

The cost-effectiveness of long-term antiviral therapy in the management of HBeAg-positive and HBeAg-negative chronic hepatitis B in Singapore

L. F. Lacey¹ and E. Gane² ¹LaceySolutions Ltd, Skerries, Republic of Ireland; and ²Gastroenterology Department, Middlemore Hospital, Otahuhu, New Zealand

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SUMMARY. The purpose of this study was the economic evaluation of short-duration treatments of chronic hepatitis B (CHB) and longer duration antiviral treatment for up to 5 years. Two 10-health state Markov models were developed for hepatitis B e antigen (HBeAg)-positive and HBeAg-negative CHB patients respectively. The perspective of this economic evaluation was the Singapore healthcare system and CHB patient. The models followed cohorts of HBeAg-positive and HBeAg-negative CHB patients, respectively, over a period of 40 years, by which time the majority of the cohorts would have died if left untreated. Costs and benefits were discounted at 5% per annum. Annual rates of disease progression and the magnitude of treatment effects were obtained from the literature, with a focus on data obtained in Asian patients and meeting the criteria for therapy as described in internationally recognized management guidelines. Short-course therapy with α -interferon, or 1-year treatment

with pegylated interferon α -2a, lamivudine or adefovir had limited impact on disease progression. In contrast, treatment of CHB with antiviral therapy for 5 years substantially decreased the rate of disease progression. Treatment with lamivudine for 1-year is highly cost-effective compared with no treatment of CHB but has limited effect on reducing the rate of disease progression. Compared with 1-year treatment with lamivudine, sequential antiviral therapies for up to 5 years (i.e. lamivudine plus adefovir on emergence of lamivudine resistance or adefovir plus lamivudine on emergence of adefovir resistance) are highly cost-effective by international standards. These conclusions are robust to uncertainties in model inputs and are consistent with the findings of other recently published studies.

Keywords: α -interferon, adefovir, chronic hepatitis B, cost-effectiveness, lamivudine, pegylated interferon α -2a.

INTRODUCTION

Burden of chronic hepatitis B (CHB)

Worldwide more than 350 million people are chronically infected with hepatitis B virus (HBV) and at increased risk of death from cirrhosis of the liver and hepatocellular carcinoma (HCC) [1].

Abbreviations: ALT, aminotransferase; CC, compensated cirrhosis; CHB, chronic hepatitis B; DCC, decompensated cirrhosis; GNI, Gross National Income; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR QoL, health-related quality of life; ICERs, incremental cost-effectiveness ratios; PEG-IFN, pegylated interferon; PPP, purchasing power parity; QALY, quality adjusted life year.

Correspondence: Larry Lacey, PhD, The Beaches, South Strand, Skerries, County Dublin, Republic of Ireland. E-mail: larrylacey@unison.ie

Chronic hepatitis B is characterized by elevated serum aminotransferase (ALT) levels, high or fluctuating levels of serum HBV-DNA and active liver disease on biopsy [2]. Persistently elevated serum HBV-DNA levels are associated with increased long-term risk of cirrhosis, HCC and liver failure [3–5].

Persons with CHB may have hepatitis B e antigen (HBeAg) or antibodies to HBeAg (anti-HBe) in their sera. HBeAg seroconversion is associated with clearance of HBeAg from serum and with the appearance of anti-HBe. In persons who are HBeAg-positive, spontaneous HBeAg seroconversion can occur, often accompanied by a transient elevation in ALT levels. After HBeAg seroconversion, most persons have persistently normal ALT levels and suppressed levels of HBV-DNA, usually $<10^3$ copies/mL. However, almost 20% of patients have active liver disease following spontaneous HBeAg-seroconversion, due to the development of mutations in the precore stop codon or core promoter region. HBeAg-

negative, anti-HBe-positive type CHB is now recognized as an important and increasingly prevalent form of CHB, often associated with certain HBV genotypes (B, C and D but not A or G) [2]. More than 95% of HBV infections in Asia-Pacific countries are HBV genotypes B or C, explaining the high prevalence of HBeAg-negative CHB in this region.

Chronic hepatitis B remains an important public health problem in Singapore. Although the incidence of HBV infection is decreasing, as a result of the compulsory vaccination of babies born to infected mothers, nevertheless, between 160 000 and 230 000 Singaporeans were chronically infected as of 2001 [6]. The annual healthcare costs for the year 2003 of managing CHB, compensated cirrhosis (CC), decompensated cirrhosis (DCC) and HCC, were estimated by Li et al., 2004 [6]. Direct healthcare costs were classified in terms of outpatient consultations, inpatient admissions, antiviral drug treatment, other medications, laboratory tests, imaging and procedures. Lost income and lost productivity from illness will be additional indirect costs of CHB for the population. The annual cost of treatment increases dramatically as the disease progresses from CC to DCC or HCC respectively (Fig. 1).

Asian-Pacific guidelines for the management of CHB

The Asia-Pacific consensus guidelines (2005) [7] on the management of CHB state: '... sustained viral suppression is the key to the reduction or prevention of hepatic injury and disease progression. Therefore, the primary goal of treatment for CHB is to eliminate or permanently suppress HBV. The ultimate long-term goal of therapy is to prevent hepatic decompensation, to reduce or prevent progression to cirrhosis and/or HCC, and to prolong survival'.

Current treatment options

Conventional interferon- α has been used in the treatment of CHB for many years. Treatment is administered by subcutaneous injection, at a dosage of 5–10 MU three times a week for 4–6 months. Predictors of a nonresponse to interferon- α include Asian ethnicity, childhood infection, HBeAg-negative CHB, high serum HBV-DNA levels and low serum ALT levels [8].

Pegylated interferon α -2a is administered by subcutaneous injection (180 μ g) once-weekly for 48 weeks. Although

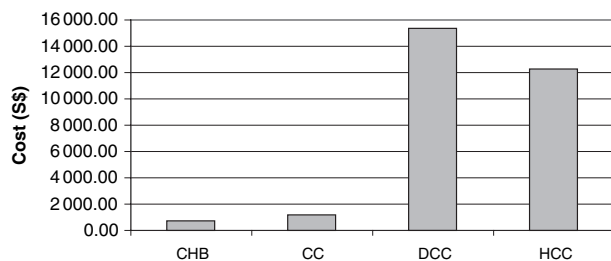


Fig. 1 Average cost per patient per disease state.

pegylated interferon has more antiviral efficacy than conventional interferon, the side-effect profile appears to be similar for both formulations [8].

For most patients with CHB, sustained viral suppression is only attainable through long-term nucleos(t)ide analogue therapy, as short-course therapies (4–12 months) only achieve sustained responses in a minority of patients [7].

The disadvantage of long-term antiviral monotherapy is the emergence of virological breakthrough secondary to the selection of drug resistant mutants [9]. If resistance develops in patients with compensated liver disease, an alternative antiviral drug should be used to control the disease. The patient can either have a second drug added or can be switched to another drug with the option of a 1- or 2-month overlap. If resistance emerges in patients with advanced liver disease, a second drug should be added to continued ongoing therapy with the first drug [9].

Lamivudine was the first nucleoside analogue to be licensed by the FDA for use in the chronic treatment of HBV infection in 1998. It is well tolerated and results in HBV suppression, ALT normalization and reduction of hepatic inflammation, although resistant strains emerge when lamivudine is used long term [10].

Adefovir dipivoxil is a new CHB antiviral treatment option that is well tolerated and long-term therapy results in incremental increase in rate of viral suppression below the level of detection, ALT normalization and histological improvement. In comparison with lamivudine, resistance to adefovir is delayed and less frequent [11].

Mechanisms of resistance to lamivudine and adefovir have distinct structural differences, and mutations conferring cross-resistance to both drugs have not been reported [9].

Economic evaluation of CHB treatments

A new treatment is usually regarded as cost-effective when it provides improved outcomes at an acceptable increased cost. Cost-utility is a form of cost-effectiveness analysis that involves the estimation of incremental cost per quality adjusted life year (QALY). QALYs take into consideration quality of life as well as quantity of life [12]. The 'Q' in QALY is a utility weight with values from 0 to 1. Death has a utility value of 0 and perfect health has a utility value of 1. Cost per QALY potentially allows for comparison between the cost-effectiveness of treatments in different disease areas with very different clinical outcome measures. This can facilitate healthcare resource allocation decisions [12].

The decision rule that payers apply to judging whether a new healthcare intervention is cost-effective is often not stated explicitly. However, US health economists generally agree that if an intervention can save 1 year of life for less than US\$ 50 000, it is cost-effective. Moreover, the UK National Institute for Clinical Excellence recently stated that the cost-effectiveness threshold is between £20 000 and £30 000 (approximately US\$ 36 000–54 000) [13].

As US\$ 1 = approximately S\$ 1.6, therefore a cost-effective threshold of \$50 000 is equivalent to approximately S\$ 80 000 in Singapore. However, adjusting for differences in purchasing power parity (PPP) based Gross National Income (GNI) per capita (2001) provides a cost-effectiveness threshold in Singapore of approximately S\$ 53 000 ($\$80\,000 \times \text{US\$ } 22\,850/\text{US\$ } 34\,280$) [14].

The purpose of this study was to establish the economic evaluation of short-duration treatments of CHB and long-duration antiviral treatments for up to 5 years. The context for the economic evaluation was the Singapore healthcare system and the healthcare needs of the CHB patient, in which only direct costs were included. As a result, indirect costs, such as lost productivity, from time off work due to illness or premature death were excluded.

METHODS

Treatment scenarios

Three different treatment scenarios were investigated:

1. No treatment
2. Short-duration therapy with conventional interferon- α (IFN) or 1-year treatment with pegylated interferon- α 2a (PegasysTM), lamivudine or adefovir
3. Five-year antiviral treatment with adefovir or lamivudine monotherapy, with switch to the alternative antiviral agent as 'rescue' therapy upon emergence of resistance (i.e. sequential monotherapy with either lamivudine followed by adefovir as rescue for lamivudine-resistance or adefovir followed by lamivudine as rescue for adefovir-resistance). If resistance emerged in patients with more severe disease (Metavir stage 3 or 4 fibrosis), the alternative antiviral agent was added to rather than switched with the initial agent and combination therapy with both adefovir plus lamivudine was continued long term.

Patient populations and model design

The pharmaco-economic models comprise two 10-health state Markov models, adapted from Crowley et al. (2000) [15]. The HBeAg-positive CHB model (Fig. 2a) included equal numbers of male and female patients from Singapore; the average patient age at start of treatment was 30 years [15,16]. HBeAg-seroconversion is the criterion for treatment cessation. The HBeAg-negative CHB model (Fig. 2b) included patients with an average age of 40 years at start of treatment, because of differences in age profiles between HBeAg-positive and HBeAg-negative populations studied in clinical trials (e.g. [17,18]). HBeAg-seroconversion is the only criterion for treatment cessation in HBeAg-negative CHB. Both models evaluate short-course treatments and longer duration treatments up to 5 years, with duration of

follow-up of a total of 40 years, by which time the majority of the cohort will have died, if left untreated. This enabled long-term costs and outcomes to be determined.

Data sources

Disease progression rates in the absence of treatment were derived mainly from a recent systematic literature review of CHB disease progression in the Asia-Pacific region and Africa [19] and are given in Table 1.

Disease progression rates in the presence of treatment were derived from studies investigating the effect of lamivudine treatment on disease progression and are given in Table 1.

HBeAg-seroconversion rates in HBeAg-positive patients were obtained from the published literature and are given in Table 2a. HBV treatment response rates in HBeAg-negative patients were obtained from the published literature and are given in Table 2b.

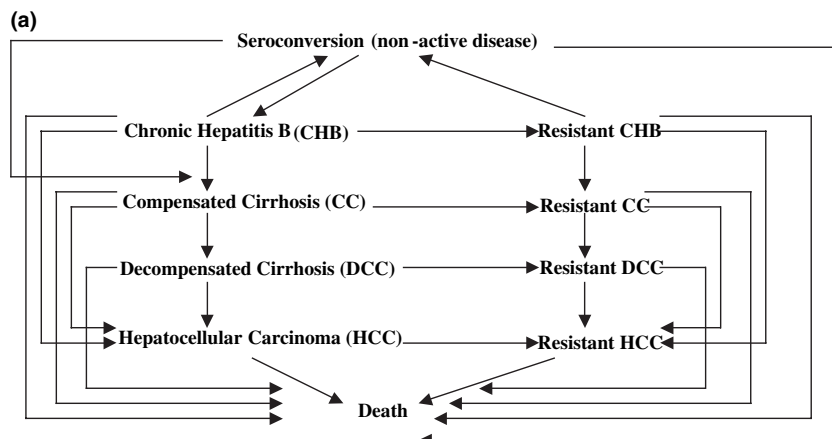
Healthcare costs used are those applying in Singapore. The healthcare costs for managing CHB, CC, DCC, HCC, for the year 2003 were obtained from Li et al. (2004) [6] (Fig. 1). Drug acquisition costs for CHB treatment alternatives for the year 2005 are given in Table 3.

Health state utilities were adapted from Crowley et al. (2000) [15] and are given in Table 4.

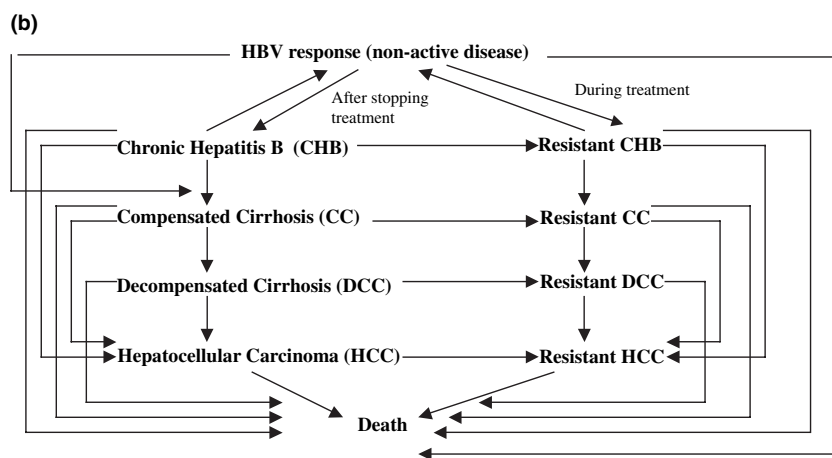
Treatment effects incorporated into the model

The following aspects of treatment effects were incorporated into the model:

1. *HBeAg-seroconversion or HBV response*: In HBeAg-positive CHB, HBeAg-seroconversion was used as a treatment-stopping criterion. In HBeAg-negative CHB, HBV response occurred when suppression of HBV viral load occurred to non-detectable levels (<300–400 copies/mL). Patients who underwent HBeAg-seroconversion or HBV response were assumed to have a much reduced rate of disease progression (limited to a 1% rate of progression to CC per annum).
2. *Seroconversion or loss of HBV response*: Seroconversion (loss of HBeAg-seroconversion and reoccurrence of active CHB) could occur in HBeAg-positive CHB and loss of HBV response (reappearance of detectable levels of HBV and active CHB) could occur in HBeAg-negative CHB (Fig. 2a,b).
3. *Antiviral resistance*: Emergence of resistance could occur with time during antiviral therapies (Fig. 2a,b). The rates of emergence of resistance for each treatment alternative were assumed to be the same in HBeAg-positive and HBeAg-negative CHB. Antiviral treatments were assumed to be ineffective in patients who developed antiviral resistance, unless the appropriate salvage therapy was administered.



Note: the 'resistant' health states pertain to the presence of antiviral resistance and assumes lack of treatment effect for antiviral mono-therapy



Note: the 'resistant' health states pertain to the presence of antiviral resistance and assumes lack of treatment effect for antiviral mono-therapy

Fig. 2 Structure of (a) HBeAg-positive chronic hepatitis B (CHB) Economic Model; (b) HBeAg-negative CHB Economic Model.

4. *Direct effects of treatment on reducing the rates of disease progression:* In addition to effects mediated by HBeAg-seroconversion or HBV response, direct effects of treatments on disease progression were factored in [16]. All short-duration treatments were assumed to have the same magnitude of direct effect on reducing the rates of disease progression as that achieved with lamivudine administered for 1 year. For long-duration therapies, the direct effects on disease progression lasted for the duration of therapy in those patients who did not develop antiviral resistance (Table 1).
5. *Effect of treatment on HR QoL as a result of side-effects:* The side-effects of interferon- α were assumed to have a negative effect on health-related quality of life (HR QoL) for the duration of treatment, reducing the CHB utility during treatment [15]. This was also assumed to be the case for pegylated interferon- α 2a but with an impact on CHB utility 50% less than that of interferon- α . Lamivudine and adefovir are well tolerated in CHB patients and

were assumed to have at least the same utility as untreated CHB patients (Table 4).

Model outcomes

During annual cycles of the Markov models the proportion of patients remaining alive in each health state and their associated healthcare costs and QALYs were determined for each treatment scenario. The total healthcare costs, life years and QALYs over the 40-year time horizon of the model were calculated for each treatment scenario, in the presence and absence of discounting.

Model assumptions

There is a hierarchy of assumptions. The patient population pertains to those CHB patients with ALT levels $\geq 2 \times$ ULN; all patients are in the CHB health-state at the outset and all are

Table 1 Disease progression rates for CHB derived from the literature and the effect of antiviral treatment on reducing the rates of disease progression

Model input	Treatment	Estimate	Source
Annual rate of progression from CHB to CC (HBeAg-positive)		0.0260	From Lin X et al. 2005 [19]*
Annual rate of progression from CHB to CC (HBeAg-negative)		0.0900	From de Franchis et al. 2003 [23]
% Decrease in annual rate of progression from CHB to CC in absence of resistance	LAM	85.7%	From Crowley et al. 2002 [16]
	IFN & PEG-IFN	85.7%	From Crowley et al. 2002 [16]
	ADF	85.7%	Assumption [†]
% Decrease in annual rate of progression from CHB to CC in presence of resistance	LAM; ADF	0.0000	Conservative assumption
Annual rate of progression from CHB to HCC		0.0066	From Lin X et al. 2005 [19]*
% Decrease in annual rate of progression from CHB to HCC in presence of resistance	LAM; ADF	0.0000	Conservative assumption
Annual rate of progression from CC to DCC		0.0420	From Lin X et al. 2005 [19]*
% Decrease in annual rate of progression from CC to DCC in absence of resistance	LAM	22.6%	From Liaw et al. 2004 [5] [‡]
	IFN & PEG-IFN	22.6%	Assumption
	ADF	22.6%	Assumption [†]
% Decrease in annual rate of progression from CC to DCC in presence of resistance	LAM; ADF	0.0000	Conservative assumption
Annual rate of progression from CC to HCC		0.0430	From Lin X et al. 2005 [19]*
% Decrease in annual rate of progression from CC to HCC in absence of resistance	LAM	17.6%	Derived from Liaw et al. 2004 [5] [§]
	IFN & PEG-IFN	17.6%	Assumption
	ADF	17.6%	Assumption [†]
% Decrease in annual rate of progression from CC to HCC in presence of resistance	LAM; ADF	0.0000	Conservative assumption
Annual rate of progression from DCC to HCC		0.0710	From Lin X et al. 2005 [19]*
Annual rate of progression from Seroconversion or HBV response to death	Life table values		From age-specific life tables [28]
Annual rate of progression from CHB to death		0.0060	From Lin X et al. 2005 [19]*
Annual rate of progression from CC to death		0.0540	From Lin X et al. 2005 [19]*
Annual rate of progression from DCC to death		0.1630	From Lin X et al. 2005 [19]*
Annual rate of progression from HCC to death		0.4300	From Lin X et al. 2005 [19]*

CHB, chronic hepatitis B; CC, compensated cirrhosis; HCC, hepatocellular carcinoma; DCC, decompensated cirrhosis; LAM, lamivudine; PEG-IFN, pegylated-interferon; ADF, adefovir; HBV, hepatitis B virus.

*Weighted average derived from Lin X et al. 2005 [19] (base case estimate). [†]Control is assumed to be as good with adefovir as with lamivudine in those who do not develop resistance. [‡]Derived from Liaw et al. 2004 [5] (annualized % decrease) from increase in Child-Pugh score. [§]Derived from Liaw et al. 2004 [5] (annualized % decrease).

eligible for therapy. Where available, model inputs were obtained or derived from the literature for this population. However, for some model inputs the ALT status was either elevated or unknown.

A list of all model assumptions is given in Appendix I.

Discounting

Costs and benefits were discounted at 5% per annum, although in year 1 there was no discounting. The effect of discounting was investigated in the sensitivity analyses.

Sensitivity analyses

Sensitivity analyses were carried out for the longer duration CHB antiviral therapies (lamivudine plus adefovir as rescue medication or adefovir plus lamivudine as rescue medication) administered for up to 5 years. One-way sensitivity analyses were carried out by changing individual model inputs over ranges of values obtained from the literature or using pessimistic estimates for the magnitude of treatment effectiveness. In addition, sensitivity analyses were also carried out in which several model inputs were varied simultaneously.

Table 2 (a) Annual HBeAg-seroconversion rates, relapse rates and resistance rates for different treatments of HBeAg-positive CHB derived from the literature; (b) Annual HBV response rates and lack of durability of response rates for different treatments of HBeAg-negative CHB for different treatments derived from the literature

Model input	Treatment	Estimate	Comment
<i>(a)</i>			
HBeAg-seroconversion rates for patients with ALT levels $>2 \times$ ULN in the absence of resistance	No treatment/placebo	0.1020	Derived from Perrillo et al. 2002 [29]
	LAM	0.3070	Derived from Perillo et al. 2002 [29]*
	IFN	0.2250	Derived from Perillo et al. 2002 [29]
	PEG-IFN	0.2660	From Lau et al. 2005 [17]
	ADF	0.1520	Derived from Marcellin et al. 2002 [30] [†]
HBeAg-seroconversion lack of durability (% who relapse back to CHB state)	LAM	0.1020	Derived from Dienstag et al. 2003 [26] [‡]
	No treatment; IFN	0.1020	From Crowley et al. 2002 [16]
	PEG-IFN	0.0440	Derived from Lau et al. 2005 [17] [§]
	ADF	0.0800	From Chang et al. 2004 [27] [¶]
Emergence of resistance during treatment	LAM	0.2570	Derived from the cumulative rates given in Lai et al. 2003 [10]**
	No treatment; IFN & PEG-IFN	0.0000	
	ADF	0.0640	Derived from the cumulative rates given in Locarnini 2005 [31] (Adefovir monotherapy trials) ^{††}
<i>(b)</i>			
HBV response rates for patients with ALT levels $>2 \times$ ULN in the absence of resistance	No treatment/placebo	0.0000	Hadziyannis et al. 2003 [32]
	LAM	0.8950	From Marcellin et al. 2004 [18] ^{‡‡}
	PEG-IFN	0.6330	Marcellin et al. 2004 [18]
	ADF	0.5120	Hadziyannis et al. 2003 [32] ^{§§}
Annual lack of durability of response (% who relapse back to CHB state)	LAM	0.9030	Derived from Marcellin et al. 2004 [18] & Hadziyannis et al. 2005 [33]
	No treatment	0.9030	Derived from Marcellin et al. 2004 [18] & Hadziyannis et al. 2005 [33]
	PEG-IFN	0.6960	Marcellin et al. 2004 [18]
	ADF	0.9030	Derived from Marcellin et al. 2004 [18] & Hadziyannis et al. 2005 [33]

CHB, chronic hepatitis B; ALT, aminotransferase; LAM, lamivudine; PEG-IFN, pegylated-interferon; ADF, adefovir; HBV, hepatitis B virus.

*Annual HBeAg-seroconversion rate = 25.4% based on all patients with ALT levels $\geq 2 \times$ ULN, which is equivalent to an annual seroconversion rate = 30.7% in those without resistance and 10.2% in those with resistance. Assumption: These rates remain constant with time. [†]Annual HBeAg-seroconversion rate = 14.9% based on all patients with ALT levels $\geq 2 \times$ ULN, which is equivalent to an annual seroconversion rate = 15.2% in those without resistance and 10.2% in those with resistance. Assumption: These rates remain constant with time. [‡]Assumption: % relapse rate per year is average of that occurring over years 1–3 after stopping treatment. [§]The annual rate of loss of HBeAg seroconversion for LAM was 10.2% (derived from Dienstag et al. 2003) [26]. Therefore, the corresponding estimate for PEG-IFN would be $10.2\% \times (18.1/41.8) = 4.4\%$, where 18.1% and 41.8% were the 6-month seroreversion rates obtained for PEG-IFN and LAM, respectively (Lau et al. 2005) [17]. [¶]Baseline ALT levels unknown. ^{**}Assumption: Resistance rates for years 1–5 is the average of that observed over years 1–4. ^{††}Assumption: Resistance rate is zero for year 1. The annual resistance rate estimate (6.4%) for years 2–5 is the average of that observed over years 2–4. ^{‡‡}The rate of HBV DNA suppression is 73.5% after 1-year treatment with LAM. In the same study YMDD variants occurred in 17.9% after 1 year. Therefore, the corresponding rate in the absence of resistance = $[0.735 / (1 - 0.179)] = 89.5\%$, assuming loss of suppression in those with resistance. Assumption: Annual response rate for years 2–5 in the absence of resistance is the same as for year 1. ^{§§}Assumption: Annual response rate for ADF in the absence of resistance for years 2–5 is the same as for year 1.

Table 3 Annual drug acquisition costs (2005)

Drugs	Annual acquisition costs (wholesale) of drugs (\$S)
LAM	2774.00
ADF	3606.20
IFN*	7329.75
PEG-IFN [†]	20 740.00

LAM, lamivudine; PEG-IFN, pegylated-interferon; ADF, adefovir.

*IFN costs are the average for Roferon-A and Intron-A (range of doses) and 6–12 months treatment durations.

[†]PEG-IFN costs are the average of those for Pegasys and Peg-Intron for a duration of 12 months.

RESULTS

Disease progression in the presence of treatment

Short-course therapy with α -interferon, or 1-year treatment with pegylated interferon α -2a, adefovir, or lamivudine had limited impact on disease progression (Fig. 3a for HBeAg-positive CHB and Fig. 3b for HBeAg-negative CHB).

In contrast, both lamivudine plus adefovir as rescue medication or adefovir plus lamivudine as rescue medication administered for up to 5 years substantially decrease the rate of disease progression. For example, at the end of the treatment phase the proportion of the HBeAg-positive cohort that had developed complications had been reduced by approximately 70% in those receiving these therapies (Fig. 4a). The corresponding impact on disease progression in the HBeAg-negative cohort is shown in Fig. 4b. A comparison of these figures shows that disease progression occurred at a faster rate in HBeAg-negative patients than in HBeAg-positive patients.

Outcomes, costs, cost-effectiveness of treatment alternatives

The discounted incremental costs, benefits and cost-effectiveness ratios (ICERs) for treatment alternatives compared with no treatment and lamivudine 1-year are given in Tables 5a and 6a, respectively, for patients with HBeAg-positive CHB, and Tables 5b and 6b, respectively, for patients with HBeAg-negative CHB. (Similar results were obtained in the absence of discounting).

A cost-effectiveness threshold of approximately S\$ 53 000 was estimated for Singapore based on an international cost-effectiveness threshold of US\$ 50 000 per QALY and after

Table 4 Disease health state utilities derived from the literature and the effect of antiviral resistance

Health state utility	Estimate	Source
Seroconversion	0.783	From Crowley et al. 2002 [16]
CHB	Untreated = 0.692 LAM = 0.692* ADF = 0.692* IFN = 0.467 PEG-IFN = 0.5795 [†]	Adapted from Crowley et al. 2002 [16]
CC	0.561	From Crowley et al. 2002 [16]
DCC	0.150	From Crowley et al. 2002 [16]
HCC	0.118	From Crowley et al. 2002 [16]
Resistant CHB	Untreated = 0.692 LAM = 0.692 ADF = 0.692 IFN = 0.467 PEG-IFN = 0.5795	Adapted from Crowley et al. 2002 [16] [‡]
Resistant CC	0.561	From Crowley et al. 2002 [16] [‡]
Resistant DCC	0.150	From Crowley et al. 2002 [16] [‡]
Resistant HCC	0.118	From Crowley et al. 2002 [16] [‡]

CHB, chronic hepatitis B; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LAM, lamivudine; ADF, adefovir; PEG-IFN, pegylated-interferon.

Assumptions

*LAM and ADF are well tolerated in CHB patients and have at least the same utility as untreated patients. [†]PEG-IFN is better tolerated than IFN but less well tolerated than LAM or ADF, resulting in a utility mid-way between that for IFN and LAM/ADF. [‡]No effect of resistance *per se* on the health state utility.

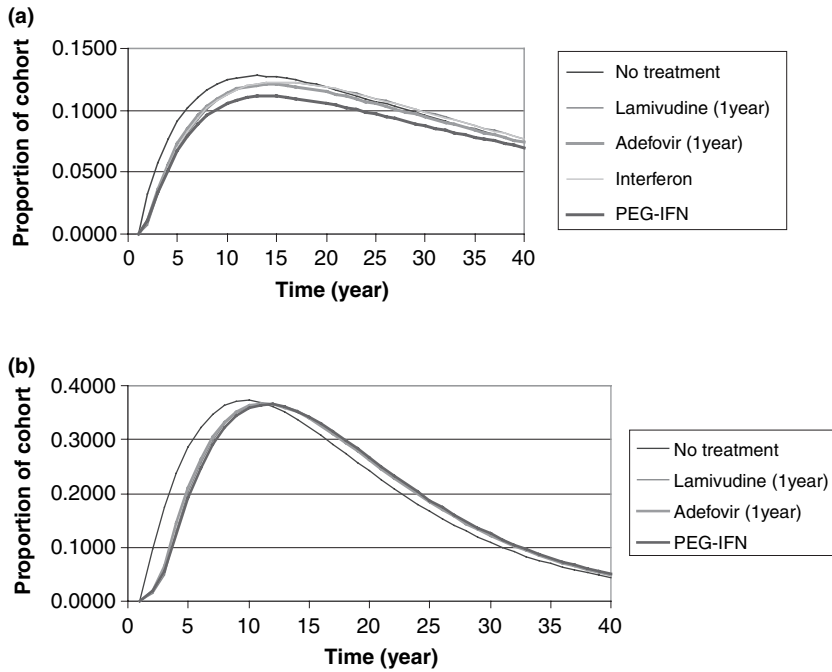


Fig. 3 Short-duration treatment of (a) HBeAg-positive chronic hepatitis B (CHB); (b) HBeAg-negative CHB – proportion of cohort in compensated cirrhosis (CC), decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC) states during each cycle.

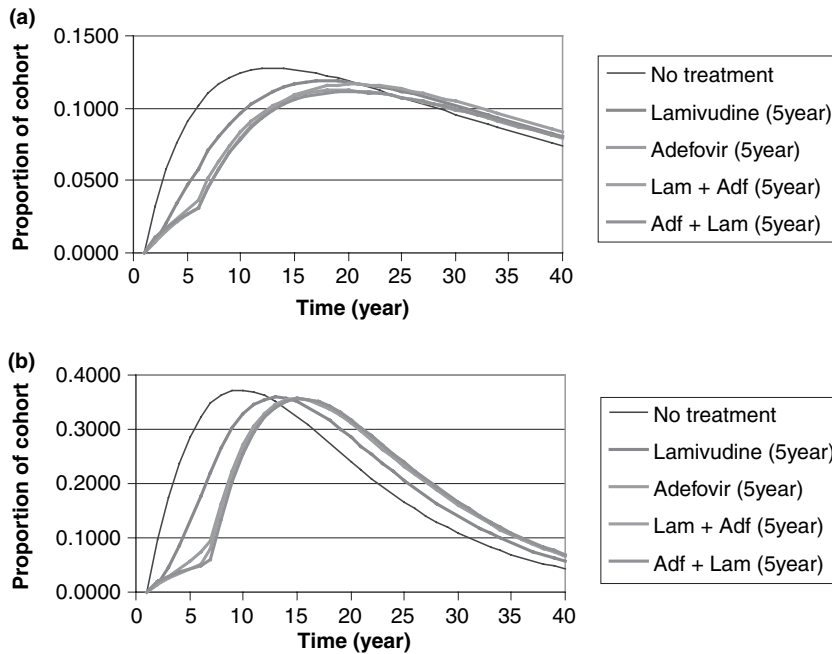


Fig. 4 Long-duration treatment of (a) HBeAg-positive chronic hepatitis B (CHB); (b) HBeAg-negative CHB – proportion of cohort in compensated cirrhosis (CC), decompensated cirrhosis (DCC) or hepatocellular carcinoma (HCC) states during each cycle.

adjusting for differences in PPP-based GNI per capita (2001) [13,14].

In comparison with no treatment of HBeAg-positive CHB, short-course α -interferon was not a cost-effective therapy (Table 5a). In contrast, base-case estimates of 1-year treatment with pegylated interferon α -2a were below the international threshold for cost-effectiveness in both HBeAg-positive and HBeAg-negative CHB (Table 5a,b respectively).

Lamivudine administered for 1 year is highly cost-effective in comparison with no treatment of both HBeAg-positive and HBeAg-negative CHB (Table 5a,b). One-year treatment of HBeAg-positive CHB with lamivudine resulted in better outcomes (life years and QALYs) at lower cost than either short-course α -interferon or 1-year treatment with adefovir. Although pegylated interferon α -2a resulted in better outcomes than 1-year treatment with lamivudine, it was not cost-effective in comparison with lamivudine (Table 6a).

Table 5 (a) The discounted incremental costs, benefits and cost-effectiveness ratios (ICERs) for treatment alternatives in comparison with no treatment of HBeAg-positive chronic hepatitis B (CHB); (b) The discounted ICERs for treatment alternatives in comparison with no treatment of HBeAg-negative CHB

Treatment alternatives	Cost (\$\$)	Life year gained	QALY	Cost per Life Year gained (\$\$/LY)	Cost per QALY gained (\$\$/QALY)
<i>(a)</i>					
IFN	6818.65	0.273	0.110	24 952.35	61 940.92
PEG-IFN (1 year)	19 216.05	0.566	0.570	33 977.06	33 718.47
Lamivudine (1 year)	2247.74	0.324	0.319	6943.59	7053.58
Adefovir (1 year)	2982.83	0.275	0.298	10 830.09	9993.50
Lamivudine (5 years)	8031.34	0.644	0.631	12 476.32	12 724.48
Adefovir (5 years)	11 237.25	0.738	0.740	15 223.13	15 176.56
Lamivudine + adefovir as rescue (5 years)	8455.30	0.872	0.854	9695.47	9905.72
Adefovir + lamivudine as rescue (5 years)	10 845.16	0.805	0.813	13 472.82	13 344.85
<i>(b)</i>					
PEG-IFN (1 year)	19 785.52	0.642	0.486	30 833.44	40 707.14
Lamivudine (1 year)	1928.59	0.625	0.568	3086.05	3393.32
Adefovir (1 year)	2863.18	0.516	0.471	5546.03	6078.79
Lamivudine (5 years)	10 807.30	1.133	1.077	9535.13	10 034.00
Adefovir (5 years)	13 471.57	1.731	1.665	7784.26	8090.25
Lamivudine + adefovir as rescue (5 years)	10 750.93	1.838	1.740	5848.71	6178.02
Adefovir + lamivudine as rescue (5 years)	13 111.95	1.887	1.816	6948.67	7218.64

Table 6 (a) The incremental costs, benefits and cost-effectiveness ratios (ICERs) for treatment alternatives in comparison with 1-year course of lamivudine of HBeAg-positive chronic hepatitis B (CHB); (b) The ICERs for treatment alternatives in comparison with 1-year course of lamivudine of HBeAg-negative CHB

Treatment alternatives	Cost (\$\$)	Life year gained	QALY	Cost per Life Year gained (\$\$/LY)	Cost per QALY gained (\$\$/QALY)
<i>(a)</i>					
IFN	4570.91	-0.050	-0.209	nv	nv
PEG-IFN (1 year)	16 968.32	0.242	0.251	70 161.69	67 540.78
Adefovir (1 year)	735.09	-0.048	-0.020	nv	nv
Lamivudine (5 years)	5783.60	0.320	0.313	18 073.04	18 507.18
Adefovir (5 years)	8989.51	0.414	0.422	21 689.93	21 313.88
Lamivudine + adefovir as rescue (5 years)	6207.56	0.548	0.535	11 319.95	11 604.85
Adefovir + lamivudine as rescue (5 years)	8597.43	0.481	0.494	17 864.69	17 403.02
<i>(b)</i>					
PEG-IFN (1 year)	17 856.93	0.017	-0.082	1 065 894.63	nv
Adefovir (1 year)	934.59	-0.109	-0.097	nv	nv
Lamivudine (5 years)	8878.72	0.508	0.509	17 461.19	17 453.01
Adefovir (5 years)	11 542.99	1.106	1.097	10 439.73	10 524.11
Lamivudine + Adefovir as rescue (5 years)	8822.34	1.213	1.172	7271.76	7528.61
Adefovir + Lamivudine as rescue (5 years)	11 183.36	1.262	1.248	8861.37	8960.64

nv, alternative treatments dominated by 1-year course of lamivudine (i.e. better outcomes achieved at lower costs when lamivudine is used).

One-year treatment of HBeAg-negative CHB with lamivudine resulted in better outcomes at lower cost than either adefovir or pegylated interferon α -2a (Table 6b).

In comparison with treatment of CHB for 1 year with lamivudine, longer duration antiviral therapies (lamivudine plus adefovir as rescue medication or adefovir plus

lamivudine as rescue medication) administered for up to 5 years were found to be highly cost-effective by international standards in both HBeAg-positive and HBeAg-negative CHB. The base-case cost/QALY for treatment with lamivudine plus adefovir as rescue medication for 5 years was S\$ 11 605 in HBeAg-positive CHB (Table 6a) and S\$ 7529 in HBeAg-negative CHB (Table 6b). These values are only 22% and 14% of the internationally accepted cost-effectiveness threshold value respectively. These conclusions of cost-effectiveness were found to be robust to uncertainties in model inputs as demonstrated by the sensitivity analyses.

Sensitivity analyses

The following model inputs were found to have the greatest effect on the cost-effectiveness of the longer duration antiviral therapies (lamivudine plus adefovir as rescue medication or adefovir plus lamivudine as rescue medication) administered for up to 5 years in the treatment of HBeAg-positive or HBeAg-negative CHB:

1. *Discounting of costs and benefits:* In the base case analyses, costs and benefits were discounted at 5% per annum, which is a conservative approach. The ICER estimates decreased (i.e. became more cost-effective) when there was no discounting or when only costs were discounted.
2. *Rates of disease progression:* When the maximum rates of disease progression obtained from Lin et al. (2005) [19] were used, particularly for the rate of progression from CHB to CC, the ICER estimates decreased. Higher ICER estimates were obtained when minimum rates of disease progression were used.

3. *Treatment effects:* The following elements of treatment effect were investigated individually and in combination by increasing these model inputs by a magnitude of 25% or decreasing them by 20%:
 - Annual seroconversion rates (HBeAg-positive CHB) or annual HBV response rates (HBeAg-negative CHB)
 - Annual seroreversion rates (HBeAg-positive CHB) or annual rate of loss of HBV response (HBeAg-negative CHB)
 - Annual antiviral resistance rates
 - Magnitude of treatment reductions on the rates of disease progression in those patients who do not achieve HBeAg-seroconversion (HBeAg-positive CHB) or who do not have a positive HBV treatment response (HBeAg-negative CHB). The biggest effect on the ICER estimates occurred when varying the magnitude of treatment reduction on the rate of disease progression from CHB to CC.

4. *Health state utilities:* A 25% increase in health state utilities resulted in a 20% decrease in the ICER estimates, whereas a 20% decrease in health state utilities resulted in a 25% increase in ICER estimates.
5. *Healthcare costs (for the different health states and CHB antiviral drug costs):* A 25% increase in healthcare costs resulted in a 25% increase in the ICER estimates, whereas a 20% decrease in healthcare costs resulted in a 20% decrease in ICER estimates.

The minimum, base-case and maximum estimated ICERs for lamivudine plus adefovir as rescue medication administered for up to 5 years in the treatment of HBeAg-positive or HBeAg-negative CHB are shown in Fig. 5a. The corresponding estimated ICERs for adefovir plus lamivudine as rescue medication for up to 5 years are shown in Fig. 5b.

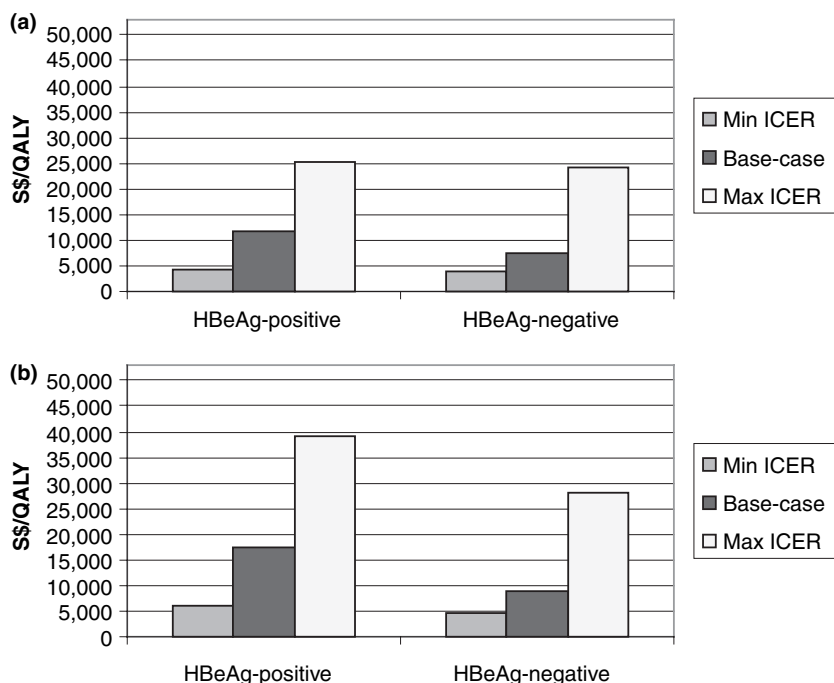


Fig. 5 Summary of sensitivity analyses for (a) lamivudine plus adefovir as rescue (5 years) vs lamivudine (1 year) (b) adefovir plus lamivudine as rescue (5 years) vs lamivudine (1 year).

DISCUSSION

Effectiveness and cost-effectiveness of 5-year antiviral treatment

In comparison with no treatment (Table 5a,b), the most cost-effective short-course treatment for CHB is lamivudine, administered for 1 year. However, short-course and 1-year CHB therapies have limited impact on disease progression (Fig. 3a,b).

In contrast to short-course and 1-year CHB treatment options, lamivudine plus adefovir as rescue medication or adefovir plus lamivudine as rescue medication, administered for up to 5 years, substantially decreased the rate of disease progression in both HBeAg-positive and HBeAg-negative CHB (Fig. 4a,b). Furthermore, by reducing the rates of disease progression, 5-year antiviral treatments decrease non-drug healthcare costs, partially off-setting the antiviral drug acquisition costs. As a result, in comparison with no treatment or treatment with lamivudine for 1-year, both lamivudine plus adefovir as rescue medication or adefovir plus lamivudine as rescue medication administered for up to 5 years are highly cost-effective, with lamivudine plus adefovir as rescue medication having the lowest cost per QALY (Tables 5a,b and 6a,b respectively).

Choice of antiviral treatment regimen

Although lamivudine plus adefovir as rescue medication had a lower cost per QALY than adefovir plus lamivudine as rescue medication in both HBeAg-positive CHB (Tables 5a & 6a) and HBeAg-negative CHB (Tables 5b & 6b), both regimens were highly cost-effective by international standards. Therefore, physicians have a choice as to which antiviral treatment option to use in the long-term management of their CHB patients. Initiating patients with adefovir therapy has the clinical advantage of a lower risk of resistance emerging, especially in the early stages of treatment, whereas lamivudine has a lower acquisition drug cost for those patients of more modest means who need to pay out of pocket for their medication.

Comparisons with other CHB economic evaluations

Crowley et al. (2002) [16] found that antiviral treatment (lamivudine) for 4 years was an economically dominant strategy compared with no treatment or short-duration treatment with α -interferon. However, the analysis by Crowley et al. (2002) [16] was limited in so far as the evaluation only included patients with HBeAg-positive CHB and there was a failure to take into account the emergence of anti-viral resistance during therapy.

Kanwal et al. (2005) [20] used a Markov model incorporating the emergence of antiviral resistance to evaluate the cost-effectiveness of alternative CHB treatment strategies.

Their economic evaluation concluded that lamivudine plus adefovir as rescue (salvage) therapy may be highly cost-effective across most healthcare settings. The main differences between the economic modelling performed by Kanwal et al. (2005) [20] and the present evaluation are:

1. The price differential between adefovir and lamivudine is much greater in the US than in Singapore (i.e. an approximate 250% increase vs a 30% increase in the acquisition cost of adefovir in comparison with lamivudine respectively) or in other Asian countries.
2. The present study investigated antiviral treatment of CHB for up to 5 years in comparison with life-time treatment. This reduced the extent of assumptions that needed to be made concerning treatment effectiveness and rates of emergence of anti-viral resistance beyond those observed in clinical trials.

These differences may partly explain why Kanwal et al. (2005) [20] concluded that α -interferon might be most cost-effective in healthcare systems with tight budgetary constraints and with a high prevalence of HBeAg-negative disease. However as pointed out by Weitzman and Jacobson (2005) [21], α -interferon treatment is equivalent to a 'do nothing' strategy for more than 70% of patients. In contrast, the present evaluation found that short-course α -interferon was not cost-effective in HBeAg-positive CHB. However, when compared with no treatment, 1-year treatment with pegylated interferon α -2a was below the international threshold for cost-effectiveness in both HBeAg-positive and HBeAg-negative CHB (Tables 5a & 6a).

Sullivan et al. (2006) [22] evaluated the cost-effectiveness of 1-year treatment with pegylated interferon α -2a compared with 1-year lamivudine in HBeAg-positive CHB from the perspective of the Taiwan Bureau of Nation Health Insurance. They concluded that pegylated interferon α -2a provided QALY gains at a favourable cost-effectiveness ratio. Sullivan et al. (2006) [22] used a Markov model structure that was similar to that of Crowley et al. (2000) [15], i.e. emergence of anti-viral resistance was not included. When we repeated the economic evaluation using the present model based on Taiwanese drug acquisition and healthcare costs, similar results and conclusions were obtained to those of Sullivan et al. (2006) [22]. Thus, conclusions of cost-effectiveness cannot be extended from one country to another without performing a country-specific economic evaluation. In addition, our analysis found that up to 5 years treatment with lamivudine and adefovir as rescue therapy provided better outcomes at lower cost than pegylated interferon α -2a in Taiwan.

We also conducted threshold analyses to estimate the acquisition cost in Singapore that would be required for pegylated interferon α -2a to achieve a similar cost per QALY (in comparison with no treatment) to that achieved with long duration sequential antiviral therapies. In HBeAg-positive CHB, the acquisition cost of pegylated interferon α -2a would

need to be decreased by approximately 55% to be as cost-effective as adefovir plus lamivudine as rescue medication for up to 5 years and by 65% to be as cost-effective as lamivudine plus adefovir as rescue medication. In HBeAg-negative CHB, the acquisition cost of peg-IFN would need to be decreased by approximately 80% to be as cost-effective as the long-duration sequential antiviral therapies.

Study limitations

The economic evaluation was limited to CHB patients, with elevated ALT levels at least twice upper limit of normal and who, on initiation of treatment, did not have cirrhosis or HCC. If patients with lower baseline ALT levels or advanced liver disease were included, it might be expected that the benefits of long-duration nucleoside analogue therapies over both short-term therapies including interferons, would be further enhanced given that high pre-treatment levels of ALT is a predictive factor for end-of-treatment response and interferons are contra-indicated in patients with DCC [23].

There was limited published data on the annual loss of response following treatment with pegylated interferon α -2a. More recently, longer duration post-treatment data have been published as abstracts. Lau et al. (2006) [24] appeared to provide a 12-month seroreversion rate in HBeAg-positive patients of 9% ($n = 6/69$) for pegylated interferon α -2a. This compares with our derived estimate of 4.4%. As Lau et al. (2006) [24] referred to 'relapse/no response', there is reason to suspect that an estimate of 9% would be an over-estimate. Moreover, a seroreversion rate of 4.4% would favour pegylated interferon α -2a in comparison with antiviral treatment alternatives. Marcellin et al. (2006) [25] provided 6- to 24-month post-treatment data in HBeAg-negative patients. However, the HBV response data were based on a HBV-DNA cut-off of 100 000 copies/mL level. This is much higher than the threshold for not-detectable HBV-DNA used for the comparative treatments (300–400 copies/mL) and hence these data from Marcellin et al. (2006) [25] could not be used in the model.

Another limitation of the present economic evaluation is that patient adherence during long-term antiviral treatment in the real-world setting may be worse than occurred in the adefovir and lamivudine clinical trials. A lower level of adherence may be expected to decrease the rate of HBeAg seroconversion or HBV treatment response, and decrease the magnitude of treatment effect on disease progression. Nonetheless, it would require the choice of pessimistic estimates across several variables before there would be any real uncertainty as to the cost-effectiveness of 5-year antiviral treatment with adefovir or lamivudine as rescue medication in comparison with no treatment or 1-year treatment with lamivudine, in both HBeAg-positive and HBeAg-negative CHB.

This economic evaluation pertains specifically to Singapore. However, given the highly cost-effective conclusions in

relation to 5-year antiviral therapies in both HBeAg-positive and HBeAg-negative CHB, these conclusions might be applicable to other countries that have similar ratios of annual antiviral acquisition costs to the healthcare costs of managing the complications of disease progression. However, country-specific economic evaluations would be required to confirm this.

This economic evaluation only included direct healthcare costs. However, if indirect costs (such as productivity losses for time off work due to CHB-related sickness) had been taken into account, it would be expected that the cost-effectiveness of long-duration antiviral therapies from a societal perspective would be further enhanced.

Lastly, newer anti-viral treatments, such as entecavir, sequential interferon/antiviral based-strategies and combination lamivudine plus adefovir as initial therapy, were not investigated in this economic evaluation.

CONCLUSIONS

1. In Singapore, antiviral treatment of CHB with lamivudine or adefovir for up to 5 years using the alternative antiviral agent as rescue medication (upon emergence of anti-viral drug resistance) is predicted to substantially decrease the rate of disease progression at the end of the treatment period, in both HBeAg-positive and HBeAg-negative CHB. By reducing the rates of disease progression, 5-year antiviral treatments decrease non-drug healthcare costs, partially off-setting the antiviral drug acquisition costs.
2. In Singapore, antiviral treatment of CHB with lamivudine or adefovir for up to 5 years using the alternative antiviral agent as rescue medication was found to be highly cost-effective, in comparison with no treatment or 1-year treatment with lamivudine, in both HBeAg-positive and HBeAg-negative CHB, with lamivudine and adefovir as rescue medication being the most cost-effective strategy.
3. Sensitivity analyses indicate that these economic conclusions are robust to uncertainties in model inputs.
4. Combination therapy was only considered for rescue of patients who had developed resistance to either lamivudine or adefovir monotherapy. Further studies should include combination lamivudine plus adefovir as initial therapy. Moreover, newer antiviral treatments such as entecavir and other sequential treatment strategies (e.g. using interferons and antivirals) should be evaluated.

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APPENDIX

Appendix 1

Assumptions for model inputs

Model input	Treatment	Assumption
HBeAg-seroconversion rates for patients with ALT levels $\geq 2 \times \text{ULN}$	Lamivudine	Annual seroconversion rate for years 2–5 is the same as for year 1 in the absence of resistance
	Adefovir	Annual seroconversion rate for years 2–5 remains constant in the absence of resistance
HBeAg-seroconversion lack of durability (% who relapse back to CHB state)	Lamivudine	% Relapse rate per year is average of the annual rates occurring over years 1–3 after stopping treatment (from Dienstag et al. 2003 [26]). The rate of relapse does not change with time
	IFN	From Crowley et al. 2002 [16], relapse rates are assumed to be the same for IFN and lamivudine. The rate of relapse does not change with time
	PEG-IFN	Derived from Dienstag et al. 2003 [26] and Lau et al. 2005 [17]
	Adefovir	From Chang et al. 2004 [27], baseline ALT levels unknown. Therefore, assuming that ALT levels $\geq 2 \times \text{ULN}$. The rate of relapse does not change with time
HBV response rates for patients with ALT levels $> 2 \times \text{ULN}$	Lamivudine	Annual response rate for years 2–5 in the absence of resistance is the same as for year 1
	Adefovir	Annual response rate for adefovir in the absence of resistance for years 2–5 is the same as for year 1
Annual lack of durability of HBV response (% who relapse back to CHB state)	All treatments	The annual rate of relapse does not change with length of time post-treatment
Emergence of resistance during treatment	Lamivudine	Resistance rates for years 1–5 is the average of the annual rates occurring over years 1–4.
	IFN/PEG-IFN	No resistance occurs during treatment
	Adefovir	Resistance rate for years 2–5 is the average of the annual rates occurring over years 2–4. There is no resistance in year 1
Annual rate of progression from CHB to CC for those who do not seroconvert or have HBV response	In absence of treatment	Rate used is applicable to Singaporeans
% Decrease in rate of progression from CHB to CC in the absence of resistance	Lamivudine	For years 2–5 it is assumed that control is maintained in those who do not develop resistance
	IFN/PEG-IFN	It is assumed that the direct effect of IFN/PEG-IFN on disease progression during treatment is the same as for lamivudine
	Adefovir	Assumes that control is as good with adefovir as with lamivudine in those who do not develop resistance
% Decrease in rate of progression from CHB to CC in presence of resistance	All treatments	Assumption of no effect
Annual rate of progression from CHB to HCC	In absence of treatment	Rate used is applicable to Singaporeans

Appendix 1
(Continued)

Model input	Treatment	Assumption
% Decrease in rate of progression from CHB to HCC in presence of resistance	All treatments	Assumption of no effect
Annual rate of progression from CC to DCC	In absence of treatment	Rate used is applicable to Singaporeans
% Decrease in rate of progression from CC to DCC in absence of resistance	Lamivudine	Increase in Child-Pugh score is indicative of progression to DCC.
	IFN/PEG-IFN	It is assumed that the effect of IFN/PEG-IFN during treatment is the same as for lamivudine
	Adefovir	Assumes that control is as good with Adefovir as with lamivudine in those who do not develop resistance
% Decrease in rate of progression from CC to DCC in presence of resistance	All treatments	It is assumed that the effect of IFN/PEG-IFN during treatment is the same as for lamivudine.
Annual rate of progression from CC to HCC	In the absence of treatment	Rate used is applicable to Singaporeans
% Decrease in rate of progression from CC to HCC in absence of resistance	Lamivudine	For years 2–5, it is assumed that control is maintained in those who do not develop resistance
	IFN/PEG-IFN	It is assumed that the effect of IFN/PEG-IFN during treatment is the same as for lamivudine
	Adefovir	It is assumed that control is as good with adefovir as with lamivudine in those who do not develop resistance
% Decrease in rate of progression from CC to HCC in presence of resistance	All treatments	Assumption of no effect
Annual rate of progression from DCC to HCC	In the absence of treatment	Rate used is applicable to Singaporeans
Annual rate of progression from seroconversion or HBV response to death	Life table values (Singapore 2001)	From age-specific life tables
Annual rate of progression from CHB to death	In the absence of treatment	Rate used is applicable to Singaporeans
Annual rate of progression from CC to death	In the absence of treatment	Rate used is applicable to Singaporeans
Annual rate of progression from DCC to death	In the absence of treatment	Rate used is applicable to Singaporeans
Annual rate of progression from HCC to death	In the absence of treatment	Rate used is applicable to Singaporeans
Annual acquisition costs (wholesale) of drugs	All treatments	IFN costs are average for Roferon-A and Intron-A and 6–12 months treatment durations. PEG-IFN costs are the average of those for Pegasys and Peg-Intron for a duration of 12 months
Annual cost following HBeAg-seroconversion (S\$)	In the absence of treatment	Not available from Li et al. 2004 [6]. Assumed that the annual costs are 50% of the cost of CHB (from Crowley et al. 2002) [16]
Utility for CHB	All treatments	Lamivudine and adefovir are well tolerated in CHB patients and have at least the same utility as untreated patients. PEG-IFN is better tolerated than IFN but less well tolerated than lamivudine or adefovir, resulting in a utility mid-way between that for IFN and lamivudine/adevovir

Appendix 1
(Continued)

Model input	Treatment	Assumption
Utility for resistant CHB	All treatments	No effect of resistance <i>per se</i> on the health state utility For other assumptions refer to those for Utility for CHB
Utility for resistant CC	Irrespective of treatment	No effect of resistance <i>per se</i> on the health state utility
Utility for resistant DCC	Irrespective of treatment	No effect of resistance <i>per se</i> on the health state utility
Utility for resistant HCC	Irrespective of treatment	No effect of resistance <i>per se</i> on the health state utility