Assessing the clinical and economic impact of increasing treatment uptake in chronic hepatitis B infection using a Markov model

Short running title: Varying treatment uptake rates in HBV

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgh.13679

List of abbreviations used:

CC – compensated cirrhosis

CEAC – cost-effectiveness acceptability curves

CEP – cost-effectiveness planes

CHB – chronic hepatitis B

CUA – cost-utility analysis

DC – decompensated cirrhosis

HBV – hepatitis B virus infection

HCC – hepatocellular carcinoma

LT – liver transplant

QALY – quality adjusted life years

QoL – quality of life

Authorship statement:

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Author contributions:

Study concept and design – MC, BK and AW; Acquisition of data – MC and BK; Analysis and interpretation of data – MC, BK and RW; Drafting of the manuscript – MC and BK; Critical review of the manuscript – RF, RW and AW; Study supervision – AW.

Financial support: Nil

Authors potential conflicts of interest: Nil to disclose

ABSTRACT

Treatment uptake in chronic hepatitis B virus (HBV) infection is low in South Australia and the cost-effectiveness of increasing treatment uptake rates in this population has not been assessed.

Aims & Methods: Using a cohort Markov model, cost-effectiveness was assessed for 3 different treatment uptake scenarios: 2.9% (current level –scenario 1), 10% (Scenario 2) and 15% (Scenario 3). The initial HBV population included 2550 treatment eligible patients who transitioned between six different health states over a 10- year period. Treatment transition probabilities were based on tenofovir therapy, while those not assigned to treatment followed the natural history transition probabilities. We estimated the incremental cost per quality adjusted life year (QALY) gained using the prevented number of deaths, hepatocellular carcinoma (HCC) and liver transplants.

Results: Scenario 3 was associated with the lowest mean cost/person over 10 years (AU$60,133), compared to scenario 2 (AU$61,964), and scenario 1 (AU$64,597). Scenario 3 was also associated with the highest QALY gained (8.196) compared to scenario 2 (7.985) and scenario 1 (7.684). Scenario 3 would result in 50% reduction in HCC and 30% reduction in HBV- related mortality compared to scenario 1, over a 10-year period. Higher treatment uptake was found to be cost-effective with at least 2 years of treatment at either 10% or 15% of the target population.

Conclusion: Maximizing the treatment uptake in the existing HBV population from 2.9% to 15% was cost-effective for periods of 2 years or more. This was due to a reduction in the number of expected clinical events.

Keywords: Chronic hepatitis B; Treatment; Uptake; Markov model

INTRODUCTION:

Chronic hepatitis B virus (HBV) infection is a major public health problem as it affects more than 240 million people worldwide (1). Individuals with HBV infection are at increased risk of morbidity and mortality with up to 780,000 deaths/ year (1-3) due to decompensated liver disease and hepatocellular carcinoma (HCC). HBV infection is the most important risk factor for HCC, accounting for 60-80% of HCC cases globally (4). Strategies adopted to decrease the disease burden of HBV include prevention by peri-natal vaccination programs and treatment using potent anti-viral therapies to prevent complications. Several large cohort studies have shown the effectiveness of anti-viral therapies in achieving sustained suppression of HBV replication and subsequent reduction in complications (5-7). Consequently major international guidelines advocate the use of nucleos(t)ide analogues or interferon for HBV viral suppression in patients meeting specific treatment criteria (8-10).

In Australia, recent data provide an estimated prevalence of chronic HBV of 1.02% (11). This is likely to be much higher than the actual reported prevalence which is based on notifications, since an estimated 44% of cases remain undiagnosed (12). The annual direct costs associated with managing and treating HBV infection in Australia were estimated at $171.8 million in 2008 and projected to rise to $307.9 million in 2017 (13). South Australia (SA) has a total population of 1.7 million accounting for 7.4% of the overall Australian population. The estimated HBV prevalence in SA is 0.9% which is marginally lower than the national figure (11). However, this is expected to increase due to the ageing HBV population and an increase in migration from areas of high HBV prevalence. Only a proportion of individuals with chronic HBV would be eligible for treatment and based on International and Australian estimates, this would range from 10-25% (14). However, the treatment uptake in SA is low with only 2.9% of the overall HBV patients receiving therapy in 2011 compared to

the national uptake of 5.3% (15). Based on this, the first SA Hepatitis B action plan aimed to increase treatment uptake to a target rate of 10% among the overall HBV patients (16). At the same time, a national treatment uptake target was set at 15% following the 2nd National Hepatitis B Strategy which was aimed at preventing adverse outcomes (14).

Although there is agreement on the need for higher treatment rates amongst eligible HBV patients, no formal cost-effectiveness analysis of these proposed treatment uptake regimes has been performed. The aims of this study were therefore to compare the long-term cost-effectiveness of the two specified treatment uptake rates with that of current treatment rate. A model-based probabilistic cost-effectiveness analysis was undertaken comparing costs and outcomes associated with the current and proposed treatment rates.

METHODS:

Development of the cost-effectiveness model

Using a cohort Markov model, the cost-effectiveness was estimated for 3 scenarios:

Scenario 1: 2.9% treatment uptake – current levels (15)

Scenario 2: 10% treatment uptake – state target (16)

Scenario 3: 15% treatment uptake – proposed national target (14)

Modelling was based on the most current estimates of prevalence, treatment uptake and outcomes of HBV available in South Australia (SA) (11-16). This population consists of an estimated 2,550 treatment eligible HBV patients (17.7% of the overall HBV population of 14,400) (11). Based upon cross-sectional estimates of outcomes in HBV (13), we calculated that amongst 2550 HBV cases eligible for treatment, 2,051 would have either eAg +ve/-ve chronic hepatitis B with no cirrhosis (CHB); 448 compensated cirrhosis (CC); 15 decompensated cirrhosis (DC) and 36 HCC. In our modelling we *a priori* assigned anyone

with DC or HCC to treatment for each of the 3 scenarios (Supplementary Table 1a). Therefore, increasing treatment uptake translated into treating a higher proportion of subjects with CHB or CC **(Table 1)**.

Modelling was performed using TreeAge Pro 2009 software (17) and a Markov modelling approach (18-19). Briefly, this entails dividing a patient's possible course of disease progression into a number of health states with prior transition probabilities assigned for the movement between these states over a discrete time period (Markov cycle). For each scenario, individuals assigned to treatment were assigned transition probabilities derived from known probability distributions following treatment with tenofovir, chosen mainly because of the availability of comprehensive long term histological data with serial liver biopsies on the therapy **(Table 2)**. Individuals who were not assigned to treatment were assumed to follow transition probabilities associated with the natural history of HBV. Long-term costs and health outcomes were assessed by attaching estimates of resource use and health outcomes to each of the 6 states in the model. Model-based predictions of costs and outcomes were compared between each scenario in a cost-utility analysis (CUA) from a health payer (Australian Medicare) perspective.

***Model structure and inputs**:*

The structure of the Markov model is shown in **Figure 1**. The time horizon for the model was 10 years and a cycle length of one year (deemed appropriate in models similar to ours) (20-22) was used. Model parameters were based on the best available estimates from published data (13, 23-27) **(Table 2)**. As done elsewhere (20), the risks of adverse effects were not incorporated into the model as these are generally considered mild and assumed to have no effect on costs, mortality, or quality of life. The Markov process for each arm began by identifying the initial distribution of patients within any of the six states based on the

estimated 2011 HBV prevalence from South Australia. The six health states were CHB, CC, DC, HCC, Spontaneous seroclearance (sAg loss) and liver transplant (LT). Patients could remain in any state or move to one of the other five possible health states unless they died before the end of the time horizon for the model. In the initial patient distribution (existing HBV treatable population), there were no sAg loss or LT cases and so the initial probability assigned to these two health states was 0. The transition probabilities governing movement between the six states for both the natural history and treatment (tenofovir) arms are shown in **Table 2**. Known 5 and 3-year transition probabilities (Supplementary Table 1b) were converted into the respective annual probabilities using the 'ProbToProb' function in TreeAge.

Direct costs and Utility values:

Average direct total costs for each health state were obtained from Butler et al (28) and inflated to 2014/15 prices using seasonally adjusted Australian consumer price indices for health services (inflation factor = 1.91) (29). All costs are reported in Australian dollars and, where appropriate, were discounted at 5% as recommended by the Australian Pharmaceutical Benefits Advisory Committee (30). Total costs for individuals assigned to a natural history progression included costs of outpatient visits, lab tests and imaging, and inpatient admissions (except the drug costs). Total costs for the treated individuals included all costs associated with a natural history progression plus the cost of anti-viral therapy (tenofovir). To reflect the accurate cost of treatment with tenofovir, the current 2014 cost per person per year of the drug (AU $5,878) was used in calculating total costs and this was then weighted across the health states based on the cost distributions for health states, similar to previous modelling (13). Drug costs for LT states were not reported in Butler et al (28). On average,

drug costs in Butler et al., made up 9% of all total costs and this figure was used to estimate drug costs for the LT states. All cost data are shown in **Table 3**.

All utility scores, which reflect the health-related quality of life associated with each health state in the model were obtained from the literature (31) and are shown in **Table 3**. The starting quality of life (QoL) values for individuals in the model were obtained from Australian age-specific QoL estimates (32). Utility scores for health states occurring thereafter were applied mid-way through each one-year cycle and those for the subsequent health states at the start of the next cycle. Future health state utility scores were modelled as multiplicative values of the Australian age-specific utility estimate (32) and the utility score of each particular health state.

Analysis:

The analysis was undertaken from a Australian health system (Medicare) perspective with the primary outcome being the incremental cost per quality adjusted life year (QALY) gained (33). Clinical outcomes (number of deaths, liver transplants and HCC cases) were also estimated. Probabilistic analyses were used based on 50,000 Monte Carlo simulations, with cost-effectiveness planes (CEPs) and cost-effectiveness acceptability curves (CEACs) reported (34-35). Dirichlet distributions were applied to the probability of following the natural history or the treatment arm and to probabilities of being in each state at the start of the Markov process. Beta distributions were used to model the probability of dying, the probability of transitioning between different health states as well as the uncertainty around the utility values. Gamma distributions were fitted to all costs used in the model for consistency. The parameters used for these distributions are shown in Tables 1, 2 and 3.

In sensitivity analyses we varied the time horizon for each model from 10 years to between 1 and 7 years. This time horizon was chosen to represent a plausible range within which the

cost-effectiveness of each scenario could be assessed against the cost-effectiveness threshold of $50,000/QALY gained, which is the implicit criterion used in Australian studies (36). We then relaxed the assumption that all individuals with DC or HCC will always get treated and allowed the same treatment uptake to be applied uniformly across all health states. Lastly, we applied higher values for utilities of the modelled health states that are reported in Woo et al. (37). The mean utility values (95% confidence intervals) were 0.92 (0.91-0.94) for CHB, 0.88 (0.85-0.92) for CC, 0.73 (0.39-1.00) for DC, 0.81 (0.67-0.94) for HCC, and 0.84 (0.77-0.91) for LT. In the latter two sensitivity analyses, the time horizon was also varied as was the case in the first sensitivity analysis.

RESULTS:

Health economic outcomes:

The mean long-term (10 year) costs and QALYs gained per patient are presented in **Table 4**. Scenario 3 was associated with the lowest mean costs (AU $60,133) followed by scenario 2 (AU $61,964) and then scenario 1 (AU $64,597). Further, scenario 3 was again associated with the highest QALY gains (8.196) followed by scenario 2 (7.985) and then scenario 1 (7.684) meaning that scenario 3 was both cheaper and more effective (dominates) than either scenario 1 or 2 while scenario 2 was also cheaper and more effective than scenario 1 **(Figure 2A)**. The CEPs **(Figure 2B)** show the joint distribution of the mean incremental costs and mean QALYs gained with all results in the north-east and south-east quadrants indicating some uncertainty in the results.

Sensitivity analysis:

Figure 2C shows the results obtained when: (i) time horizons were varied (ii) time horizons were varied and the same treatment uptake applied uniformly across all health states and (iii) time horizons were varied and higher values for utilities of the modelled health states were applied. A similar pattern was observed in all scenarios comparing higher to lower treatment uptake (Supplementary table 1c). For the sake of brevity, only results for the comparison between scenarios 1 and 3 are shown in Figure 2C. In all sensitivity analyses, the ICERs for higher treatment uptake (scenario 3) compared to lower treatment uptake (scenario 1) were all below AU $50,000 per QALY gained provided the time horizon was at least 2 years, with higher treatment uptake dominating lower treatment uptake (i.e. cheaper and more effective) for all time horizons greater than 4 years (sensitivity analysis ii), 5 years (sensitivity analysis iii) and 6 years (sensitivity analysis i) (Supplementary table 1c).

Cost-effectiveness acceptability curves (CEAC):

The CEACs **(Figure 3)** show that assuming a value per QALY-gained of at least AU $50,000, the probability of scenario 2 being cost-effective compared to scenario 1 was at least 86% while the corresponding probabilities of scenario 3 being cost-effective compared to scenario 1 and then to scenario 2 were at least 85% and 84%, respectively (**Figures 3A, 3B, 3C**). At lower QALY thresholds, the probability of the intervention being cost-effective compared to the control was lower, dropping to 70% at around AU $20,000 per QALY-gained for all three comparisons.

Clinical outcomes:

Compared to scenario 1, scenario 3 would result in a 50% reduction in cumulative HCC incidence and a 30% reduction in HBV related mortality over a 10- year period **(Table 4)**. However, the greatest benefit with increasing treatment uptake would be seen in the number of liver transplants avoided with a reduction of 60% for scenario 3 compared to scenario 1. Scenario 2 also resulted in reduction in HCC incidence, mortality rates and liver transplantation compared to scenario 1 but the magnitude of the benefits were slightly lower.

DISCUSSION:

This study showed that increasing HBV treatment uptake in those eligible to either 10% or 15% from the current 2.9% was cheaper and also cost-effective; this was primarily due to a reduction in the estimated number of clinical events, particularly HCC, DC and liver transplant as shown in Table 4. This is relevant as the incidence and mortality of HCC has increased significantly in both genders over the last 2 decades in Australia and it is predicted to increase further for at least another decade. The rising HCC incidence in Australia has been attributed to the increasing HBV and chronic hepatitis C virus (HCV) linked cases among Asia-Pacific born residents (38). A linkage study from New South Wales (NSW) showed that the overall age-standardized HCC incidence rate among an HBV monoinfected cohort was similar to the rates observed in an HCV cohort (39). Hence, increasing treatment uptake with appropriate anti-viral therapy should result in reduced clinical events for medium to long-term projection periods.

However, this would be challenging, as almost 44% of the overall HBV cohort remain undiagnosed. As outlined in the current national hepatitis B strategy (14), the most important step would be to increase the screening rates in priority at risk populations – people from culturally and linguistic diverse backgrounds, indigenous Australians, injecting drug users and men having sex with men. This would require a concerted, targeted effort with appropriate education and public health awareness initiatives.

Varying the time horizons of the model from the 10 years period used in the base case analysis and assuming a threshold of AU $50,000/QALY (36) showed that increased treatment uptake only became cost-effective when the time horizon was at least 2 years. This was because of the lag time between increased treatment uptakes and reduction in clinical events, and it became significant only after this time. Applying a uniform treatment uptake to all health states and higher values of utilities for the health states did not change the base case appreciably: strategies that involved a higher treatment uptake still dominated those that were based on a lower uptake when the time horizon was at least 6 years. This is because most of reduction in clinical events was from the treating those with compensated cirrhosis.

This is the first economic analysis comparing different HBV treatment rates in South Australia. Butler and colleagues (13) used Markov mathematical simulation to model the current and projected burden of CHB in Australia over a 10 year period but based their analysis on a representative cohort of people with CHB in 2008. In their study, they compared natural history, 2008 treatment and management practices (treatment rate) and enhanced treatment and management practices. Outcomes were also not expressed in terms of costs per QALYs gained but as incremental cost per HBV-related death averted and incremental cost per life-year saved. Similar to our study, they also projected a reduction in HBV-related deaths (39%) due to an increase in treatment effect (28.04%). The lower ratio

between treatment effect and number of deaths may have been due to differences in baseline estimates of HBV prevalence assumed in the two studies.

Two cost-utility analyses of lamivudine for the treatment of CHB have been conducted in Australia (40-41)**.** Both studies concluded that lamivudine was associated with a favourable cost-effectiveness ratio when compared against other treatment scenarios but none of the scenarios included tenofovir or comparison of different treatment uptake rates. The reductions seen in the lifetime risk of developing CC, DC and HCC (5, 11 and 11%, respectively) were however similar to the ones obtained in our study.

This study has several strengths. It is the first to model the benefits of increased treatment uptake with tenofovir – a potent nucleotide analogue with a high barrier to resistance. Our estimated annual transition probabilities between states were reliably based using data from a large cohort of tenofovir patients who underwent serial liver biopsies (23). Also, the SA HBV population used for primary analysis was based on the published estimated prevalence of HBV in South Australia (16) and their corresponding known distribution of states, rather than hypothetical prevalence estimates. Thirdly, sensitivity analysis was performed to: (i) assess the cost-effectiveness of this strategy with varying time-horizons and (ii) vary the treatment uptakes in each health state to assess the robustness of the model.

There are several limitations to this study. Firstly, only tenofovir was assessed in calculating annual treatment transition probabilities. This was mainly because of the availability of comprehensive long term data on tenofovir therapy. This may not reflect the real life practice as various nucleos(t)ide analogues are used, however, the other commonly used oral anti-viral, entecavir, has similar potency and high barrier to resistance. Furthermore, the transition probabilities used in this study were obtained from a controlled trial setting and we acknowledge that this might not entirely reflect the real-world practices because of

compliance issues. Secondly, the transition probabilities used in this study were derived from studies in different patient population as no SA data is available. However, the majority of these cohorts had a significant proportion of Asian individuals, similar to the current South Australian HBV population. Thirdly, as mentioned in the methods section, we assessed only the direct costs involved from a health payer perspective and did not include the indirect costs such as loss of productivity. Though some like the US 'Panel on Cost-Effectiveness in Health and Medicine' (42) argue that valuations of health-related quality of life incorporate indirect costs related to productivity changes, we take the view of many others (43-45) that indirect costs are best captured using other techniques such as the friction-cost and human-capital approaches. Lastly, since there was no recent SA data for the cost of managing these patients, we used data obtained more than a decade ago based on a CHB population that may not be entirely representative of current one in SA and extrapolated to its current value. However, these remain the best available Australian CHB cost estimates.

In conclusion, our analysis has demonstrated that increasing HBV treatment uptake is cost effective. Varying the time horizons of the model from the 10-year period used in the base case analysis and assuming a threshold of AU $50,000 showed that strategies involving higher treatment uptakes were still more cost effective provided the time horizon was at least 2 years.

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Table 1: Starting distributions for each health state in each of the 3 scenarios:

Scenarios	Treatment uptake [overall HBV cohort: n=14400]	Meeting criteria for treatment: n=2550 (%)	CHB: n=2051 (%)	CC: n=448 (%)	DC: n=15 (%)†	HCC: n=36 (%)†
1	418 (2.9%)	418 (16.4%)	301 (14.7%)	66 (14.7%)	15 (100%)	36 (100%)
2	1440 (10%)	1440 (56.5%)	1137 (55.4%)	252 (56.3%)	15 (100%)	36 (100%)
3	2160 (15%)	2160 (84.7%)	1722 (84%)	387 (86.4%)	15 (100%)	36 (100%)

CHB – chronic hepatitis B, no cirrhosis; CC – compensated cirrhosis; DC – decompensated cirrhosis; HCC – hepatocellular carcinoma.

† - Assumption that everyone in DC and HCC were treated across all 3 scenarios.

Table 2: Estimates of transition probabilities & distributions used in the reference case and sensitivity analyses

	Tenofovir treatment arm			Natural history arm		
	Estimate[a]	**Distribution[b]**	**Source**	**Estimate[a]**	**Distribution[b]**	**Source**
Probability of moving between health states						
Probability of moving from CHB[c] to CC[d]	0.002	Beta	Marcellin (23)	0.044	Beta	Butler (13)
Probability of moving from CHB[c] to HCC[e]	0.003	Beta	Marcellin (23)	0.006	Beta	Butler (13)
Probability of moving from CHB[c] to sAg loss[f]	0.008	Beta	Marcellin (23)	0.012	Beta	Liaw (24)
Probability of moving from CC[d] to CHB[c]	0.236	Beta	Marcellin (23)	0.000	Beta	Expert opinion
Probability of moving from CC[d] to DC[g]	0.020	Beta	Kanwal (25)	0.073	Beta	Kanwal (25)
Probability of moving from CC[d] to HCC[e]	0.010	Beta	Marcellin (23)	0.034	Beta	Kanwal (25)

	Tenofovir treatment arm			Natural history arm		
	Estimate[a]	**Distribution[b]**	**Source**	**Estimate[a]**	**Distribution[b]**	**Source**
Probability of moving from DC[g] to CC[d]	0.350	Beta	Kanwal (25)	0.080	Beta	Kanwal (25)
Probability of moving from DC[g] to LT[h]	0.020	Beta	Lim (27)	0.250	Beta	Kanwal (25)
Probability of moving from HCC[e] to LT[h]	0.300	Beta	Expert opinion	0.300	Beta	Kanwal (25)
Probability of death for those who have suffered an event						
Probability of death from CC[d]	0.003	Beta	Marcellin (23)	0.049	Beta	Kanwal (25)
Probability of death from DC[g]	0.034	Beta	Lim (27)	0.190	Beta	Kanwal (25)

	Tenofovir treatment arm			Natural history arm		
	Estimate[a]	**Distribution[b]**	**Source**	**Estimate[a]**	**Distribution[b]**	**Source**
Probability of death from HCC[e]	0.400	Beta	Expert opinion	0.400	Beta	Butler (13)
Probability of death from LT[h] (Year 1)	0.090	Beta	Lynch (26)	0.090	Beta	Lynch (26)
Probability of death from LT[h] (Year 2 +)	0.048	Beta	Lynch (26)	0.048	Beta	Lynch (26)
Probability of death for all causes						
Probability of death	0.020	Beta	Australian Bureau of Statistics (2015)	0.020	Beta	Australian Bureau of Statistics (2015)

[a] Five and three year probabilities were converted into annual probabilities using the ProbToProb function in TreeAge; [b] Distributions used in probabilistic sensitivity analysis; [c]CHB = Chronic Hepatitis B, no cirrhosis; [d]CC = Compensated cirrhosis; [e]HCC = Hepatocellular carcinoma; [f]sAg loss = Spontaneous seroclearance; [g]DC= Decompensated cirr hosis; [h]LT = Liver transplant

Table 3: Utility estimates and direct costs for various health states:

Health states	Utilities	Direct costs (AU $)*	
		Natural history	With treatment
CHB	0.68 (0.66 - 0.70)	$2,267	$3,592
CC	0.69 (0.66 - 0.71)	$2,027	$2,793
DC	0.35 (0.32 - 0.37)	$21,923	$23,574
HCC	0.38 (0.36 - 0.41)	$21,993	$23,126
sAg loss‡	0.79 (0.77 – 0.80)	$0	$0
LT (year 1)¶	0.57 (0.54 - 0.60)	$285,083	$285,083
LT (year 2+)¶	0.67 (0.64 - 0.69)	$45,726	$45,726

CHB – chronic hepatitis B, no cirrhosis; CC – compensated cirrhosis; DC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant.

‡ - Individuals achieving sAg loss were discharged and hence their cost is $0.

¶ - Assumption that everyone post liver transplant will be on anti-viral therapy hence, no difference in costs between the natural history and treatment arm.

*As only point estimates were obtained for these costs, the standard error was assumed to be equal to the mean as has been done elsewhere (46)

Gamma distributions were used for calculating all costs in this model

Table 4: Economic and clinical outcomes assuming a 10-year horizon for each scenario:

Time Horizon	Direct costs/QALYs (per patient)	Scenario 1	Scenario 2	Scenario 3
10 years	Mean total health care costs	AU $64,597	AU $61,964	AU $60,133
	Mean QALYs gained	7.684	7.985	8.196
	ICER	Dominated by Scenarios 2 and 3	Dominated by Scenarios 3	Dominant scenario
	Clinical outcomes/Cost savings for entire cohort of HBV patients	**Scenario 1**	**Scenario 2**	**Scenario 3**
	Total number of liver transplants	869	563	348
	Number of liver transplants avoided (compared to Scenario 1)	-	306	522
	Cost savings due to LT avoided (compared to Scenario 1)		AU $13,913,173	AU $23,783,162
	Total number of HCC cases	320	225	159
	Number of HCC cases prevented (compared to Scenario 1)	-	95	161

Time Horizon	Direct costs/QALYs (per patient)	Scenario 1	Scenario 2	Scenario 3
	Cost savings due to HCC cases prevented (compared to Scenario 1)		AU $2,042,563	AU $3,463,634
	Total number of DC cases	560	348	198
	Number of DC cases prevented (compared to Scenario 1)	-	212	361
	Cost savings due to DC cases prevented (compared to Scenario 1)		AU $4,594,016	AU $7,826,425
	Total number of deaths	779	635	534
	Number of deaths prevented (compared to Scenario 1)	-	144	245

QALY – quality adjusted life years; ICER - Incremental cost effectiveness ratio;HBV - hepatitis B virus; HCC – hepatocellular carcinoma; DC – decompensated cirrhosis.

Cost savings were estimated as the number of cases avoided/prevented multiplied by the cost associated with HCC, DC and LT health states in the natural history and treatment arms as shown in table 3.

Figure 1: Markov structure

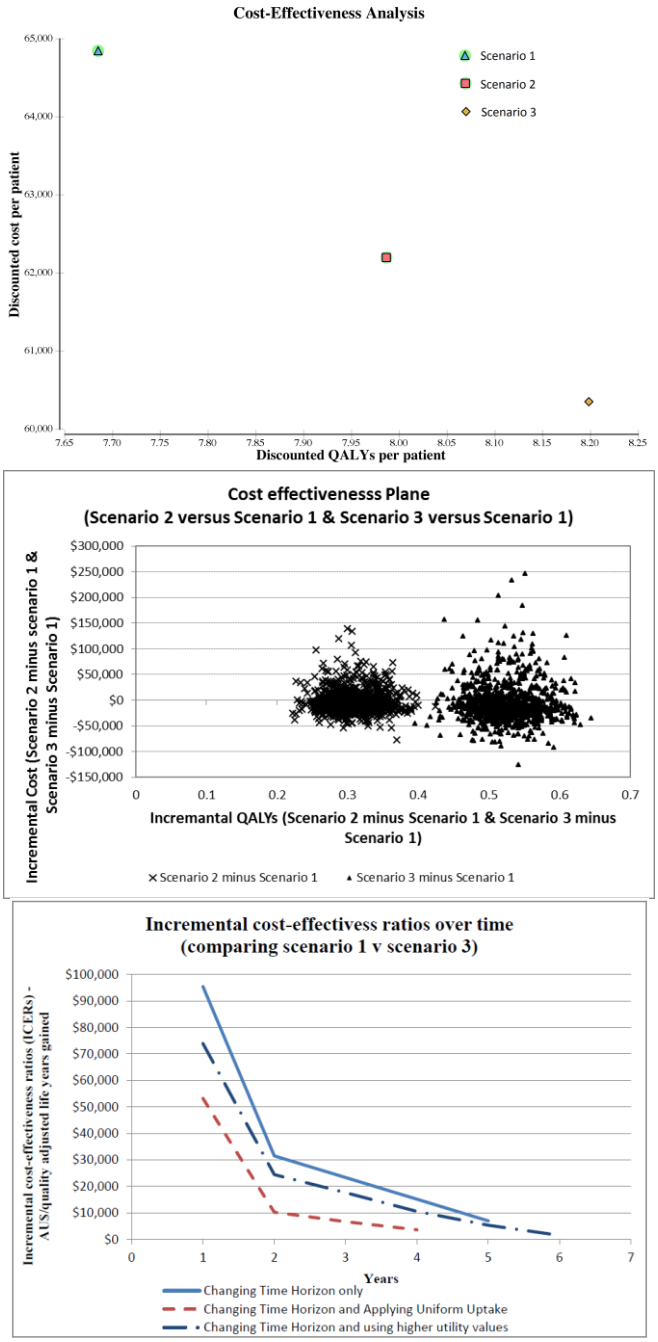

Figure 2 A, B&C: Cost-effectiveness analysis, cost effectiveness plane (CEP) and Incremental cost-effectiveness ratio with varying time horizons while comparing various scenarios:

Footnote: QALY – quality adjusted life years

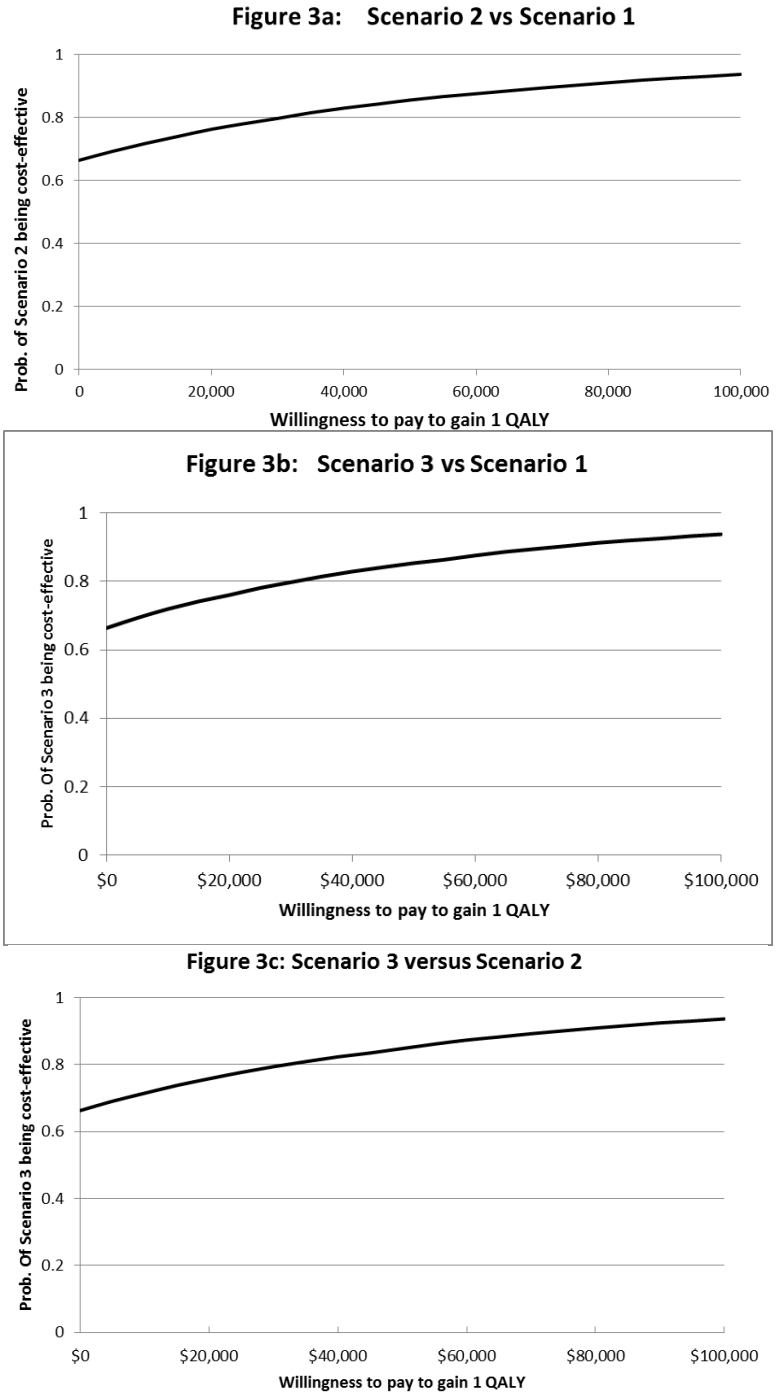

Figure 3: Cost-effectiveness acceptability curves (CEAC) comparing:

A) Scenario 2 v Scenario 1

B) Scenario 3 v Scenario 1

C) Scenario 3 v Scenario 2