Decompensated cirrhosis	8, 930	7,251–10,755	[34]
Hepatocellular carcinoma	9,427	7,667–11,346	[34]
Transplantation	47,737	38,770–57,578	[34]
First-year posttransplant	16,357	13,298–19,736	[34]
Posttransplant	10,210	8,277–12,274	[34]

All costs and probabilities were reported on an annual basis.
ADV, adefovir; CHB, chronic hepatitis B; ETV, entecavir; HBsAg, hepatitis B surface antigen; LAM, lamivudine; Peg-IFN α-2a, pegylated interferon alpha-2a; TDF, tenofovir.
* Where a range was reported, the mean value was used to inform the point estimate. Where only a mean value was reported, a range of 10% was assumed.

inflated according to the pay and prices index [48]. A detailed breakdown of costs is provided in Table 2.

Uncertainty

Uncertainty surrounding the natural progression of CHB was accounted for by assigning a probability distribution to each parameter on the basis of point estimates and standard errors. To preserve correlations in treatment effects, uncertainty in the probability of response to treatment was obtained directly from the joint posterior distributions of the Markov chain Monte-Carlo analysis reported in WinBUGS. The model was run 1000 times, each time randomly selecting a value for each parameter from its respective distribution. Mean costs and QALYs were calculated by averaging across all simulations. Average NB was also calculated using a threshold value of £20,000 per QALY gained. The proportion of model simulations in which each comparator had the highest total NB was used to rank order the cost-effectiveness of each strategy and generate the cost-effectiveness frontier. Sensitivity analyses were conducted to evaluate the impact of using alternative data and assumptions on the base-case results.

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The sponsor of this study had no role in study design, data collection, analysis, interpretation, or writing of this report. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

Results

Base Case

The results of the model showed that peg-IFN α-2a is the most effective first-line antiviral treatment for people with HBeAg-

Table 3 – Probability of antiviral resistance in NA-naive patients.

Treatment	Cumulative resistance				
	Year 1	Year 2	Year 3	Year 4	Year 5
HBeAg-positive CHB					
LAM	24.0% [35,36]	42.0% [35,36]	53.0% [35,36]	70.0% [35,36]	80.0% [35,36]
ETV	0.2% [37]	0.3% [37]	1.2% [37]	NR*	NR*
TDF	0.0% [33,38]	0.0% [33,38]	0.0% [33,38]	NR*	NR*
HBeAg-negative CHB					
LAM	6.3% [39]	50.0% [40,41]	70.0% [42]	70.0% [42]	NR*
ETV	0.0% [39,43]	0.0% [43]	1.2% [43]	NR*	NR*
TDF	0.0% [21,38,44]	0.0% [38]	0.0% [38]	NR*	NR*

CHB, chronic hepatitis; ETV, entecavir; HBeAg, hepatitis B e-antigen; LAM, lamivudine; NA, nucleos(t)ide analogues; NR, not reported; TDF, tenofovir.
* Where data were not identified in the literature, the probability from the previous year was applied.

positive and HBeAg-negative CHB. In those who fail to achieve HBeAg seroconversion or viral suppression, peg-IFN α-2a → TDF → TDF + LAM is the most effective sequence for people with HBeAg-positive CHB, with a cost of £7488 per QALY gained compared with no treatment. In those with HBeAg-negative CHB, peg-IFN α-2a → ETV → TDF is the most effective sequence, with a cost of £6981 per QALY gained compared with no treatment.

The NB framework allows us to rearrange the decision rule by calculating the probability that each strategy will have the greatest overall benefit at different threshold values. It provides a method for rank-ordering interventions by eliminating the need to consider dominance and calculate incremental cost-effectiveness ratios. Under this framework, we see that there is a high degree of uncertainty as to whether peg-IFN α-2a should be administered alone or in combination with LAM and whether ETV or TDF represents the most cost-effective second-line antiviral therapy. Table 4 presents total costs and QALYs for the five most cost-effective strategies for each population, ranked according to maximum expected NB, and Figure 2 shows the probability that the optimal option would be cost-effective at different thresholds.

Sensitivity Analyses

Threshold analyses showed that following initial peg-IFN α-2a therapy, ETV was the most cost-effective NA for HBeAg-positive patients when the cost of therapy was less than £3912 per year. In a separate analysis, ETV was also found to be more cost-effective than TDF at an increased rate of HBeAg seroconversion in HBeAg-positive patients. In HBeAg-negative patients, TDF followed by ETV was the most cost-effective NA following peg-IFN α-2a when the annual cost of ETV was less than £2936.

Limited data exist regarding the off-treatment durability of NAs; that is, the maintenance of response after discontinuation of treatment. In sensitivity analysis, we found that the conclusions of the analysis were unchanged if we assumed that serologic durability did not differ by drug class.

Prolonged use of TDF has been reported to lead to reduced bone mineral density in patients with comorbid HIV [50].

Table 4 – Probabilistic results of base-case analysis.

Strategy	Total cost (£)	Total QALYs	ICER*	NMB (£)†	NMB rank (max – min)	Probability most CE (%)
HBeAg-positive CHB						
No treatment	32,754	14.618	Baseline	259,606	18	1
Peg-IFN α-2a → TDF → TDF + LAM	45,794	16.359	£7488	281,395	1 (6 – 1)	79
Peg-IFN α-2a + LAM → TDF → TDF + LAM	46,495	16.351	Dominated	280,523	2 (7 – 1)	18
Peg-IFN α-2a → TDF → ETV	46,856	16.358	Dominated	280,303	3 (7 – 2)	0
Peg-IFN α-2a → ETV → TDF	47,547	16.355	Dominated	279,554	4 (8 – 2)	1
Peg-IFN α-2a + LAM → TDF → ETV	47,680	16.349	Dominated	279,292	5 (10 – 2)	0
HBeAg-negative CHB						
No treatment	50, 388	12.18	Baseline	193,198	18 (19 – 1)	11
Peg-IFN α-2a → ETV → TDF	60, 241	13. 59	£6981	211,571	1 (14 – 1)	45
Peg-IFN α-2a + LAM → ETV → TDF	60,848	13.60	£4577	211,103	2 (14 – 1)	21
Peg-IFN α-2a → TDF → TDF + LAM	61,493	13.59	£4524	210,383	3 (15 – 1)	13
Peg-IFN α-2a + LAM → TDF → TDF + LAM	62,106	13.60	£4566	209,913	4 (15 – 1)	9
Peg-IFN α-2a → TDF → ETV	63,202	13.59	£4,650	208,631	5 (16 – 2)	0

→, indicates; CE, cost-effective; ETV, entecavir; ICER, incremental cost-effectiveness ratio; LAM, lamivudine; NMB, net monetary benefit; Peg-IFN α-2a, pegylated interferon alpha-2a; QALY, quality-adjusted life-year; TDF, tenofovir.
* Compared with the next most effective strategy, less effective and more expensive interventions are said to be "dominated."
† At a threshold of 20,000 per QALY gained.

Prospective long-term studies, however, have not been published and patients are currently not routinely monitored. The model revealed that adding the cost of bone density testing to the cost of TDF monitoring did not change the conclusions of the analysis.

Few trials have evaluated the effectiveness of combination antiviral therapies. Reducing the effectiveness of TDF by half when administered in combination did not alter the conclusions of the model.

The results of the model were not affected by an increased rate of withdrawal due to adverse events associated with peg-IFN α-2a or a decrease in utility (of 0.01–0.10) for patients treated with peg-IFN α-2a.

On substituting the utility values from Woo et al. [34] with those from Levy et al. [47], we found that these values did not change the conclusions of the analysis. Because of the high probability of LAM resistance, clinical experts of the GDG did not think that adding LAM to peg-IFN α-2a or TDF was likely to be of value in the HBeAg-positive population (see Appendix Table 6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.007).

Discussion

We developed a probabilistic Markov model with a lifetime horizon for the economic evaluation of relevant combinations and sequences of drugs for the treatment of HBeAg-positive and HBeAg-negative CHB. The model was developed as part of the 2013 NICE guideline on the diagnosis and management of CHB [5]. Model parameters were based on best available data regarding the natural history of CHB, efficacy and tolerability of treatments, incidence of antiviral resistance, and durability of response. Costs were measured from a UK NHS perspective, and benefits were measured in terms of QALYs.

Our findings show that peg-IFN α-2a is the most cost-effective first-line antiviral treatment for people with CHB. In those who fail to achieve HBeAg seroconversion or viral suppression, TDF is the most effective and cost-effective second-line therapy for people with HBeAg-positive CHB, whereas ETV is the most effective and cost-effective second-line therapy for HBeAg-negative patients. Because the incremental cost-effectiveness ratio of each strategy falls well below NICE's £20,000 to £30,000 threshold, these strategies are likely to be considered cost-effective by UK policymakers. The results of this analysis were used to inform recommendations within the guideline [5].

Probabilistic sensitivity analysis revealed TDF to be the optimal NA in 97% of the simulations in the HBeAg-positive population that has failed treatment with peg-IFN α-2a. There was greater uncertainty in the HBeAg-negative population, in which ETV had a 66% probability of being the optimal NA after peg-IFN α-2a. This finding adds clarity to previously published cost-utility evaluations that have reported a high degree of uncertainty in the relative cost-effectiveness of TDF and ETV across both populations [4].

Results were robust to most of the sensitivity analyses. Although sensitive to the price of ETV, the cost required to result in a change in strategy was below the lower bound of our estimated range. The model was also sensitive to HBeAg seroconversion rates. Because raised alanine aminotransferase level is associated with higher rates of seroconversion, ETV may be the most cost-effective second-line therapy in HBeAg-positive patients with elevated alanine aminotransferase levels. In the base-case analysis, the addition of LAM to peg-IFN α-2a was associated with increased costs compared with peg-IFN α-2a alone, but there was uncertainty regarding its impact on effectiveness. As a result, peg-IFN α-2a alone was found to be the more cost-effective choice. ADV and LAM were not included as first-line treatment options because both are less effective and ADV is more expensive than TDF and ETV [5]; their inclusion would not change the results of the analysis.

Many studies have evaluated the cost-utility of antiviral therapies for the treatment of CHB; however, none has been as exhaustive in their inclusion of comparators as the one presented here. This is a critical difference, because the results of other analyses are conflicting and suggest that results are sensitive to the choice of comparators, clinical inputs, and assumptions regarding gaps in the evidence, particularly around drug resistance. Jones et al. [51] found that peg-IFN α-2a was more cost-effective than NA as a first-line treatment, though they did not include ETV or TDF. Two studies [4,7] found that regardless of HBeAg status, TDF was the most cost-effective first-line treatment, though they did not include peg-IFN α2a in their analyses. Earlier studies [16,46,52,53] found that ETV was most cost-effective, but only one of these analyses included peg-IFN α-2a [46] and none included TDF.

It is also the first to allow for transitions from HBeAg-positive to HBeAg-negative CHB and account for differences in the cost of monitoring according to the known adverse-effect profile of each drug class. Estimates of HBeAg seroconversion and HBV DNA suppression were obtained from the most recent available NMA, which is the only analysis to include trials of TDF conducted in people with CHB. We believe our model represents the most comprehensive representation of the disease process and treatment effectiveness to date.

In common with other models, ours is limited by a lack of long-term evidence of efficacy, resistance, and off-treatment durability (i.e., maintenance of response after discontinuation of treatment). In addition, few trials have evaluated the effectiveness of sequential treatment strategies in patients who develop resistance to the initial NA, the effectiveness and safety of most of the antiviral combinations, or on-treatment rates of HBsAg seroconversion.

Historically, NAs have been the most common first-line treatment for CHB due to relatively few adverse events compared with interferon. Previous evaluations of NAs assumed that adverse effects do not differ and have no effect on costs or quality of life [7,16,25,26], nor did they differentiate the cost of monitoring for toxicity between drugs [7,25,26,46,54]. The only previously published study to compare NAs with peg-IFN α-2a assumed that influenza-like symptoms would be treated by over-the-counter drugs and depression would be treated with 6 months of antidepressant medication at an average additional cost of $22 per patient [46]. Whether interferon has an adverse impact on quality of life compared with NAs has not been well studied, but sensitivity analysis showed that the model was not sensitive to any of these assumptions.

There remain many unanswered questions as a result of the relatively recent approval of these drugs for the treatment of CHB. Future clinical trials and long-term follow-up studies should include HBsAg seroconversion and off-treatment durability as outcomes because they represent the ultimate goal of therapy [55]. Definitive resistance to TDF has not been substantiated, but is a possibility. It is important to know whether resistance to ETV will increase over time and if combination therapy represents a long-term solution to the development of cross-resistance in patients with high levels of viremia. Prospective studies designed to capture the incidence of renal toxicity and changes in bone mineral density are also needed [50]. Finally, additional research to inform estimates of disutility associated with interferon treatment may be needed, though the model was not sensitive to variation in this parameter.

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Supplemental Materials

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