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Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B - a systematic review and economic evaluation

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Commercial in confidence data

This document contains no commercial in confidence data.

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Summary

Aim

The aim of this systematic review and economic evaluation was to assess the clinical-effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alfa (PEG) for the treatment of adults with chronic hepatitis B infection (CHB). This independent assessment will be used by the National Institute for Health and Clinical Excellence (NICE) to issue guidance to the health service in England and Wales on treatment for patients with CHB.

Epidemiology and background

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV). Key routes of transmission include injecting drug use, sexual contact, and from mother to child (particularly in South East Asia). A safe and effective vaccine is available and many countries employ universal vaccination programmes for newborns and adolescents, although this is not currently the case in the UK.

Acute infection is largely asymptomatic, and is cleared by 95% of adults. Chronic disease results from an inadequate immune response to the primary infection, allowing continued viral replication and presence of the surface antigen (HBsAg). Those who develop chronic disease may remain asymptomatic for some time before developing symptoms of liver disease.

Patients with CHB are divided into two sub-groups based on the presence or absence of the 'e' antigen:

- HBeAg-positive CHB (also referred to as 'wild type' CHB), is common in Western countries and is generally the first stage of infection. Patients can seroconvert and develop antibodies (anti-HBe) either spontaneously or following anti-viral treatment (e.g. with interferon alfa taken up to a year). Many then enter the low or non-replicative phase of chronic infection, associated with relatively low levels of viral replication and less progressive disease. A proportion may relapse and undergo seroreversion (losing anti-HBe, and re-gaining HBeAg).
- HBeAg-negative CHB (also known as 'pre-core mutant' or 'variant' hepatitis B), was identified relatively recently and is a variant HBV strain usually carrying a mutation within the pre-core region of the HBV genome that permits viral replication but prevents production of HBeAg (or a mutation within the core region of the genome that diminishes HBeAg expression). This variant may be acquired at infection or following HBeAg seroconversion. A proportion of these individuals have active viral replication as evidenced by high viral load and require treatment.
    - The goal of treatment is to normalise biochemical alanine aminotransferase levels (ALT), lower HBV Deoxyribonucleic acid (DNA) levels, and reduce inflammation of the liver to limit progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death. Interferon alfa may be given initially to reduce HBV DNA replication and ALT. Those requiring long term treatment, or those at a more advanced stage of disease can be given a nucleotide/nucleoside analogue (e.g. lamivudine), although this is compromised by the development of resistance over time. This sub-group is

predominant in South East Asia, and the Mediterranean region, and now comprises the majority of chronic cases in the UK. Only a small proportion of patients (whether HBeAg positive or negative) ever undergo HBsAg seroconversion, which is considered to signify resolution of CHB infection.

The UK is considered to be a low prevalence country (<2%) and there are approximately 156,000 people in England and Wales infected with CHB (180,000 / 0.3% in the UK), with around 7,000 estimated new cases every year (mostly from immigration of established HBV carriers, many of whom are thought to be in the asymptomatic 'immunotolerant' phase). Intravenous drug use remains the single greatest risk factor for UK acquired acute HBV infection, with maternal transmission responsible for many of the chronic cases. Because of shared routes of transmission a proportion of those infected with HBV are also co-infected with Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV) and Hepatitis D Virus (HDV).

Methods

Literature searches were conducted to identify studies of clinical-effectiveness; cost-effectiveness; quality of life; resource use/costs; and epidemiology/natural history. The searches were applied to several electronic bibliographic databases including: Cochrane Systematic Reviews Database; Cochrane Central Register of Controlled Trials; Medline and Embase. Other searches included reference lists of retrieved reports, relevant websites and industry submissions to NICE.

For the clinical-effectiveness review we included randomised controlled trials (RCTs) which compared pegylated interferon alfa 2a and adefovir dipivoxil to currently licensed treatments for chronic hepatitis B (including non-pegylated interferon alfa, lamivudine, and best supportive care). Short term outcomes were biochemical, histological and virological response to treatment, drug resistance, and adverse effects. Long term outcomes included survival, progression to advanced disease states (e.g. cirrhosis) and health related quality of life.

The trials were reviewed in a narrative synthesis but meta-analysis was not undertaken due to heterogeneity in the interventions and comparators evaluated.

Results – clinical effectiveness

A total of 1085 references to clinical effectiveness studies were identified. After screening, six fully published RCTs and one systematic review met the inclusion criteria:

- Four RCTs evaluated the effectiveness of adefovir dipivoxil, two as monotherapy compared to placebo, and two in lamivudine resistant patients. In the latter, patients either continued taking lamivudine, switched to adefovir dipivoxil, or received adefovir in addition to on-going lamivudine.
- Two RCTs reported results for pegylated interferon alfa-2a. One compared pegylated interferon alfa-2a monotherapy with pegylated interferon alfa/lamivudine dual therapy, and lamivudine monotherapy.
- Four of the six RCTs evaluated the effectiveness of treatment in patients with HBeAg positive CHB, whilst the other two included HBeAg negative patients.

- Most patients had compensated liver disease with only a small proportion having cirrhosis (Additional studies in patients with decompensated cirrhosis and following liver transplant are reviewed). Most patients were treatment naïve (apart from two studies which included lamivudine resistant patients).
- In nearly all studies, results are presented at the end of 48 to 52 weeks of treatment, although the pegylated interferon alfa studies reported outcomes 24 weeks following cessation of 48 weeks of treatment.
- In addition to the six fully published RCTs, two conference abstracts were reviewed. One reports interim results from an on-going phase II adefovir dipivoxil RCT, and the other reports a completed, but as yet not fully published, phase III RCT of pegylated interferon alfa-2a in HBeAg positive patients.
- Some of the adefovir dipivoxil RCTs have been extended, with patients treated for up to 5 years. Only 3 year results are currently available, as conference abstracts.
- The published trials were of good quality, although details of randomisation and allocation of concealment were poorly reported.

Adefovir dipivoxil

- In terms of reductions in HBV DNA:
  - Adefovir dipivoxil was significantly more effective than placebo. Response rates were in the range 21% to 51% compared to 0, respectively.
  - For patients resistant to lamivudine, response rates were significantly higher for those treated with adefovir dipivoxil in addition to on-going lamivudine than those who continued on lamivudine with placebo (35% to 85% compared to 0-11%, respectively).
  - Reductions in serum HBV DNA levels after 48 weeks of adefovir dipivoxil therapy were not significantly different when comparing participants by genotype or race.

- Significant ALT reductions to normal levels were observed in all studies:
  - Response rates for adefovir dipivoxil monotherapy after a year's treatment were in the range of 48% to 72%, compared with 16% to 29% for placebo.
  - In lamivudine resistant patients, significantly higher response rates were observed for patients who were given adefovir dipivoxil in addition to lamivudine, compared to those who continued on lamivudine with placebo (37% vs 9%). Response rates for patients who switched to adefovir dipivoxil (+ placebo) were significantly higher than rates in patients who continued on lamivudine (+ placebo).

- In terms of HBeAg loss and seroconversion:
  - Rates of HBeAg loss and seroconversion were generally higher in treatment naïve patients than in patients who were resistant to lamivudine.
  - For treatment naïve patients, seroconversion rates were 12% to 14% for adefovir dipivoxil compared to 6% for placebo (statistically significant).
  - Rates were higher for lamivudine resistant patients who received adefovir dipivoxil in addition to on-going lamivudine, than those who continued on lamivudine (with placebo) (8% vs 2%, respectively. No significance value reported).

  - Similarly, rates were higher for lamivudine resistant patients who switched to adefovir dipivoxil, than those who continued on lamivudine (with placebo) (11% vs 0, respectively. Not statistically significant).
  - HBsAg loss or seroconversion associated was observed in a minority of patients (<5%) taking adefovir dipivoxil.

- Two adefovir dipivoxil studies reported changes in liver histology. In general, histological improvement and necroinflammatory activity/ fibrosis scores were significantly better in adefovir dipivoxil groups than in placebo groups.

- Dose discontinuations for safety reasons were low for patients receiving adefovir dipivoxil. With the exception of headache, the most commonly reported adverse events were often seen in the placebo groups in similar proportions to the adefovir dipivoxil groups, with different trials reporting conflicting results.

- A pooled analysis of 629 patients from five studies reports cumulative resistance rates of 0% in year one, 2.05% in year two, 7% in year three and 14.5% in year four.

- Some of the patients in adefovir dipivoxil trials are continuing to receive treatment for up to 5 years. Result after three years of continuous therapy are available only through conference abstracts.

- A number of observational studies evaluating adefovir dipivoxil in pre- and post-liver transplant patients were identified. HBV DNA and ALT levels are generally observed to reduce in these patients. Three year survival rates in the largest of these studies were in excess of 80%.

Pegylated interferon alfa-2a

- In the two pegylated interferon alfa-2a combination therapy trials, pegylated interferon alfa / lamivudine dual therapy, and pegylated interferon alfa monotherapy were similar in effect on HBV DNA and ALT levels, and were both significantly superior to lamivudine monotherapy:
  - For HBeAg positive patients, end of follow-up HBV DNA response rates were 32%, 34% and 22%, respectively (based on unpublished data).
  - For HBeAg negative patients, end of follow-up HBV DNA response rates were 43%, 44% and 29%, respectively.
  - For HBeAg positive patients, end of follow-up ALT response rates were 41%, 39% and 28%, respectively (based on unpublished data).
  - For HBeAg negative patients, end of follow-up ALT response rates were 59%, 60% and 44%, respectively.
  - HBV DNA response rates tended to decrease between cessation of treatment and follow-up, whereas ALT response rates tended to increase (HBeAg negative patients only. Data not currently available for HBeAg positive patients).

- HBeAg seroconversion rates at follow-up were significantly higher for pegylated interferon alfa monotherapy patients than for those receiving either a combination of pegylated interferon alfa and lamivudine or lamivudine monotherapy (32%, 27% and 19% respectively).

- For the comparison between pegylated interferon alfa-2a and non-pegylated ('standard') interferon alfa-2a, there was a significant difference in the combined outcome of ALT normalisation, HBV DNA response, and HBeAg seroconversion at follow-up (12% vs 24% respectively, p=0.036). When data from three different doses of pegylated interferon alfa were pooled, differences between the two interferons according to ALT, HBV DNA, and seroconversion rates as single outcomes were not significant.

- Changes in liver histology were reported by only one study. There was no statistically significant difference in histological improvement between the pegylated interferon alfa monotherapy group, the lamivudine monotherapy group and the dual therapy group, although a higher percentage of improvers was reported by the pegylated interferon alfa group.

- Two pegylated interferon alfa trials reported small percentages (up to 5%) of HBsAg loss or seroconversion among patients receiving pegylated interferon alfa either as monotherapy or in combination with lamivudine, but no HBsAg loss or seroconversion was reported in those receiving lamivudine monotherapy.

- Health related quality of life scores, as measured by the SF-36, decreased during treatment, but returned to at least baseline levels at follow-up (based on unpublished data). For HBeAg positive patients, there were no significant differences in scores between pegylated interferon alfa monotherapy, dual therapy with lamivudine, or lamivudine monotherapy between baseline and follow-up. Decreases in scores during treatment were smaller than observed in similar studies of chronic hepatitis C, based on indirect comparison.

- Dose discontinuations for safety reasons were significantly higher for patients receiving pegylated interferon alfa than for patients receiving lamivudine monotherapy. The most commonly reported adverse events in the pegylated interferon alfa studies were headache, pyrexia, fatigue, myalgia and alopecia. These were all experienced in greater numbers by patients receiving pegylated interferon alfa than by those receiving lamivudine monotherapy.

Results: Cost effectiveness

Systematic review of cost-effectiveness studies

A systematic review of economic evaluations comparing pegylated interferon alfa and adefovir dipivoxil with existing treatments was undertaken. No fully published economic evaluations of either intervention were identified. One conference abstract reported a USA cost-effectiveness study of adefovir dipivoxil as salvage therapy for chronic hepatitis B with lamivudine resistance. Included patients had both HBeAg positive and negative CHB without cirrhosis. A Markov model was used to estimate cost effectiveness of interferon alfa (6-12 months); lamivudine; and lamivudine

followed by adefovir dipivoxil when resistance occurs. Adefovir dipivoxil generated the most (undiscounted) life years, but at highest costs, with an incremental cost-effectiveness ratio of $14, 204 per life year gained.

The systematic review also identified six cost-effectiveness studies of existing treatments for CHB, published between 1995 and 2002. We reviewed their methods to set the context for our own assessment of cost-effectiveness.

- The studies modelled a range of treatment scenarios based on interferon alfa and lamivudine as both mono and dual therapies, and supportive care (i.e. monitoring and treatment of the symptoms of disease progression, instead of anti-viral treatment). Countries included the USA, UK, Poland and Australia.
- State transition / decision tree models were used to translate short term virological or biochemical outcomes into long term effects, including disease progression, life years and quality adjusted life years (QALYs) (two of the studies use the same model).
- Clinical-effectiveness data were taken from existing published RCTs, as opposed to prospectively conducted RCTs with integral economic evaluations.
- None of the evaluations included patients with HBeAg negative CHB.
- Costs for treatment and monitoring and utility values were derived from a number of sources, including expert clinical opinion. HBeAg seroconversion and its effect on disease progression (e.g. development of cirrhosis) was the primary outcome.
- Although some of the studies were similar in terms of scope (i.e. to evaluate the clinical effectiveness of anti-viral treatment for CHB), they also varied in terms of assumptions, time horizons, transition probabilities, supporting data and scenarios modelled, making it difficult to draw comparisons between them.

Systematic review of health related quality of life studies

There is little published literature on health related quality of life in patients with CHB.

- Only one study reporting health state values/utilities for patients with CHB was identified. The study derived utility scores for asymptomatic, mildly symptomatic and severely symptomatically HBV states using ratings expressed by 200 physicians in a US Medical School, using a form of time trade off-technique via questionnaire. As expected utility scores declined with increased disease severity 0.812 (asymptomatic), 0.670 (mildly symptomatic) and 0.218 (severely symptomatic).
- Two studies have reported on health-related quality for chronic hepatitis B patients who were not on anti-viral therapy using a generic quality of life instrument (SF-36). The limited evidence available suggests that the impact on quality of life for CHB infection is not as great as for hepatitis C, when in the asymptomatic state. However there is no evidence of a difference in the impact of CHB and HCV on quality of life once patients have progressed to cirrhotic and decompensated disease.

SHTAC cost-effectiveness analysis

We developed a model to estimate the cost-effectiveness (cost-utility) of pegylated interferon alfa-2a and of adefovir dipivoxil compared to non-pegylated interferon alfa, lamivudine and best supportive care in a UK cohort of adults with chronic hepatitis B.

The perspective of the cost-effectiveness analysis was that of the NHS and personal social services.

A Markov state transition model was constructed, informed by a systematic search of the literature to identify source material on the natural history, epidemiology and treatment of chronic hepatitis B. The state transition model indicates that within the natural history of the disease patients with CHB may remain in that state, may move on to more progressive stages of liver disease (such as cirrhosis or hepatocellular carcinoma), or may clear the disease spontaneously/move into remission. A cohort of treated and untreated patients pass through the eight disease states of the model at different rates:

- chronic hepatitis B
- HBeAg seroconversion/remission
- HBsAg seroconversion
- compensated cirrhosis
- decompensated cirrhosis
- hepatocellular carcinoma
- liver transplant
- death

Furthermore, there are 12 'tunnel states' for each of the states which allow the model to take into account each patient's treatment history, specifically whether or not they have developed drug resistance and have switched treatments. The model has a lifetime horizon and a cycle length of one year, with a half-cycle correction applied.

The principal effect of anti-viral treatment is to change patients' serological, biochemical, histological, or virological status to place them in health states where they are less likely to develop progressive liver disease. For treated patients clinical effectiveness results (HBeAg seroconversion rates and ALT normalisation rates) were taken from the Phase II/III RCTs identified in our systematic review. Transition probabilities for untreated patients were taken from the published literature.

The baseline cohort comprised individuals with a median age of 31 years (HBeAg positive CHB) and 40 years (HBeAg negative CHB). 70% of HBeAg positive and 90% of HBeAg negative patients are male. All have chronic hepatitis B, but have not progressed to cirrhosis.

To estimate changes in health related quality of life published age-specific quality of life weights for both CHB and chronic hepatitis C were taken from the published literature. Resource and health state costs for assessment, investigation, treatment, and monitoring were derived from the published literature and from discussion with clinical colleagues, and supplied by an English NHS Hospitals Trust. Costs are discounted at 6% and health outcomes discounted at 1.5%.

For the interventions assessed comparisons are made to their closest comparator (for pegylated interferon alfa this is to non-pegylated interferon alfa, for adefovir dipivoxil to lamivudine) and all interventions and comparators are also evaluated against the best supportive care option.

In addition, the cost-effectiveness of a series of more clinically meaningful sequential treatment scenarios are modelled. For example, interferon alfa as first-line treatment with lamivudine or adefovir dipivoxil reserved as second-line treatment for those patients who fail to respond to interferon alfa. We report the results of these comparisons in terms of the incremental gain in quality adjusted life years (QALYs) and the incremental costs determined in the cohort analysis.

Incremental cost per QALY estimates (baseline cohort of all patients) were:
- £5,994 - Non-pegylated interferon alfa (24 weeks) compared to best supportive care
- £6,119 - Pegylated interferon alfa (48 weeks) compared to non-pegylated interferon (24 weeks)
- £3,685 - Lamivudine compared to best supportive care
- £16,569 - Adefovir dipivoxil compared to lamivudine

Incremental cost per QALY estimates (HBeAg positive patients only) were:
- £7,936- Non-pegylated interferon alfa (24 weeks) compared to best supportive care
- £16,166 - Pegylated interferon alfa (48 weeks) compared to non-pegylated interferon (24 weeks)
- £3,489- Lamivudine compared to best supportive care
- £15,289- Adefovir dipivoxil compared to lamivudine

Incremental cost per QALY estimates (HBeAg negative patients only) were:
- £3,922- Non-pegylated interferon alfa (48 weeks) compared to best supportive care
- £ 2,162 - Pegylated interferon alfa (48 weeks) compared to non-pegylated interferon (24 weeks)
- £ 4,131 - Lamivudine compared to best supportive care
- £18,620 - Adefovir dipivoxil compared to lamivudine

In terms of sequential treatment strategies, incremental cost per QALY estimates ranged from £3,604 (non-pegylated interferon alfa followed by lamivudine, versus non-pegylated interferon alfa alone) to £11,402 (Non-pegylated interferon alfa followed by lamivudine with adefovir salvage, versus non-pegylated interferon alfa followed by lamivudine). Separating these results out for patients with HBeAg positive and negative disease reveals different patterns in the cost-effectiveness of these sequential treatment strategies. In all of these cases the incremental cost-effectiveness ratios are well within the range that would conventionally be regarded as being cost-effective.

In the deterministic sensitivity analysis for pair-wise comparisons, variations in assumptions which had little impact on cost-effectiveness ratios included:
- Excluding transitions from the HBeAg seroconverted state to hepatocellular carcinoma
- Excluding the HBsAg seroconverted state
- Varying the composition of the initial cohort of patients in the model.

Factors which were sensitive included:

- Excluding the transition from compensated cirrhosis to HBeAg seroconversion. This had greatest impact on the cost per QALY for adefovir dipivoxil (increasing it to £30,494).
- Increasing the rate of resistance to adefovir (the highest cost per QALY being £25,565)
- Varying the assumption over the relapse rate for pegylated interferon responders with HBeAg negative disease (increasing the cost per QALY to £15, 640).
- Changing the discount rates to 3.5% for costs and outcomes. This increased the costs per QALYs for all drugs, particularly adefovir dipivoxil (£30,982).
- Changing the HBeAg seroconversion rate to carry forward the year 4 rate for all subsequent years in which a patient was treated, or to apply the spontaneous rate for years subsequent to year 4. This had a dramatic effect on the cost-effectiveness ratio for adefovir dipivoxil. It increased from £16,569 in the base case to £21,363 for the model that extrapolates beyond four years, and £50,168 for the model with no extrapolation (i.e. the spontaneous rate).

In terms of the results of the deterministic sensitivity analysis for sequential treatment strategies:

- The results appear to be robust to changes in the composition of the baseline cohort. However, reducing the proportion of the cohort that is assumed to be HBeAg positive dramatically reduces the incremental cost-effectiveness ratios for strategies that include pegylated interferon alfa and adefovir dipivoxil.
- In common with the pair-wise deterministic sensitivity analysis, excluding transitions from the compensated cirrhosis health state to HBeAg seroconversion produces a substantial increase in the cost-effectiveness ratio for strategies including adefovir, whereas the results appear to be little influenced by variation in transitions from the HBeAg seroconverted state to hepatocellular carcinoma or to HBsAg seroconversion.
- Changing the discount rates applied to costs and health outcomes to 3.5% has a similar effect as in the pair-wise sensitivity analysis, greatly increasing the cost-effectiveness ratio for strategies including adefovir dipivoxil.
- The incremental cost-effectiveness ratios for pegylated interferon appear to be particularly sensitive to variation in the relapse rate for HBeAg negative patients who achieve a response (by normalising ALTs) following treatment.

The probabilistic sensitivity analysis found that:

- Lamivudine is a cost-effective option at lower threshold levels of willingness-to-pay for health outcomes, but as the threshold is increased adefovir is increasingly likely to be the optimal intervention.
- Where a willingness to pay threshold of above £10,000 per QALY is employed, pegylated interferon alfa is highly likely to be the optimal intervention compared to non-pegylated interferon alfa (based on a cohort of HBeAg positive and negative patients).
- When restricting this comparison to HBeAg positive patients, the balance between the probability of non-pegylated interferon alfa and pegylated interferon alfa is less clear. For patients with HBeAg negative disease pegylated interferon alfa is highly likely to be the optimal intervention.
- The analysis of all scenarios suggests that interferon alfa (non-pegylated or pegylated) followed by lamivudine would be the optimal strategy at lower

threshold values of willingness to pay. As the threshold increases the sequential treatment strategy of pegylated interferon alfa, followed by lamivudine with adefovir added as salvage therapy is increasingly likely to be the optimal intervention.

Conclusions

Adefovir dipivoxil and pegylated interferon alfa-2a are both clinically-effective and cost-effective in the treatment of chronic hepatitis B in relation to current standard treatments and supportive care. The results of randomised controlled trials show that both drugs are associated with significant improvements on a number of biochemical, virological and histological outcomes in both HBeAg positive and negative patients. For a small proportion of patients this is associated with resolution of infection. For another proportion it leads to remission and a reduced risk of progressing to cirrhosis, hepatocellular carcinoma, liver transplant, and death. For others who do not respond or who relapse, re-treatment with another agent is necessary.

Further data are required on the effects of long term treatment, and durability of response following treatment cessation. Adefovir dipivoxil may be particularly suitable for long term treatment, particularly in advanced disease states due to relatively low rates of resistance.

Fully published economic evaluations of the two drugs were lacking as is data on health related quality of life. We developed a state transition Markov model to underpin our own cost-effectiveness assessment, supported by literature and clinical judgement. Results of our cost-effectiveness analysis demonstrate that incremental costs per QALY for a range of comparisons were between £5,994 to £16,569, and within the range considered by NHS decision-makers to represent good value for money. When subjected to sensitivity analysis most costs per QALY estimates remained under £30,000.

Recommendations for further research

Further randomised controlled trial evidence of the effectiveness of anti-viral treatment is required particularly for sub-groups of patients with different genotypes; patients with cirrhosis; patients from different ethnic groups; patients with co-infections (e.g. HIV, HCV) and co-morbidities; liver transplant patients; and children and adolescents.

Further published evidence is awaited on:

- The effectiveness of adefovir dipivoxil in combination with lamivudine in treatment naïve patients.
- The long-term effectiveness of adefovir dipivoxil treatment
- The effectiveness of pegylated interferon alfa in lamivudine non-responders, and in interferon alfa non-responders;
- Long-term follow-up of pegylated interferon alfa treatment
- Health related quality of life

LIST OF ABBREVIATIONS

µg	Microgram
AASL	American Association for the Study of the Liver
AASLD	American Association for the Study of Liver Diseases
ADV	adefovir dipivoxil
AIDS	Acquired Immuno Deficiency Syndrome
ALT	Alanine aminotransferase. An enzyme that indicates liver inflammation.
BASL	British Association for the Study of the Liver
BNF	British National Formulary
CCT	Controlled clinical trial (without random allocation to study groups)
CHB	Chronic hepatitis B
CI	Confidence interval
CIC	Commercial in Confidence
CPT	Child-Pugh-Turcotte - cirrhosis grading tool/system
CRD	NHS Centre for Reviews and Dissemination
/d	Per day
DARE	Database or Abstracts and Reviews of Effects
DAVG	DAVG is calculated as the difference between baseline serum HBV DNA and the area under the curve up to a pre-specified week.
dl	decilitre
DNA	Deoxyribonucleic acid
DoH / DH	Department of Health
EASL	European Association for the Study of the Liver
EuroQol	Also known as the EQ-5D instrument, used to estimate a patient's quality of life
FDA	Food and Drug Administration
GUM	Genito Urinary Medicine
HAI	Histological activity index
HAV	Hepatitis A virus
HAV IgM	IgM antibody to hepatitis A antigen
HBcAg	Hepatitis B s (core) antigen
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B s (surface) antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B deoxyribonucleic acid
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
Hep B	Hepatitis B
HIV	Human Immunodeficiency Virus recognised as the agent that induces AIDS
HRQOL	Health-related quality of life
HTA	Health technology assessment
IDU	Injecting drug user
IFN	Non-pegylated interferon alfa (either α-2a or α-2b)
IU	International units
ITT	Intention to treat
kg	Kilogram
kD	Kilodaltans
l	litre
LAM	lamivudine
MCHN	Managed Clinical Hepatology Networks (MCHN)
mg	Milligram
mins	minutes
MIU	Million international units
ml or mL	Millilitre
mm^3	Cubic millimetre

MU	Million units
n	Number of participants
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical and Health Excellence
NNT	Number needed to treat
NS	Not statistically significant
OR	Odds ratio
PEG	Pegylated interferon alfa-2a
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RNA	Ribonucleic Acid
s	second
SD	Standard deviation
Serum	the fluid that separates from clotted blood or blood plasma that is allowed to stand
SF-36	Short Form 36 instrument
SHTAC	Southampton Health Technology Assessment Centre
TAR	Technology Assessment Report
UL	Units per litre
/w	Per week
wk	week
wk	week
YMDD	Tyrosine-methionine-aspartate-aspartate
yrs	years

1 AIM OF THE REVIEW

The aim of this systematic review and economic evaluation is to assess the clinical-effectiveness and cost-effectiveness of adefovir dipivoxil for the treatment of chronic hepatitis B virus (CHB) infection and pegylated interferon alfa-2a for the treatment of CHB infection.

Comparators include currently licensed treatments for CHB, including interferon alfa-2a, and lamivudine, as well as best supportive care. Long term outcomes include survival, progression to advanced disease states (e.g. cirrhosis) and health related quality of life. Short term outcomes include biochemical, histological and virological response to treatment, drug resistance, and adverse effects.

This independent assessment will be used by the National Institute for Clinical and Health Excellence to issue guidance to the health service in England and Wales on treatment for patients with CHB.

2 BACKGROUND

2.1 Description of underlying health problem

2.1.1 Background

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV), and was first identified in 1965. Key routes of transmission include sexual contact (via exposure to blood, saliva and other body fluids), injecting drug use and from mother to child (particularly in South East Asia). In health care workers, needle stick injuries are also a relatively rare source of transmission. Some patients with haemophilia in the UK have been infected via contaminated blood products (as well as being infected with hepatitis C, HCV).

Upon infection the virus infects cells in the liver (hepatocytes) and the immune system will at some point mount a response to try and remove the infection (in some cases after several years). If untreated HBV can result in long term complications such as cirrhosis and liver cancer (Hepatocellular carcinoma – HCC). Carriers of the virus can remain asymptomatic for many years before presenting with symptoms of chronic liver disease.

In acute infection, the majority of cases are self limiting within 6 months, with patients developing lasting immunity to re-infection as the virus (surface antigen) is cleared from the blood and liver, although viral DNA can be detected in many cases. There may be no or few symptoms (about 70% of patients are asymptomatic), and treatment is generally not indicated. A small proportion of patients develop fulminant hepatitis which is characterised by marked liver damage and requires liver transplant.

Chronic disease results from an inadequate immune response to the primary infection, where viral replication continues and there is continuing presence of the surface

antigen (HBsAg). It can follow acute hepatitis, or from vertical transmission from mother to baby. In the latter case there may be no acute infection.

2.1.2 Initial stages of chronic infection

Figure 1 illustrates the natural history and stages of infection of hepatitis B (see also Appendix 1 for a glossary of terms). Chronic disease status is defined by the presence of hepatitis B antigen (HBsAg) for more than 6 months. The surface antigen HBsAg is present in all forms of the disease. Age at infection plays an important role in determining the disease pathway. Approximately 90% of children who acquire the infection as neonates or before their first birthday will develop chronic hepatitis B. For children who acquired the infection between ages 1 and 5 the risk is about 30%, and this reduces to 2% for older children and adults who become infected. Reasons for the high risk of chronicity in those who acquire the infection as neonates and young children remain uncertain. The risk of chronicity is low for transmission through sexual contact, IV drug use, acupuncture and transfusion, which are the main forms of transmission in the UK[1].

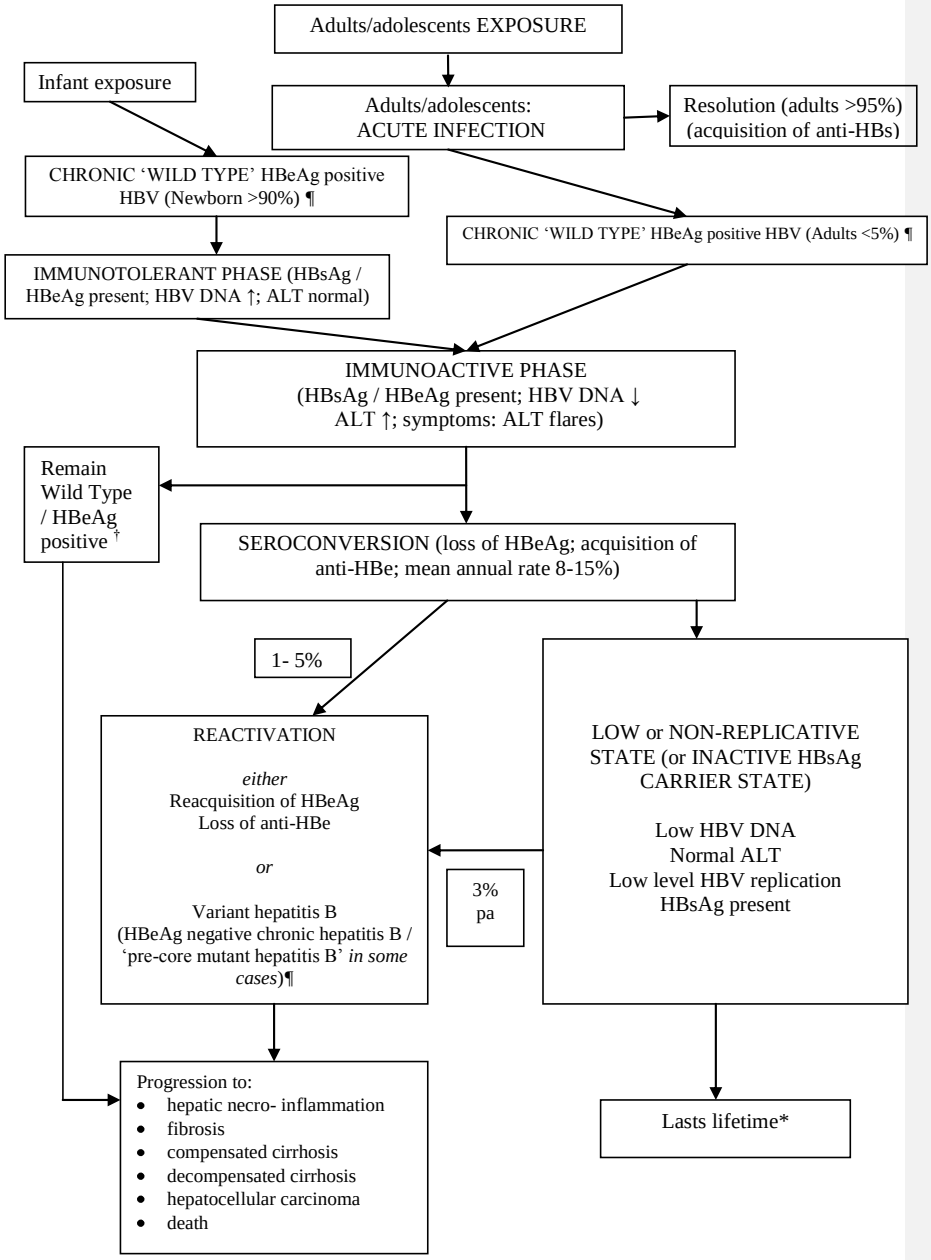
HBeAg-positive CHB (also referred to as 'wild type' CHB) is, for many, the first stage of chronic disease. This form of the disease prevails in Europe and North America. The first stage is the 'immunotolerant' phase during which the immune system does not actively fight the virus and which may last for a number of years[2]. In adults and those infected during adolescence there is no immunotolerant phase, and those who acquire the disease as neonates or in early childhood tend to have a worse response to immunotherapy and the disease continues to progress after HBeAg seroconversion[1]. During the immunotolerant phase, HBV DNA levels are increased but aminotransferase levels remain normal. Treatment is not indicated in this phase.

Progression to the 'immunoactive' phase of chronic HBeAg positive disease, whereby the immune system is actively fighting the virus is characterised by HBV DNA replication and an increase in alanine aminotransferase levels (ALT – an enzyme that indicates inflammation of the liver). Symptoms may appear during this phase, and 'flares' (short lived rises in ALT levels) of aminotransferases may occur before seroconversion from HBeAg to anti-HBe in some patients[3]. Treatment is indicated in this phase.

2.1.3 HBeAg / HBsAg seroconversion

Seroconversion results in the disease progressing either to an inactive carrier state (low- or non-replicative state) or to the HBeAg negative form of the disease. Between 50% and 70% of patients with elevated aminotransferases spontaneously seroconvert within 5-10 years of diagnosis[3], with a mean annual rate of 8-15% in Western countries. Seroconversion is more likely to occur in older people, females, and those with high aminotransferase levels. For most patients, seroconversion results in moving to the inactive HBsAg carrier state. However, between 1% and 5% of patients progress to HBeAg-negative chronic hepatitis, showing high serum HBV DNA levels, undetectable HBeAg and detectable anti-HBe levels[3].

Figure 1 – Hepatitis B natural history and stages of infection



† Some people will not seroconvert and will remain HBeAg positive in the long term, experiencing progression to fibrosis, cirrhosis, etc. Progression may not be as fast as experienced by patients who have reactivated disease, or who were HBeAg negative from the outset.
¶ Some people will develop Variant Hepatitis B (HBeAg negative / pre-core mutant HBV) from the outset, thus will not experience seroconversion applicable to people with Wild Type hepatitis B. They will experience disease progression to fibrosis, cirrhosis, etc.
* Between 1-2% of people in Western Countries will experience infection resolution each year, characterised by loss of HBsAg and acquisition of anti-HBs.

The low- non-replicative or inactive HBsAg carrier state is characterised by low HBV DNA levels and normal ALT. Unless cirrhosis is present, this stage usually has a benign prognosis, but around 3% of patients per annum may undergo reactivation and develop progressive liver disease[3] (thus moving from the 'low or non replicative state' to the 'Reactivation' box in Figure 1). It is not possible to determine from HBV DNA values alone whether patients with antibodies against HBeAg will have inactive disease or continue to experience exacerbations[1]. However, patterns of ALT elevations and HBV DNA >10 copies/ml may be typical of progressive anti-HBe positive chronic hepatitis.

A small proportion (1-5%) of patients progress directly to the HBeAg-negative state on seroconversion, and approximately 20% - 30% of patients in the inactive carrier state also become HBeAg-negative[3]. HBeAg-negative CHB (also known as 'pre-core mutant' or 'variant' hepatitis B) was identified relatively recently and is a variant HBV strain carrying a mutation within the pre-core region of the HBV genome that permits viral replication but prevents production of HBeAg (or a mutation within the core region of the genome that diminishes HBeAg expression)[4]. Although some patients acquire HBeAg negative infection on or following seroconversion, many develop the variant at an earlier stage, or from the outset.

HBeAg negative infection, common in Mediterranean areas and SE Asia, is considered to be the most severe form of the disease, and it is characterised by raised (but fluctuating) ALT and detectable HBV DNA levels. There are three main patterns of ALT activity: recurrent flares with normalization in between; recurrent flares with persistently abnormal serum aminotransferase levels in between; persistently abnormal ALT without flares[3] (Table 1).

Table 1- Chronic Hepatitis B infection

	HBsAg	**HBeAg**	**anti-HBe**	**ALT levels**	**HBV DNA levels**	**necro-inflammation**
HBeAg positive	Y	Y	N	elevated	elevated	high
Inactive HBsAg carrier state	Y	N	Y	normal	low/undetectable	minimal/none
HBeAg negative	Y	N	Y	elevated*	detectable*	high

***liable to fluctuations

Around 0.5-2% of people with CHB develop antibodies to HBsAg each year (0.05 – 0.08% in Asia) whereby they lose the surface antigen and develop anti-HBs. This is most common in the year following HBeAg seroconversion (although patients can also seroconvert from the immunotolerant phase) and signifies resolution of chronic infection.

The role of genotypes (A-G) in the natural history of HBV and in the clinical management of patients is less clear than it is in the hepatitis C virus (HCV) where genotype significantly predicts treatment outcome. There is some evidence that

genotype C is associated with higher risk of cirrhosis and HCC than genotype B. Genotype A has known molecular constraints upon pre-core mutations. European Association for the Study of the Liver (EASL) guidelines acknowledge the paucity of research in this area and recommend that the role of genotype in treatment be investigated[3].

2.1.4 Long term complications

As with hepatitis C patients with chronic hepatitis B are at increased risk of progressing to long term complications including cirrhosis (scarring) of the liver, decompensated liver disease, and/or hepatocellular carcinoma (HCC). The risk of progression varies with geographical location and mode of transmission. Evidence suggests that 2-5.5% of HBeAg positive people and 8-10% of those who are negative progress to cirrhosis annually[3], and 6% of people with compensated cirrhosis progress to hepatic decompensation each year. Decompensated liver disease occurs when the liver can no longer compensate for scarred tissue. It is characterised by ascites, variceal bleeding and hepatic encephalopathy, and is associated with irreversible liver failure, requiring liver transplantation. The five year mortality rate for chronic hepatitis B without cirrhosis is 0-2%, but this increases to 14-20% for those with compensated cirrhosis and 70-80% after the occurrence of decompensation[3].

Death from liver disease and HCC is common in chronic hepatitis B. It is estimated that there are over 1,200 new cases of HCC in the UK each year of which 430 are caused by viral hepatitis. A cohort of 3658 HBsAg positive blood donors in England and Wales was followed up for an average of 22 years[5]. In that time 5% died from HCC and 12% from non-malignant liver disease. The risk is greater in men (33.5 in men and 4.4 in women per 100 000 person years) and in older people.

2.1.5 Co-infection

Due to shared routes of transmission, many people with HBV are also at risk of becoming infected with HIV, HCV and other viruses. Over 80% of HIV-infected people have evidence of past or persistent HBV infection, with 8-11% having the persistent presence of HBsAg which defines chronic carrier status[6].

Highly active antiretroviral therapy (HAART) related restoration of immune responses may be associated with suppression of HBV replication and loss of HBeAg in some patients[3], but co-infection with HIV is generally thought to accelerate HBV disease progression, leading to a higher incidence of cirrhosis and mortality[7]. Lessels and Leen[6] reviewed the impact of HIV and HAART on HBV disease progression. They reported that HIV infection has an unclear effect on ALT, with people co-infected with HIV showing significantly lower levels of this marker in some studies, but not in others. The majority of studies they reviewed show less severe hepatic inflammation in patients co-infected with HIV, although two studies found that co-infected people showed an increased progression to cirrhosis. They also found evidence to suggest that people with HIV co-infection may have a greater risk of HBeAg reactivation, particularly if they have low CD4+ lymphocyte counts. The

initiation of therapy with protease inhibitors has reportedly led to HBsAg reactivation in some people who had apparently cleared HBsAg previously.

Lamivudine has been shown to have a beneficial effect on HBV + HIV co-infected people in terms of HBV DNA clearance, trends towards reduction in HBeAg, and lower ALT levels[6]. Lamivudine resistance is reported to be higher in HBV patients who are co-infected with HIV, and HIV viral resistance to lamivudine may also develop. Combination therapy with lamivudine and tenofovir has been shown to be beneficial in people who have HBV + HIV co-infection[6].

HBV patients who are co-infected with HCV tend to have more severe chronic hepatitis and are at greater risk of cirrhosis and HCC than HBV patients without HCV co-infection. Many studies show that HBV replication is suppressed in co-infected patients while HCV replication remains active[3]. The EASL guidelines report that there is little information on the efficacy of antiviral treatment in HBV patients co-infected with HCV[3].

EASL guidelines also make brief mention of other co-morbidities[3]. Little evidence was found regarding HDV co-infection, but treatment is recommended in patients with moderate to severe chronic hepatitis, and it was noted that there is an improvement in liver histology when a biochemical response is maintained.

2.1.6 Incidence and prevalence

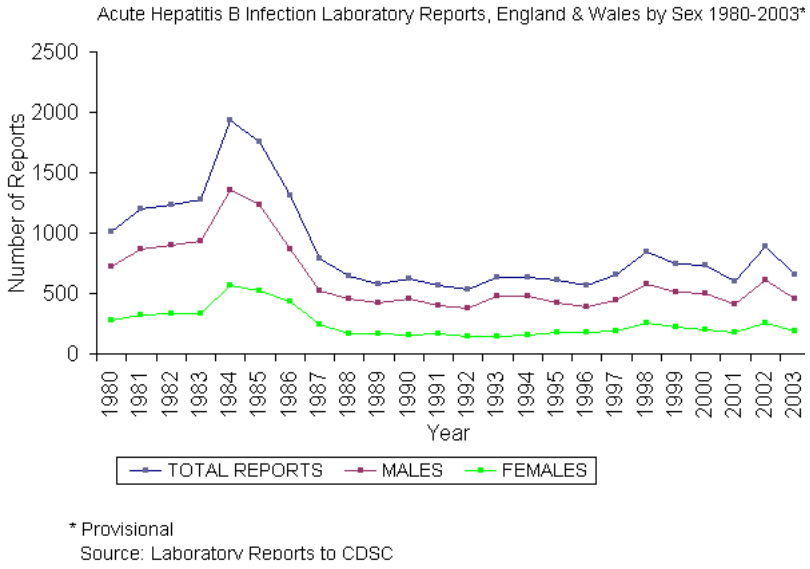
Approximately 400 million people worldwide are infected with chronic HBV, although levels vary geographically[1]. In North-western Europe, North America and Australia there is a low level of endemic HBV, and the virus is usually transmitted via needle sharing among intravenous drug users (IDU) and by sexual transmission. High levels of infection are found in Africa and Asia, where the virus is usually transmitted perinatally or during early childhood. Countries are classified by prevalence of HBV carriage as high (≥8%), intermediate (2-7%), or low (<2%)[8]. The UK is considered to be a low prevalence country with around 156,000 people in England and Wales infected with CHB[9] (180,000 / 0.3% in the UK) and around 7,000 estimated new chronic cases every year (mostly from immigration of established HBV carriers, many of whom are thought to be HBeAg negative, and in the immunotolerant phase, and thus not currently symptomatic). The lifetime risk of infection in the UK general population is 0.4% whereas in East Asia it is over 90%[10].

The incidence of acute hepatitis in England and Wales fell markedly in the late 1980s due to education campaigns and schemes to reduce needle sharing among injecting drug users (IDU), and vaccine uptake. The number of new cases fell from 1761 in 1985 to 581 in 1996. The majority of cases were adults aged 15-44 (80%) and male (70%). Mode of transmission was unknown in 46% of cases, 21% acquired the virus through intravenous drug use, 13% were acquired from sex between men and women, and 11% from sex between men[11].

More recent figures from the Health Protection Agency show an increase in acute hepatitis B reports since the late 1990s (Figure 2). In 2003 670 cases were reported, although it has been estimated that this represents only a small proportion of the true

incidence (estimated at 4,400 new cases a year[12]). The peak age group for reported infections is 25-34 years (232 in 2003), and the disease is more common in males than females (Table 2). Sex between men was the most commonly reported source of infection until 1994, but since 1995 rates of this form of transmission have decreased (possibly due to targeted vaccination campaigns), with a concurrent increase in transmission among intravenous drug users (IDUs). In 2003, of the 670 cases reported, injecting drug use was the predominant source of transmission of the cases where a cause was known (108 of 305, 35%); followed by 86 (28%) for heterosexual transmission; 60 (20%) for 'other' identified risk; and 51 (17%) for sexual transmission between men.

Figure 2 - Acute Hepatitis B infections 1980-2003



Source: Health Protection Agency (www.hpa.org.uk – accessed 21/10/04)

Table 2 - Acute hepatitis B laboratory reports: England and Wales, By Sex, 1990 – 2003

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003*
Male	457	401	376	482	473	424	384	442	574	512	505	416	615	481
Female	159	166	142	140	155	183	178	194	256	223	204	177	260	198
Not known	2	5	13	7	5	5	8	16	13	17	20	15	17	16
TOTAL	**618**	**572**	**531**	**629**	**633**	**612**	**570**	**652**	**843**	**752**	**729**	**608**	**892**	**695**

Source: Health Protection Agency (www.hpa.org.uk – accessed 20/05/05)
Note: Case Definition - HBsAg positive and Anti-HBc IgM positive with or without recent history of discrete onset jaundice or other symptoms compatible with acute infection.
* provisional
Source: Laboratory reports to CDSC

The unlinked anonymous prevalence monitoring programme found that in 2001 21% of injecting drug users had evidence of previous or current infection (anti-HBc). Intravenous drug use remains the single greatest risk factor for HBV infection. Vaccination coverage in this group was 37% to 39% in different regions. Because of shared routes of transmission a proportion of those infected with HBV are also co-infected with HIV, HCV and Hepatitis D Virus (HDV). There are no reliable estimates of the prevalence of CHB in prison populations. However, a study published in 2000 of inmates at 8 of the 135 prisons in England and Wales found that 8% were positive for anti-HBc (the core antigen)[13]. Twenty four per cent reported ever having injected drugs, 30% of whom reported injecting in prison. Among adult injecting users, 20% had anti-HBc. Infected prisoners who inject drugs and share needles are often undiagnosed represent a reservoir for infection.

UK prevalence data have been obtained from surveillance of anonymous spare sera submitted to laboratories for blood tests[14]. This found that 3.9% of adults aged 15-44 were positive for anti-HBc (the anti-body against the core antigen HBcAg), demonstrating prior exposure to the virus. Most (3.4%) were HBsAg negative, showing that their infection had resolved, 0.1% had evidence of acute infection and 0.4% were chronic carriers. The prevalence was higher in London than elsewhere. This confirmed earlier data from antenatal samples.

Figures for 2004 are available on the prevalence of infection among ante-natal women undergoing routine blood screening (National Blood Service / Health Protection Agency Centre for Infections Surveillance Scheme). Data on a total of 129,458 samples collected from 5 urban centres in England show a total HBsAg prevalence of 0.28% (360). Only around 15% (n=53) of these were HBeAg positive. Extrapolating these figures to the estimated 700,000 ante-natal cases each year gives a total of 1960 HBsAg positive women, of whom 294 will be HBeAg positive. However, the stage of progression and the proportion eligible for treatment is not known.

In summary, it is estimated that there are around 156,000 people in England and Wales infected with CHB[9] and around 7,000 estimated new chronic cases every year. Immigration to the UK is believed to account for the majority of new chronic cases, the majority of whom are HBeAg negative. Unless viral replication is high, not all of these cases will necessarily require treatment. Expert opinion suggests debate around which HBeAg negative cases should be treated.

2.1.7 Diagnosis

Hepatitis B is diagnosed by detecting the presence of HBsAg or HBV DNA in serum, and the diagnosis of mild or moderate to severe disease depends on liver biopsy and aminotransferase levels. The presence of HBsAg for at least 6 months is indicative of chronic hepatitis B infection[1]. A diagnosis of HBeAg-positive chronic hepatitis B requires the presence of HBeAg and HBV DNA in serum and no detection of anti-HBe. HBeAg negative has undetectable HBeAg, detectable anti-HBe and HBV DNA present in serum (although low and high levels of this can occur). In the inactive HBsAg carrier state, HBsAg and anti-HBe are present in serum, but serum

aminotransferase levels are normal and HBV DNA levels in serum are either low or undetectable[3].

The decision to treat will usually be made in cases where ALT concentrations are more than 1.5 times the upper limit of normal and HBV DNA concentrations are detectable by branched DNA or hybrid capture assays[1]. Liver biopsy is used to confirm CHB and to grade and stage disease severity.

2.1.8 Morbidity and quality of life

The impact of CHB on quality of life in the early stages of disease is not thought to be great. Many people do not know that they are infected and consequently may not present to health services for many years until symptoms of liver disease become evident. A study of patients at St Mary's Hospital, London found that Short Form-36 (SF-36) values for patients with HBV were lower than for the general population but only differed significantly on general health and mental health dimensions. They showed no significant reductions for physical health dimensions[15].

However, quality of life becomes significantly impaired as the disease progresses to cirrhosis, decompensated liver disease and HCC[16]. Patients who seroconvert into the low- or non-replicative state are thought to have relatively good quality of life. There is evidence to suggest that quality of life impairment in CHB is not as great as it is with chronic hepatitis C (HCV)[15;17].

2.1.9 Policy context

A safe and effective vaccine for hepatitis B has been available since 1982 and many countries operate a universal vaccination programme for newborns or adolescents. However, despite recommendations from the World Health Organisation the UK has not introduced such a policy, instead offering selective vaccination to key risk groups (e.g. men who have sex with men, injecting drug users, health care workers). Yet, uptake by risk groups has been reported to be low. Hahne and colleagues (2004)[10] reported that between 1995 and 2000 an estimated 43% of chronic infections were observed in risk groups targeted for vaccination. Therefore, nearly half of all infections could have been prevented if uptake had been successful. It has been suggested that the UK should reconsider its vaccination policy, and that universal immunisation should be offered to overcome low uptake and to reach those who may rarely come into contact with health services[18]. However, such a strategy would first need to be evaluated for its cost-effectiveness.

In terms of health policy HBV infection has been one of a number of infectious diseases addressed in a recent Department of Health strategy 'Getting ahead of the curve'[9]. The aim of the strategy is to describe the scope and nature of the threat posed by existing and new infectious diseases to the health of the population of England, and to establish priorities for action. A number of actions are proposed including: strengthened disease surveillance; new action plans for tuberculosis; blood-borne and sexually transmitted viruses; better public information and involvement on infectious diseases; stronger professional education and training; and a research and innovation

programme. Hepatitis B is one of the blood-borne viruses discussed, alongside HCV and HIV, with specific goals set for prevention and surveillance:

- Better understanding of the true incidence, prevalence and epidemiology and natural history
- Greater understanding of the causes of chronic liver disease, and the relative role of viruses
- Improved primary prevention (drug misuse; sexual practices; immunisation uptake particularly amongst gay and bisexual men, and prisoners)
- Improved secondary prevention (voluntary testing and counselling of high risk groups; contact tracing; antenatal testing).
- Improved treatment and care through managed clinical networks.

The prevention of hepatitis B has also been addressed at policy level through the Department of Health's National Strategy for Sexual Health and HIV (2001)[19] which sets targets for HBV vaccination particularly among high risk groups. For example, genito-urinary medicine clinics are required to offer HBV vaccinations to high risk groups (particularly men who have sex with men).

More generally hepatology has been the subject of a national plan for liver services in the UK, devised by the British Liver Trust, the British Association for the Study of the Liver and the British Society for Gastroenterology[20]. The aims of the plan are to advise commissioners on the most appropriate clinical arrangements for hepatology services in the UK; to provide clinical standards and guidelines against which local services should be monitored and assessed; and to provide a framework to ensure equitable access to high quality cost effective management of liver disease. Its key recommendations include the establishment of Managed Clinical Networks for hepatology; the establishment of systems for the collection of key data on outcomes of treatments and clinical effectiveness to enable health planning, and adoption of best clinical practice. It is envisaged that the plan will improve patient services by enhancing equitable access to high quality liver services; systems for effective planning of services; a structure for development of new hepatology centres; collection of data on the clinical effectiveness of treatment provision.

Despite these initiatives there have been calls for more concerted efforts to prevent and manage HBV infection. At the end of 2004 the Foundation for Liver Research launched a report entitled 'Hepatitis B: Out of the Shadows'[12] lobbying for a coherent policy for action and to raise the profile of the disease noting the relative dominance of hepatitis C which has its own governmental strategy and action plan[21]. The report makes a number of recommendations including:

- increased funding for research (particularly into epidemiology and the influence of immigration);
- more focus on determining the precise economic burden of HBV to the UK health service (and society in general);
- improving access to services and service provision; universal vaccination coverage, an urgent review of commissioning of specialised liver disease services, and
- greater public and professional awareness of hepatitis B.

Finally, in terms of clinical guidelines there do not appear to be any published British guidelines on the general management of hepatitis B, although the British HIV

Association have published guidelines on the management of viral hepatitides A,B and C[22], as well as patients co-infected with HIV and CHB[23]. European guidelines are available, published by EASL in 2003[3], based on a consensus conference attended by international experts in virology, epidemiology, natural history, prevention and treatment of hepatitis B.

2.2 Current service provision

Management of people with hepatitis B is the responsibility of a variety of people. In the health care setting hepatologists, gastroenterologists, and infectious disease specialists are commonly involved. Specialist hepatology nurses also have a role, particularly in terms of administering treatment.

The National Plan for Liver Services in the UK provides an overview of the organisation of hepatology services in the NHS[20]. There are three categories of hospitals providing hepatology services:

- District general and university-associated hospitals that have a gastroenterologist with a primary interest in liver disease.
- Teaching hospitals with a major interest in liver disease that do not undertake liver transplantation
- Liver transplant centres (n=7).

They estimate that there are around 10-15 hospitals that would qualify as a hepatology centre, and propose a set of criteria for qualification.

Managed Clinical Networks have recently been established which bring together commissioners (PCTs), service providers, voluntary agencies, local authorities and service users to plan and deliver high quality services, including prevention, screening, diagnosis, treatment and supportive care. It is envisaged that the number of networks will increase over the next few years and that one of their functions will be to increase capacity for delivering anti-viral treatment.

In spite of initiatives to foster cohesive service provision it is suggested that there are large disparities in the management of CHB across England and Wales. Variations exist in the frequency and intensity of monitoring, the proportion of patients receiving treatment and the management of patients who develop drug resistance[24]. A survey of 41 specialists from 33 NHS Trusts reported variations in service demand, provision and treatment. Some centres reported treating only between 10% and 20% of patients with CHB. Others reported treating between 40% and 60%. It was also reported that a typical District General Hospital may see between 10 and 15 new patients per month[12]. It is suggested that of the 156,000 people in England and Wales chronically infected with HBV, around 26% are diagnosed[24].

Anti-viral treatment for hepatitis B is dependent a number of factors, notably the stage of disease the patient is in (e.g. acute HBV; immunotolerant infection; immunoactive CHB; compensated cirrhosis, etc), the presence or absence of the ‘e’ antigen, and the potential for drug resistance and subsequent inability to use particular drugs at later stages of chronic liver disease. These and other factors govern when to start treatment, the type of treatment indicated, and its duration.

There are two modes of anti-viral treatment for CHB:

1. Short term or finite, circumscribed therapy with interferon alfa. The goal is to achieve an immune response in terms of HBeAg seroconversion (for patients who are HBeAg positive), suppression of HBV DNA, and where possible HBsAg seroconversion. This mode of treatment is a first line attempt to 'switch' the immune system into clearing the infection, or into remission. Although interferon alfa appears to be commonly used in this scenario some clinicians may use a nucleotide / nucleoside analogue.
2. Long term maintenance treatment for patients who have failed interferon alfa or for whom disease has advanced such that interferon alfa is contra-indicated. This would usually involve lamivudine, a nucleotide analogue. This mode of treatment may be particularly suitable for those HBeAg negative patients with high levels of HBV DNA and ALT levels. In these patients long term suppression of HBV replication with either nucleoside or nucleotide analogues will be necessary until the infected cells have been eliminated. The half-life of these cells may be 10 or more years[25]. Reducing levels to 'normal' levels will likely limit disease progression.

There is considerable debate regarding the place of monotherapy vs. combination therapy in either strategy.

As is evident from the above, some patients will be treated in more advanced disease states such as compensated cirrhosis, decompensated liver disease, pre- and post-liver transplant, and HCC. The purpose of treating pre-transplant patients is to suppress viral replication in order to reduce the likelihood of HBV infection recurring in the transplanted liver. However, post-transplant re-infection rates tend to be high necessitating continuing anti-viral therapy. Recurrent HBV infection is associated with rapid progression to cirrhosis and decompensation. Transplant patients may therefore receive life-long hepatitis immunoglobin (HBIG), immunosuppressive agents and anti-viral drugs such as lamivudine. However, the potential for resistance means that this drug can only be used with limited success in this patient group. Adefovir dipivoxil, associated with lower resistance, might be more suitable (see Sections 2.3.1and 4.1.2.9

The following sub-sections describe in greater detail the currently licensed drugs for CHB and their current use and place in the treatment of chronic infection, followed by a discussion of the newer drugs to be appraised by NICE.

2.2.1 Interferon alfa

Interferon alfa-2a (Roferon-A; Hoffman La-Roche) and 2b (IntronA; Viraferon; Schering-Plough) have been used as first line treatment of CHB for a number of years. Interferons are naturally occurring proteins with complex effects on immunity and cell function, and there are at least 15 different molecular species. Interferon alfa was the first pure human protein found to be effective in the treatment of cancer and has been used to treat chronic myelogenous leukaemia and other myeloproliferative disorders, renal carcinoma and infections such as chronic hepatitis C. The logical basis for using interferon alfa in the treatment of CHB was established by Ikeda and

colleagues[26] who found that some carriers have a reduced capacity to produce interferon alfa in vivo.

EASL guidelines recommend an initial course of 5 MIU per day or 9-10 MU three times a week over 4-6 months for patients who are HBeAg positive (Interferon alfa is administered by subcutaneous injection). For patients who are HBeAg negative and without cirrhosis the guidelines recommend (if there is no contra-indication to interferon alfa therapy) an initial 12-24 month course of interferon alfa 5-6 MIU three times a week. Patients who achieve HBeAg seroconversion can cease active treatment, and be monitored over time[3].

It is suggested that 5-10% of patients with CHB will receive interferon alfa in England and Wales[24]. Disadvantages include significant side effects (e.g. influenza like effects, depression, fatigue), and contra-indication in patients with advanced (decompensated) liver disease. Severe side effects are rare. However, long term therapy (e.g. > one year) can be hard for patients to tolerate.

2.2.2 Lamivudine

In 1998 lamivudine (Epivir, Zeffix; GlaxoSmithKline), a nucleoside reverse transcriptase inhibitor, was licensed for the treatment of CHB. It is also used to treat Human Immunodeficiency Virus (HIV) in patients with Acquired Immuno Deficiency Syndrome (AIDS). The advantage of lamivudine over interferon alfa is that it can be taken orally, there are fewer adverse effects, it can be used in patients with decompensated liver disease, and it is relatively cheaper.

EASL guidelines suggest that lamivudine be used if interferon alfa is contra-indicated (e.g. patients with decompensated liver disease), or if a patient does not respond to or cannot tolerate interferon alfa. For HBeAg positive patients the dose is 100mg daily for 1 year. HBeAg negative patients can be treated for longer[3]. Expert opinion suggests a lack of consensus around exactly how long to treat. Once treatment is withdrawn the virus nearly always emerges. However, maintenance therapy is compromised by the fact that a high proportion of patients become resistant after one year (up to 32% in 1 year; up to 70% by 5 years) as the result of tyrosine-methionine-aspartate-aspartate (YMDD) mutation. The manufacturer suggests that many patients who develop drug resistance continue to receive the medication despite reduced efficacy[24].

Lamivudine can be used as first line treatment for some patients, and expert opinion suggests that it is used more commonly as first line therapy than interferon alfa. Further, Roche UK report that, based on UK market share (sales figures 2003) and consultation with UK clinicians treating hepatitis B, the most common treatment for patients with HBeAg negative & compensated liver disease is lamivudine (used in approximately 80%). Lamivudine can also be used as dual therapy with interferon alfa, in both HBeAg-positive and -negative patients.

2.3 Description of new intervention

2.3.1 Adefovir dipivoxil

Adefovir dipivoxil, a prodrug of adefovir, was launched in 2003 as the first licensed nucleotide for the treatment of CHB. Adefovir dipivoxil is rapidly converted to adefovir in plasma and tissues with a plasma half life of 5 to 7 hours and is excreted in urine. Adefovir dipivoxil diphosphate inhibits viral polymerases and, after incorporation into viral DNA, causes DNA chain termination. It selectively blocks viral replication.

The drug is currently licensed in the UK for CHB infection with *either* compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase levels and histological evidence of active liver inflammation and fibrosis *or* decompensated liver disease'. The recommended dose is 10mg per day, taken orally.

EASL guidelines recommend that adefovir dipivoxil, like lamivudine, can be used as second line therapy in patients who have not responded to interferon alfa. Adefovir dipivoxil can also be used as second line therapy in patients who have become resistant to lamivudine (where it might be given as a replacement for lamivudine, or added to on-going lamivudine). Expert opinion suggests that many clinicians would use it as first line therapy but for its cost (around 4 times more expensive than lamivudine). Like lamivudine it can be used in the treatment of pre- and post- liver transplant, and might be more suitable than lamivudine due to a lower rate of resistance (see Section 4.1.2.9).

In terms of adverse events adefovir dipivoxil is associated with nephrotoxicity at high doses, although this is more likely in patients with decompensated liver disease. It is recommended that renal function should be monitored every three months.

In May 2005 the Scottish Medicines Consortium (SMC) issued guidance to the NHS in Scotland on the use of adefovir dipivoxil. They recommend restricted use for the treatment of chronic hepatitis B in adults with either compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease. Its use is restricted to patients who demonstrate lamivudine resistance.

2.3.2 Pegylated interferon alfa-2a

A newer ‘pegylated’ derivative of interferon alfa has become available recently. Pegylation involves the attachment of an inert polyethylene glycol polymer to the interferon alfa molecule to produce a larger molecule with a prolonged half life. Pegylation prolongs the biological effect necessitating fewer injections and therefore is more convenient for patients.

Two versions are available (i) 40 kD Pegylated interferon alfa-2a (Pegasys; Hoffman-La Roche) and (ii) 12 kD Pegylated interferon alfa-2b (PegIntron, ViraferonPeg; Schering-Plough). (NB. The scope for this appraisal issued by NICE does not include

the latter as a licence has not yet been granted for its use in the treatment of CHB). The pharmacokinetic characteristics of these two agents differ.

Pegylated interferon alfa is the current gold standard treatment for chronic moderate to severe hepatitis C, in combination with ribavirin. In 2004 NICE issued guidance to the health service recommending this combination, based on a Technology Assessment Report by SHTAC[27]. In February 2005 pegylated interferon alfa-2a received its marketing authorisation from the EU Commission for the treatment of both HBeAg positive and HBeAg negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis. Pegylated interferon alfa is therefore likely to supersede interferon alfa as first line treatment in both HBeAg positive and negative patients (Expert clinical opinion suggests that it is currently used by many clinicians).

Cooksley[28] outlines the potential place of pegylated interferon alfa as being first line treatment with reservation of other antiviral agents (e.g. lamivudine/adefovir dipivoxil) for patients who have failed pegylated interferon alfa treatment in whom remission is unlikely. It may also be used as dual therapy with lamivudine as well as in the re-treatment of patients failing non-pegylated interferon alfa. Withdrawal rates due to adverse effects with pegylated interferon alfa are reported to be less than with non-pegylated interferon alfa, and lower than those observed in hepatitis C[29].

Pegylated interferon alfa is unlikely to be used as maintenance therapy because of certain adverse effects (meaning that it may be harder to tolerate in the long term) and its contraindication in patients with decompensated liver disease.

3 METHODS

This review was guided by the general principles for conducting a systematic review outlined in NHS CRD Report 4[30]. It was undertaken as systematically as time allowed, and followed the protocol reviewed by expert advisers and NICE.

3.1 Search strategy

A sensitive search strategy was developed, tested and refined by an information scientist. Specific searches were conducted to identify studies of clinical-effectiveness; cost-effectiveness; quality of life; resource use/costs; and epidemiology/natural history (see Appendices 2, 3 and 4 for search strategies). The strategies were applied to the following electronic databases:

- Cochrane Systematic Reviews Database;
- Cochrane Central Register of Controlled Trials;
- NHS CRD (University of York) databases:
    - DARE (Database of Abstracts of Reviews of Effects),
    - Health Technology Assessment (HTA) database,
    - NHS EED (Economic Evaluations Database);
- Medline (Ovid);
- PreMedline;

- Embase (Ovid);
- EconLit (Silver Platter);
- National Research Register;
- ISI Web of Science - Science Citation Index;
- ISI Proceedings;
- BIOSIS;
- Clinical trials.gov;
- Current Controlled Trials.

Searches for clinical-effectiveness, cost-effectiveness, costs of illness, quality of life, and epidemiology/natural history studies were carried out for the period from 1995/1996 to the April 2005. All searches were limited to the English language.

In addition to database searches, the websites of the following organisations were searched for relevant publications: the Department of Health; Health Protection Agency; European Agency for the Evaluation of Medicinal Products; British Association for the Study of the Liver (BASL), European Association for the Study of the Liver (EASL), American Association for the Study of the Liver (AASL); British Society of Gastroenterology; Foundation for Liver Research; The British Liver Trust, The British Association for Sexual Health and HIV; The British HIV Association; the European Medicines Agency; the Food and Drug Administration (FDA).

Finally, bibliographies of related papers were assessed for relevant studies; experts were contacted for advice and peer review, and to identify additional published and unpublished references; and manufacturer and sponsor submissions to the National Institute for Clinical and Health Excellence (NICE) were searched for studies that met the inclusion criteria.

3.2 Inclusion and exclusion criteria

Studies identified by the search strategy were assessed for inclusion through two stages. Firstly, the titles and abstracts of all identified studies were screened by one reviewer, and a random sample of 10% of these were checked by a second reviewer. Secondly, full text versions of relevant papers were retrieved, and an inclusion worksheet (see Appendix 5) was applied by two independent reviewers. Any differences in judgement at either stage were resolved through discussion.

The inclusion criteria, as specified in the study protocol, were set as follows.

3.2.1 Interventions

- Interventions (alone and in combination with other treatment options):
  - pegylated interferon alfa-2a
  - adefovir dipivoxil
- Comparators (alone and in combination with other treatment options):
  - pegylated interferon alfa-2a*
  - adefovir dipivoxil*
  - interferon alfa-2a
  - interferon alfa-2b

- lamivudine
- best supportive care

*Intervention was not compared with itself

3.2.2 Patients

- Adults with chronic hepatitis B infection, including those who were HBeAg-positive and HBeAg-negative, and with compensated or decompensated disease.
- The clinical effectiveness of treatment in different patient subgroups (e.g. genotype) were analysed where data allowed.

3.2.3 Types of studies

- Systematic reviews of randomised controlled trials (RCTs) and RCTs comparing the different drugs with placebo or each other or best supportive care were included in the review of clinical effectiveness.
- With the exception of two RCTs which are not yet fully published, studies published as abstracts or conference presentations were not generally included in the primary analysis of clinical and cost-effectiveness. However, their key characteristics were recorded and described to provide context around the discussion of effectiveness and summaries are provided where appropriate (labelled as 'unpublished data').
- Full economic evaluations of the specified interventions in patients with CHB were included.
- A range of designs for studies on health related quality of life, and epidemiology/natural history were be considered.

3.2.4 Outcomes

- The following outcome measures were included:
  - survival
  - health related quality of life
  - drug resistance
  - time to treatment failure
  - histological response (e.g. inflammation/fibrosis – on biopsy)
  - biochemical response (e.g. liver function - aminotransferase)
  - virological response (e.g. seroconversion rate –& viral replication - HBV-DNA)
  - seroconversion (e.g. HBeAg loss/anti-HBe; HBsAg loss/anti-HBs)
  - adverse effects of treatment

3.3 Data extraction strategy

Data were extracted from the included clinical-effectiveness studies using a standardised template. Data extraction was undertaken by one reviewer and checked by a second, with any disagreements resolved through discussion. Full data extraction forms of all the included studies can be seen in Appendices 6 to 11.

3.4 Quality assessment strategy

The quality of included systematic reviews and RCTs was assessed using NHS CRD (University of York) criteria[30] (see Appendix 13). Quality criteria were applied by one reviewer and checked by a second, with any disagreements resolved through discussion.

3.5 Methods of analysis/synthesis

A narrative synthesis was undertaken with the main results of the included clinical-effectiveness and cost-effectiveness studies described qualitatively, and in tabular form. A meta-analysis was not possible due to heterogeneity in the interventions and comparators evaluated by the included clinical trials. Where data allowed, clinical and cost-effectiveness was assessed according to patient sub-types (e.g. according to genotypes).

4 CLINICAL EFFECTIVENESS

4.1 Results

4.1.1 Quantity and quality of research available

Our initial literature search generated a total of 806 references (152 on pegylated interferon alfa, 682 on adefovir dipivoxil and 28 which contained both terms). Additional references were added as the review progressed. In total, 1085 titles and abstracts were inspected, of which 163 papers were retrieved. Of these, 155 were excluded according to our criteria, leaving 8 included studies.

Of the 155 excluded studies:

- 88 were conference abstracts;
- 21 were non-systematic reviews;
- 29 were general background reviews or guidelines; and
- 17 were excluded for various reasons, such as incompatible patient group, or methodological reasons, such as reporting a non-randomised controlled clinical trial or cohort study.

Of the 88 conference abstracts identified, 44 reported adefovir dipivoxil as monotherapy, 16 reported pegylated interferon alfa monotherapy, 22 reported adefovir dipivoxil with lamivudine and 17 reported pegylated interferon alfa with lamivudine (11 studies compared monotherapy with dual therapy). Almost three times as many abstracts involved participants who were HBeAg positive as were HBeAg negative (31 vs. 11), and an additional 17 abstracts involved both. HBeAg status was not reported in the remaining abstracts. Participants described in 12 of the abstracts were co-infected with HIV. One abstract included sub-group analysis by genotype, and one abstract provided analysis by ethnic group. Although we prioritised fully published literature, unpublished information (e.g. conference abstracts) relating to what appear to be pivotal trials is presented, with appropriate caveats (marked as 'unpublished data').

In terms of the 8 included studies:
6 were fully published RCTs

- 1 was a systematic review
- 1 was a pooled sub-group analysis of two of the RCTs.

In addition to these, conference abstracts relating to two additional RCTs are presented.

Four of the fully published RCTs evaluated the effectiveness of adefovir dipivoxil, two as monotherapy and two in addition to lamivudine in patients who had developed drug resistance. For three of these, fully published results at the end of 48 weeks treatment are available.

- Two of these three studies are on-going with treatment continuing for up to 5 years[31 32].

- The other reports results at the end of 52 weeks treatment[33]. This study is continuing treatment in 78 participants for a further two years. Three of the trials used a dose of 10mg/d, but one of the monotherapy trials compared doses of 10mg/d and 30mg/d with placebo (Table 3).

A further trial by Sung and colleagues (2003)[34] is only available as a conference abstract. This phase II RCT included two arms, comparing the use of lamivudine plus adefovir dipivoxil with lamivudine monotherapy. Results are available (in abstract only) for 52 weeks of treatment, with the study continued for a further 52 weeks.

Two fully published RCTs evaluated the effectiveness of pegylated interferon alfa-2a, one for 48 weeks and one for 24 weeks. The former compared pegylated interferon alfa 2a with pegylated interferon alfa in combination with lamivudine, and with lamivudine alone. The latter compared 3 doses of pegylated interferon alfa-2a with non-pegylated interferon alfa-2a. A third RCT, the unpublished study by Lau and colleagues[35;36], reported the use of pegylated interferon alfa in 814 HBeAg positive participants. This trial had three arms and compared the use of pegylated interferon alfa monotherapy with pegylated interferon alfa and lamivudine dual therapy and with lamivudine monotherapy. Participants were treated for 48 weeks with a 24 week follow-up.

Table 3 - Characteristics of included studies – trial arms

Study	HBeAg status	No. of participants, duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Arm 1	Arm 2	Arm 3	Arm 4
Adefovir dipivoxil studies						
Hadziyannis et al. 2003[31] Study 438	negative	N=185 T_d=48 weeks* F_d=0 weeks Total=48 weeks	ADV 10mg/d (n=123)	placebo (n=62)		
Marcellin et al. 2003[32] Study 437	positive	N=515 T_d=48 weeks** F_d=0 weeks Total=48 weeks	ADV 10mg/d (n=172)	ADV 30mg/d (n=173)	placebo (n=170)	
Perrillo et al. 2004[33] Study 465	positive	n= 95 T_d=52 weeks*** F_d=0 weeks Total=52 weeks	LAM 100mg/d + ADV10mg /d (n=46)	LAM 100mg/d + placebo (n=49)		
Peters et al. 2004[37] Study 461	positive	n= 59 T_d=48 weeks F_d=0 weeks Total=48 weeks	ADV 10mg/d + placebo (n=19)	ADV10mg/ d + LAM100m g/d (n=20)	LAM100 mg/d+ placebo (n=19)	
Sung et al. 2003[34] (UNPUBLISHED DATA)	positive	N=115 T_d=52 weeks**** F_d=0 weeks Total=52 weeks	LAM 100mg/d + ADV10mg /d (n=55)	LAM 100mg/d + placebo (n=57)		
Pegylated interferon alfa studies						
Marcellin et al. 2004[38]	negative	n= 552, of whom 537 were	PEG 180µg/w +	PEG 180µg/w +	LAM 100mg/d	

Study 241		included in analyses T_d=48 weeks F_d=24 weeks Total= 72 weeks	placebo (n=177)	LAM 100mg/d (n=179)	(n = 181)	
Cooksley et al. 2003[39] Study 037	positive	n= 194 T_d=24 weeks F_d=24 weeks Total=48 weeks	IFN 4.5 MIU 3 × wk (n=51)	PEG 90 µg/w (n=49)	PEG 180 µg/w (n=46)	PEG 270 µg/w (n=48)
Lau et al. 2004[35;36] (UNPUBLISHED DATA) Study 240	positive	N=814 T_n=48 weeks F_d=24 weeks Total= 72 weeks	PEG 180µg qw + placebo qd (n=271)	PEG 180µg qw + LAM 100mg qd (n=271)	LAM 100mg qd (n=272)	

* After 48 weeks patients in the ADV group were re-randomised to receive placebo for 48 weeks, or 10mg ADV for 192 weeks. Patients in the placebo group received 10mg ADV for a further 192 weeks. Study due to end June 2005 when patients will have received 5 years of treatment.
** After 48 weeks patients were re-assigned so that the 30mg ADV group received placebo, the 10mg ADV group were re-randomised to receive either 10mg ADV or placebo, and the placebo group received 10mg ADV. After July 2001 the double blind phase of the study was terminated and all groups were assigned to receive 10mg ADV (open label) up to March 2005 when patients will have received 5 years of treatment.
*** 78 patients continued to receive treatment for a further two years (Study 493). Study is on-going
**** study continued for further 52 weeks.

The key characteristics of the RCTs are shown in Table 4. One of the four adefovir dipivoxil RCTs[31] and one of the two pegylated interferon alfa RCTs[38] included patients with HBeAg negative CHB. The other four published trials were based on patients who were HBeAg positive. The published trials ranged in size from 59 to 552 participants, with the trials by Marcellin and colleagues[32;38] being the largest published studies for each drug comparison. The unpublished study by Lau and colleagues[35;36] included 814 HBeAg positive patients, and the unpublished study by Sung and colleagues[34] included 115 patients, 96% of whom were HBeAg positive.

With the exception of one study[33] which did not state number of centres or countries, the trials were all multicentre RCTs, with participating centres in several different countries across Europe, Asia, North America and Australasia. Three studies[37 39 34] did not state their funding sources in the published papers, but the remaining studies were sponsored by the drug manufacturers.

Table 4 - Characteristics of included studies – participants and outcomes

Study	Methods	Key inclusion criteria	Other patient characteristics	Outcomes
Adefovir dipivoxil studies				
Hadziyannis et al. 2003[31] Study 438	*Design*: multicentre, double blind RCT *Number of centres*: 32 *Sponsor*: Gilead Sciences *Country*: Greece (also Canada, Israel, France, Italy, Austria, Taiwan and Singapore)	• People with CHB aged 16-65 yrs • **HBeAg negative** • Compensated liver disease • Total bilirubin level of no more than 2.5mg/dl • prothrombin time no more than 1s above the normal range • serum albumin level at least 3g/dl • serum creatinine level of no more than 1.5mg/d • an adequate blood count.	• Prior interferon alfa use: 39% ADV 46% placebo; prior lamivudine use: 8% ADV 7% placebo; • No seropositivity for HIV, HCV or HDV. • Race: 66% white; 30% Asian; 3% black • Average age ~ 46 yrs • Sex: 83% male	*Primary outcomes*: • histologic improvement • ranked assessments of necroinflammatory activity and fibrosis (improved, no change or worse). *Secondary outcomes*: • change from baseline in serum HBV DNA levels • change from baseline in serum ALT levels • HBsAg seroconversion • adverse events
Marcellin et al. 2003[32] Study 437	*Design*: multicentre, double blind RCT *Number of centres*: 78 *Sponsor*: Gilead Sciences *Country*: North America, Europe, Australia, Southeast Asia	• Patients with CHB aged 16 - 65yrs; *(nb baseline characteristics table lists age range as 16 to 68yrs)* • **HBeAg positive** • Compensated liver disease • Average age ~ 33 yrs	• No prior therapy >12 weeks with nucleoside or nucleotide analogue with activity against HBV; • No seropositivity for HIV, HCV, HDV; • No interferon alfa or other drugs with possible activity against HBV disease <6mths before screening, but study states 123 (24%) had received treatment with interferon alfa. • Race: 36% white; 60% Asian; 3% black; 1% Other • Average age ~ 33 yrs • Sex: 74% male	*Primary outcomes*: • Histologic improvement *Secondary outcomes*: • Change from baseline in serum HBV DNA levels; • Proportion of patients with undetectable levels of HBV DNA; • Effect of treatment on alanine aminotransferase level; • loss or seroconversion of HBeAg.

Perrillo et al. 2004[33] Study 465	*Design*: RCT with concurrent non-randomised study. Only the RCT data are included here *Number of centres*: not stated *Sponsor*: GlaxoSmith-Kilne; Gilead Sciences *Country*: not stated	• HBsAg+ adults receiving ongoing lamivudine therapy for ≥ >6months for CHB. • **HBeAg positive** • Compensated liver disease • HBV DNA concentration ≥ 10^6 copies/mL • ALT > 1.3 times ULN on at least 2 occasions in previous 6 months.	• No co-infection with HCV, HDV or HIV. • No treatment with ADV or other drugs with activity against HBV within the prior 3 months • No information provided on ethnic groups • Average age ~43 yrs • Sex: 95% male	*Primary outcomes*: • Reduction in HBV DNA *Secondary outcomes:* • ALT normalisation • HBeAg loss and seroconversion • Proportion of pts with undetectable serum HBV DNA • Proportion of pts with YMDD mutant HBV DNA
Peters et al. 2004[37] Study 461	*Design*: double blind, multicentre RCT *Number of centres*: 20 *Sponsor*: Not stated *Country*: Australia, Canada, France, Germany, UK and USA	• Aged 16-65 yrs • HBsAg present for ≥ 6 mths • **HBeAg positive** • An elevated serum ALT level 1.2-10 times ULN on at least 2 occasions at least 1 month apart within the preceding 6 months. • Ongoing lamivudine therapy for at least 6 months • Well preserved liver function and no history of variceal bleeding, ascites or encephalopathy.	• No prior use of ADV, treatment with interferon alfa or other immunomodulatory therapies within the 6 months proceeding study screening; • No co-infection with HIV; • All patients had received treatment with lamivudine for at least 6 months and had no prior use of ADV; • All 58 patients had lamivudine resistance mutations by sequencing at baseline, with all major patterns of lamivudine resistance mutations being observed. • Race: 60% white; 36% Asian; 2% black; 2% other • Average age ~ 45 yrs • Sex: 79% male	*Primary outcomes*: • time-weighted average change from baseline in serum HBV DNA level up to 16 weeks *Secondary outcomes*: • time-weighted average change from baseline in serum HBV DNA level at 48 weeks • serum HBV DNA change form baseline • % of patients with ALT normalization • HBeAg loss • Seroconversion to anti-HBe • Loss of HBsAg.
Sung et al. 2003[34] (UNPUBLISHED DATA)	*Design*: RCT *Number of centres*: Not stated *Sponsor*: Not stated *Country*: Not stated	• Inclusion criteria not stated • **HBeAg positive**	• treatment naïve • mean age 36 years • 79% male • 64% Asian • 34% Caucasian • 96% HBeAg-positive	*Primary outcomes*: • HBV DNA time-weighted ave change from baseline to week 16 ($DAVG_{16}$). *Secondary outcomes*: • ALT normalization

			• 96% ALT> ULN • 98% HBV-DNA positive	• HBV-DNA reduction • HBeAg/HBsAg loss • incidence of viral-breakthrough and YMDD mutant HBV.
Pegylated interferon alfa studies				
Marcellin et al. 2004[38] Study 241	*Design*: multicentre, partially double-blind RCT *Number of centres*: 13 *Sponsor*: Roche *Country*: 13 countries, mainly in Asia and Europe	• Adult patients with CHB and evidence of prominent necroinflammatory activity. • **HBeAg negative** • anti-HBe antibody positive • HBsAg positive • HBV DNA level >100,000 copies per ml • a serum alanine aminotransferase level > 1 but ≤10 times the upper limit of the normal range;	• No decompensated liver disease; No treatment for CHB within the previous 6 months; • No co-infection with HCV, HDV or HIV. • Race: 37% white; 61% Asian; 1% black; <1% other • Prior use of lamivudine: 6%; • Prior use of interferon alfa: 8% • Average age ~ 41 yrs • Sex: 85% male	*Primary outcomes*: • Normalization of ALT levels; • suppression of HBV DNA to below 20000 copies per ml. *Secondary outcomes*: • HBsAg loss; • HBsAg seroconversion; • histologic response; • suppression of HBV DNA to below 400 copies per ml; • ranked assessments of necroinflammatory activity and fibrosis; • safety analysis; • resistance analysis.
Cooksley et al. 2003[39]	*Design*: Multicentre, phase II open label RCT *Number of centres*: 18 *Sponsor*: Not stated *Country*: Australia; New Zealand; Taiwan; Thailand; China	• HBsAg negative > 6 months • **HBeAg positive** • HBV DNA > 500, 000 copies • ALT 2-10 times ULN • Biopsy demonstrating CHB liver disease	• Not previously treated with interferon alfa; • no nucleoside or nucleotide analogue use for longer than 6 months and/or within 6 months of study entry; • no positive test at screening for anti-HAV IgM, HCV RNA or anti-HCV, anti-HDV or anti-HIV; • no decompensated liver disease; • 97% Asian; • 9% with cirrhosis or transition to cirrhosis; • 33% with Genotype B; • 67% with Genotype C	*Outcomes*: • loss of HBeAg • suppression of HBV DNA levels to <500 000 • copies/mL • normalization of ALT, seroconversion to anti-HBe, • loss of HBsAg, • combined response of HBeAg loss, HBV DNA suppression, and ALT normalisation.

			• Average age ~ 31 yrs • Sex: 74% male	
Lau et al. 2004[35;36] (unpublished data)	*Design:* Multicentre RCT *Number of centres:* not clear *Country:* Investigators from 16 countries in North America, South America, Europe, the, Middle East, Asia and Australasia *Sponsor:* Roche	• HBsAg + for > 6 months • **HBeAg positive** • Anti-HBs negative • HBV DNA and serum ALT at predefined levels • CHB proven by liver biopsy	• No decompensated liver disease • No co-infection with HAV, HCV, HDV or HIV • No anti-HBV therapy in 6 months prior to study • ~86% Asian • ~10% Caucasian • Mean age 32 years • ~12% prior use of lamivudine • ~12% prior use of IFN α • Sex: 78% male	*Primary outcomes:* • HBeAg seroconversion • HBV DNA < 100,000 copies/mL

ADV=adefovir dipivoxil; PEG = pegylated interferon alfa-2a; IFN = interferon alfa-2a; LAM = lamivudine; /d= per day; /w = per week; Mths= months; Yrs= year

4.1.1.1 Summary of key trials

Key points regarding trial duration and publication status are summarised below.

Adefovir dipivoxil studies

Hadziyannis and colleagues 2003[31] (Study 438)

- HBeAg negative
- 2 arms: ADV10mg vs. placebo
- Fully published results up to 48 weeks of blinded, randomised treatment.
- After 48 weeks, patients in the ADV group were re-randomised to receive placebo for 48 weeks, or 10mg ADV for 192 weeks. Patients in the placebo group received 10mg ADV for a further 192 weeks. The study is due to end in June 2005 when patients will have received 5 years of treatment.
- Conference abstracts report results up to week 144[40-42].

Marcellin and colleagues 2003[32] (Study 437)

- HBeAg positive
- 3 arms: ADV10mg vs. ADV 30mg vs. placebo
- Fully published results up to 48 weeks of blinded, randomised treatment.
- After 48 weeks, patients were to be re-assigned so that the 30mg ADV group received placebo, the 10mg ADV group were re-randomised to receive either 10mg ADV or placebo, and the placebo group received 10mg ADV. However, a randomisation error meant that 91% of the 459 patients received at least one dose of incorrect medication at the start of the second year. After July 2001 the double blind phase of the study was terminated and all groups were assigned to receive 10mg ADV (open label) up to March 2005 when patients will have received 5 years of treatment.
- Conference abstracts are available with results up to week 144[43;44].

Perrillo and colleagues 2004[33] (Study 465)

- HBeAg positive, lamivudine resistant
- 2 arms: LAM + ADV 10mg vs. LAM + placebo
- Designed to test the safety and efficacy of adding adefovir dipivoxil to on-going lamivudine in patients who have developed lamivudine resistance, versus maintaining them on lamivudine.
- Fully published results up to 52 weeks of blinded, randomised treatment.
- 78 patients continued to receive treatment for a further two years (Study 493). Study is on-going.
- Conference abstracts are available for extension study 493 at 104 weeks[45;46].

Peters and colleagues 2004[37] (Study 461)

- HBeAg positive, lamivudine resistant
- 3 arms: ADV 10mg + placebo vs. LAM + ADV 10mg vs. LAM + placebo
- Designed to test the safety and efficacy of:
  - switching lamivudine resistant patients to adefovir dipivoxil monotherapy, versus maintaining them on lamivudine.

    - adding adefovir dipivoxil to on-going lamivudine in patients who have developed resistance, versus maintaining them on lamivudine
- Fully published results up to 48 weeks of randomised treatment.
- No results published beyond 48 weeks, either as conference abstract or full publication.

Sung and colleagues 2003[34] (unpublished data)
- HBeAg positive
- LAM + ADV (10mg) vs. LAM + placebo
- Designed to test the safety and efficacy of dual therapy vs monotherapy in patients not previously treated.
- 52 week data available as a conference abstract
- Study is ongoing and will continue for total treatment duration of 104 weeks.

Pegylated interferon alfa-2a studies

Marcellin and colleagues 2004[38] (Study 241)
- HBeAg negative
- 3 arms: PEG + placebo vs. PEG + LAM vs. LAM
- Designed to assess the safety and efficacy of combination therapy in this patient group.
- Fully published data for 48 weeks partially double-blinded, randomised treatment plus 24 weeks follow up.
- No further follow-up published or available as conference abstract.

Cooksley and colleagues 2003[39] (Study 037)
- HBeAg positive
- 4 arms: IFN vs. PEG 90 µg/w vs. PEG 180 µg/w vs. PEG 270 µg/w
- Fully published data for 24 weeks of open label treatment with 24 week follow up.
- No further follow-up published or available as conference abstract.

Lau and colleagues 2004[35;36] (unpublished data) (Study 240)
- HBeAg positive
- 3 arms: PEG 180 µg/w + placebo vs. PEG 180 µg/w + LAM vs. LAM
- Designed to compare pegylated interferon alfa-2a as combination therapy and monotherapy with lamivudine.
- Conference abstract available for 48 weeks treatment plus 24 week follow-up. Not yet fully published.

The published RCTs used similar inclusion and exclusion criteria, and most defined chronic hepatitis B by the presence of detectable HBsAg for at least 6 months, a serum HBV DNA level of at least 10^5 copies per ml (10^6 in one study[33]), and an ALT level of between 1 and 15 times the upper limit of the normal range (although the limits of this last criterion varied between studies). Some also required a biopsy confirming CHB liver disease[38;39]. Studies with HBeAg negative participants also specified undetectable HBeAg and detectable anti-HBe.

Three of the adefovir dipivoxil studies specified that patients must have compensated liver disease[31 32 33] and one[32] specified that participants must have well preserved liver function. The two published pegylated interferon alfa-2a studies both excluded patients with decompensated liver disease. Lau and colleagues[35;36] (unpublished data) employed similar inclusion and exclusion criteria to those of the published studies, and reported efficacy in HBeAg positive participants. People with decompensated liver disease were excluded from the study.

Four of the studies included small proportions of patients with compensated cirrhosis/ bridging fibrosis. Three of these were pegylated interferon alfa studies: 9% in the study by Cooksley and colleagues[39]; 16% in the study by Lau and colleagues[35;36]; 27% in the study by Marcellin and colleagues[38]. The only adefovir dipivoxil study to include patients with compensated cirrhosis/bridging fibrosis was that by Hadziyannis and colleagues[31] (11% of patients).

The studies were mixed in terms of prior treatment history. Approximately 40-45% of participants in the adefovir dipivoxil study of HBeAg negative patients[31] had previously used interferon alfa and less than 10% had previously used lamivudine. The studies by Peters and colleagues[37] and Perrillo and colleagues[33] included patients who were resistant to lamivudine. The adefovir dipivoxil studies of HBeAg positive participants specified no prior therapy within three[32;33] or six[37] months of the studies' initiation, and one of these[32] reported that 24% of participants had previously received interferon alfa treatment. The unpublished study by Sung and colleagues was based on patients who were treatment naïve[34]. The study by Marcellin and colleagues[38] which reported pegylated interferon alfa in HBeAg negative participants stated that 6% had previously used lamivudine and 8% had previously used interferon alfa. Approximately 12% of participants in the study by Lau and colleagues had previously used lamivudine, and about 12% had previously used non-pegylated interferon alfa.

None of the six published RCTs included patients co-infected with HIV, and five of the studies also excluded patients co-infected with HCV or HDV. The unpublished study by Lau and colleagues also excluded people who were co-infected with HAV, HCV, HDV or HIV (see Section 4.1.2.12 for details of studies in these patients).

Information on ethnicity was provided by three of the published adefovir dipivoxil studies; just under two thirds of participants were white and approximately one third were Asian. The unpublished study by Sung and colleagues had a higher proportion of Asian participants (64%). There were very few participants whose ethnic origin was recorded as black or 'other'. There was a much higher proportion of Asian participants in the pegylated interferon alfa studies, with 61% in the study by Marcellin and colleagues[38], 97% in the study by Cooksley and colleagues and 85-97% in the unpublished study by Lau and colleagues. Ethnic group was recorded as white/Caucasian for the majority of the remaining participants.

The average age of the participants in the studies ranged from approximately 31 to 46. The mean age of the HBeAg positive participants in one of the adefovir dipivoxil studies[32] was 33, but those in the remaining three adefovir dipivoxil studies had similar mean ages of 43-46. The mean age of participants in the unpublished study by Sung and colleagues was 36 years. The mean ages of patients in the two published

pegylated interferon alfa trials differed by ten years, with the HBeAg negative people in study 241 by Marcellin and colleagues[38] having a mean age of 41 compared with only 31 in the HBeAg positive study by Cooksley and colleagues[39]. The average age of participants in the unpublished Lau and colleagues study was 32 – similar to the study by Cooksley and colleagues, but approximately 10 years older than the average age of participants in Study 241.

Between 74% and 95% of participants in the included studies were male. Recent figures from the Health Protection Agency[a] show that nearly 70% of laboratory reports for acute hepatitis B in 2003 were in males. The peak age group for notifications and laboratory reports in 2003 was 25-34 years, with 35-44 year olds forming the second most common group. In terms of sex and age demographics, the clinical trials in this review seem to be broadly representative of the UK acute patient group.

Only the study by Cooksley and colleagues[39] reported the genotype profile of the study population (33% genotype B; 67% genotype C). However, Westland and colleagues[47] report a pooled analysis of effects by genotype of two of the adefovir dipivoxil studies (see Section 4.1.2.8). Genotypic analyses of HBV polymerase was performed on patients in the study by Peters and colleagues[37] who had lamivudine resistance mutations by sequencing at baseline. All four major patterns of lamivudine resistance mutations were observed in these patients.

The included studies employed similar outcome measures, apart from expected differences related to the participants' HBeAg status, such as HBeAg seroconversion rates. Change from baseline HBV DNA levels or suppression of HBV DNA to a predefined threshold were primary outcomes in all but two of the studies[31;32]. The threshold of response varies between the trials due to technological improvements in measurement assays. For example, pegylated interferon alfa Study 241(Marcellin and colleagues)[38] used a serum HBV DNA threshold of 20,000 copies per ml, whereas Cooksley and colleagues'[39] earlier study define a response as suppression of HBV DNA levels to <500,000 copies/ml.

The primary outcome measure used in two of the adefovir dipivoxil trials (studies 438[31] and 437[32]) was histologic improvement, defined as a reduction of at least 2 points in the Knodell necroinflammatory score with no concurrent worsening of the Knodell fibrosis score. Study 438 also used ranked assessments of necroinflammatory activity and fibrosis as a primary outcome measure. Marcellin and colleagues[38] in their study of pegylated interferon alfa use ALT normalization as an additional primary outcome. Cooksley and colleagues[39] also use this as an outcome, but it is not clear whether it is a primary or secondary measure from the information reported in the published paper. The four published adefovir dipivoxil studies include normalization of ALT levels as a secondary outcome measure.

All four of the studies of HBeAg positive participants[32;33;37;39] use HBeAg loss or HBeAg seroconversion as a secondary outcome measure. Other common secondary

[a] http://www.hpa.org.uk/infections/topics_az/hepatitis_b/data.htm Accessed 21/10/04

outcomes are HBV DNA change (for studies 437 and 438 which do not include this as a primary outcome), and HBsAg loss or seroconversion[31;37-39].

The primary outcomes in the study by Lau and colleagues (unpublished data)[35;36] were HBeAg seroconversion and HBV DNA < 100,000 copies/mL.

Table 5 - Quality assessment table

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	Intention-to-treat analysis	Withdrawals explained
Adefovir dipivoxil studies – HBeAg negative										
Hadziyannis et al. 2003[31]	Un	Ad	Rep	Ad	Ad	Ad	Par	Ad	In	Par
Adefovir dipivoxil studies – HBeAg positive										
Marcellin et al. 2003[32]	Un	Un	Rep	Ad	Ad	Ad	Ad	Ad	In	Par
Perrillo et al. 2004[33]	Un	Un	Rep	Ad	Un	Un	Ad	Ad	In	Ad
Peters et al. 2004[37]	Un	Un	Rep	Ad	Ad	Ad	Ad	Ad	In	Ad
Pegylated interferon alfa studies – HBeAg negative										
Marcellin et al. 2004[38]	Un	Ad	Rep	Ad	Ad	Ad	Par	Ad	Par	Ad
Pegylated interferon alfa studies – HBeAg positive										
Cooksley et al. 2003[39]	Un	Un	Rep	Ad	NA	NA	NA	Ad	Ad	Par

Ad= adequate, In = inadequate, Par = partial, Rep = reported, Un = unknown, NA = not applicable

The methodological quality of reporting in the included studies was assessed using CRD criteria[30] and is shown in Table 5. None reported the actual method of randomisation, so this is recorded as 'unknown' in Table 5, and only two of the studies reported adequate concealment of allocation[31;38], with the allocation process unclear in the remaining studies. On the basis of information presented in the published papers, it is therefore not clear whether selection bias may have affected the trials. All of the included studies reported baseline characteristics, and none of the RCT authors reported any significant differences between study groups.

Blinding of participants, care providers and assessors helps to guard against systematic differences in assessment of outcomes for the different groups. The trials generally described blinding adequately, for example by stating that Knodell liver biopsy scores were assessed by an independent histopathologist unaware of patients' treatment assignments. Blinding of patients is described as 'partial' where the text states that the trial was 'double blind' but gives no further description of procedures or nature of the placebo. The RCT conducted by Cooksley and colleagues[39] was an open label study, so assessment of blinding is recorded as 'not applicable' in the table.

All six published RCTs reported primary outcomes adequately, giving point estimates and measures of variability. However, only the study by Cooksley and colleagues[39] described an adequate intention to treat method of data analysis. Hadziyannis and colleagues[31], for example, do not report all outcomes for all patients. Withdrawals were only described fully in three of the studies[33;37;38]. Marcellin and colleagues[32], for

example, describe adverse events leading to discontinuation, but do not give reasons for other people leaving the study (such as withdrawal of consent). Systematic withdrawals from the study may lead to attrition bias unless they are accounted for in the subsequent analysis.

The studies by Lau and colleagues[35;36] and Sung and colleagues[34] are currently only available as conference presentations. Consequently, it was not possible to assess their methodological quality and so they have been excluded from Table 5.

4.1.2 Assessment of effectiveness

This section presents the results of the included RCTs in terms of primary and secondary outcomes: virological response (HBV DNA); biochemical response (ALT); combined virological and biochemical response; liver histology; HBeAg loss/seroconversion; HBsAg loss/seroconversion; combined outcomes; sub-group analyses; treatment resistance and adverse events. This is followed by a summary of related systematic reviews, evidence for the treatment of patients with co-morbidities, and the treatment of pre- and post-liver transplant patients.

4.1.2.1 Virological response

Table 6 and Table 7 present virological response rates for the ADV and PEG trials, respectively.

Table 6 - Virologic response (Adefovir dipivoxil)

Study, patient type, outcome type **Outcome**	**Treatment arms**		**Difference**
Hadziyannis[31], HBeAg neg, secondary	**ADV 10mg/d (n=117)**	**placebo (n=55)**	
HBV DNA mean change (reduction) from baseline at week 48 (log copies per ml)	3.91	1.35	p<0.001
n (%) with undetectable HBV DNA levels	63/123 (51)	0/61(0)	p<0.001
Perrillo[33], HBeAg pos, primary	**LAM 100mg/d + ADV 10mg/d (n=46)**	**LAM 100mg/d + placebo (n=48)**	
No. with HBV DNA level >10^5 copies/mL at baseline (%)	46/46 (100)	46/48 (96)	
No. (%) with HBV DNA response at weeks 48 and 52	39/46 (85)	5/46 (11)	P<0.001
No. (%) HBV DNA – by polymerase chain reaction at week 52	9/46 (20)	0/48	P=0.001
Median change from baseline in HBV DNA level at week 52 (range)	-4.6 (-7.3 to 1.5)	+0.3 (-6.0 to 5.4)	P<0.001
Sung et al. (2003)[34] (UNPUBLISHED DATA) **HBeAg positive**	**LAM 100mg/d + ADV 10mg/d (n=55)**	**LAM 100mg/d (n=57)**	
HBV-DNA (log_{10} copies/ml)			
Baseline	8.84	9.17	
$DAVG_{16}$	-4.20	-4.20	
Median change: W16 W52	-4.82 -5.41	-5.04 -4.80	
<200 (LLOD) W52	21/54 (39%)	23/56 (41%)	

Breakthrough DNA§	3/54 (2%)		11/55 (20%)	
Marcellin[32], HBeAg pos, secondary	**10mg ADV (n=171)**	**30mg ADV n=173**	**Placebo (n=167)**	
HBV DNA change from baseline (log copies/ml) Results at 48 wks Mean±SD Median 95% CI P value	 -3.57±1.64 -3.52 -3.84 to –3.31 <0.001	 -4.45±1.62 -4.76 -4.72 to -4.19 <0.001	 -0.98±1.32 -0.55 -1.20 to –0.77	
Serum HBV DNA<400 copies/ml at 48wks N (%) P Value	 36 (21) <0.001	 67 (39) <0.001	 0	
Peters[37], HBeAg pos	**ADV 10mg/d + placebo (n=19)**	**ADV 10mg/d + LAM 100mg/d (n=20)**	**LAM 100mg/d + placebo (n=19)**	
$DAVG_{16}$# Mean ± SD (primary outcome measure)	-2.66* ± 0.80	-2.50* ± 0.54	-0.0±0.34	*P<0.001
$DAVG_{48}$# Mean ± SD (secondary outcome measure)	-3.88* ± 1.05	-3.09* ± 0.67	-0.10±0.39	*P<0.001
Change in serum HBV DNA (secondary outcome measure) mean ± SD (95% CI) Week 16 Week 48	 -3.11* ± 0.94 (-3.54, -2.69) -4.00*± 1.41 (-4.65, -3.35)	 -2.95* ± 0.64 (-3.23, -2.66) -3.46*±1.10 (-3.94, -2.97)	 0.0 ± 0.28 (-0.14, 0.13) -0.31± 0.93 (-0.74, 0.12)	 *P<0.001 *P<0.001
HBV DNA Undetectable at week 48 (secondary outcome measure) n (%) (<1000 copies/mL)	5 (26)	7(35)	0	P<0.005

#$DAVG_{16}$ ($DAVG_{48}$) is calculated as the difference between baseline and the area under the curve up to week 16 (week 48) in serum HBV DNA level (log_{10} copies/mL) divided by the number of days from baseline up to the last included value.
§ 1 log_{10} copies/ml, 2 consecutive occasions

Table 7 - Virologic response (pegylated interferon alfa)

Study, patient type, outcome type **Outcome**	**Treatment arms**			**Difference**
Marcellin[38] HBeAg neg	**PEG 180µg/w (n=177)**	**PEG 180µg/w +LAM 100mg/d (n=179)**	**LAM 100mg/d (n=181)**	
Primary outcome: HBV DNA <20000 copies/ml§ end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with LAM monotherapy at week 72 * odds ratio 95% CI‡	 144(81) 74.8 to 86.8 76(43) 35.5 to 50.6 0.007 1.8 (1.2 to 2.9)	 164(92) 86.6 to 95.2 79(44) 36.7 to 51.7 0.003 1.9 (1.2 to 3.0)	 154(85) 79.0 to 89.9 53(29) 22.8 to 36.5	 *P value between PEG groups is P=0.849

Secondary outcome: HBV DNA <400 copies/ml end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with LAM monotherapy			112(63) 55.7 to 70.4 34(19) 13.7 to 25.8 <0.001		156(87) 81.3 to 91.7 35(20) 14.0 to 26.1 <0.001	133(73) 66.4 to 79.8 12(7) 3.5 to 11.3	
Primary outcome: Change in HBV DNA end of treatment (week 48) Total number of patients Mean log copies/ml 95% CI log copies/ml end of follow-up (week 72) Total number of patients Mean log copies/ml 95% CI log copies/ml			166 -4.1 -3.8 to -4.5 165 -2.3 -1.9 to -2.7		165 -5.0 -4.7 to -5.3 170 -2.4 -1.9 to -2.8	174 -4.2 -3.9 to -4.5 154 -1.6 -1.2 to -2.0	
Lau[35;36] HBeAg Pos, primary (Unpublished data)			**PEG 180µg/w (n=271)**		**PEG 180µg/w +LAM 100mg/d (n=271)**	**LAM 100mg/d (n=272)**	
HBV DNA <100,000 copies/ml§ end of follow-up (week 72) n (%) p compared with LAM monotherapy			87 (32) p=0.012		92 (34) p=0.003	60 (22)	Peg vs. PEG+LAM p=0.652
Change from baseline – week 48 Change from baseline – week 72			-4.5 -2.4		-7.2 -2.6	-5.8 -2.0	
Cooksley[39] HBeAg pos	**IFN 4.5 MIU 3 × wk (n=51)**	**PEG 90 µg/w (n=49)**	**PEG 180 µg/w (n=46)**	**PEG 270 µg/w (n=48)**	**All Peg doses**	**Equality of 4 doses p value**	**All Peg vs. IFN p value**
HBV DNA suppression (<500,000 copies) at follow-up n (%) [95% CI (%, %)]	13 (25) [14, 40]	21 (43) [29, 58]	18 (39) [25, 55]	13 (27) [15, 42]	52 (36)	0.096	0.085
Change in HBV DNA (week 24) Mean log copies/ml	-2.2	-2.83¶	-3.5	-3.14¶			

¶ = estimated via graph reading

Proportion of patients achieving an HBV DNA 'response'

The proportion of patients achieving a virological response varied across the studies. Response was measured by reductions in HBV DNA levels to a given threshold. Caution is required when interpreting these results as thresholds differed between studies.

Response rates were significantly higher for patients treated with adefovir dipivoxil in comparison to placebo:

- 51% of the ADV treated patients achieved undetectable HBV DNA levels (defined as <400 copies/ml) compared to none of the placebo treated patients at week 48 ($p<0.001$) (Hadziyannis and colleagues[31]).

  - A conference abstract[40] for this study reported results for 80 patients who received adefovir dipivoxil for 96 weeks. Of the 70 people included in the analysis, 50 (71%) had undetectable HBV DNA by PCR (<1000 copies/mL).
  - A second abstract reported outcomes for patients treated for 144 weeks. At this time 79% (53/67) had undetectable HBV DNA[42].
- The percentage of patients achieving a serum HBV DNA level of <400 copies/ml at week 48 was 21% (for the 10mg ADV dose) and 39% (30mg ADV) compared to 0% for placebo treated patients (Marcellin and colleagues[32]). Both adefovir dipivoxil treatment groups were significantly better than placebo ($p<0.001$).
  - Additional information was provided in a conference abstract[43]. At week 96, 45% of 231 patients who had continued to receive 10mg of ADV had a serum HBV DNA undetectable by PCR (<1000 copies/ml). At week 144, this figure was 56% of 84 patients.

Response rates were significantly higher for lamivudine resistant patients who received adefovir dipivoxil in addition to on-going lamivudine:

- The percentage achieving an HBV DNA response at both weeks 48 and 52 was 11% for patients treated with LAM monotherapy, compared to 85% for patients treated with LAM + ADV ($P<0.001$). In this study a response was defined as an HBV DNA level $\leq 10^5$ copies/mL or a ≥ 2 $\log^{10}$ reduction (Perrillo and colleagues [33]).
- HBV DNA levels were undetectable (<1000 copies/ml) in 26% of ADV + placebo patients and 35% of ADV + LAM patients, in comparison to no patients receiving LAM + placebo ($p<0.005$) (Peters and colleagues 2004[37]).

Response rates were similar for patients treated with pegylated interferon alfa-2a monotherapy as for those treated with the combination of pegylated interferon alfa-2a and lamivudine. Both groups had significantly higher rates than patients treated with lamivudine monotherapy.

- Marcellin and colleagues (2004)[38] (HBeAg negative patients) measured two thresholds of viral response at both end of treatment and end of follow-up. Response rates were lower at follow-up than end of treatment (highest in the lamivudine monotherapy group).
  - Firstly, the proportion of patients with an HBV DNA <20,000 copies/ml (the primary outcome) at the end of treatment was 81%, 92% and 85% for the PEG, PEG + LAM and LAM groups, respectively (statistical significance was not reported at end of treatment). At end of follow-up (week 72), the proportions were 43%, 44%, and 29% in the PEG, PEG + LAM and LAM groups, respectively. Differences between the PEG group and the LAM group were statistically significant ($p=0.007$), as were those between the PEG + LAM and LAM groups ($p=0.003$).
  - Secondly, the proportion of patients with an HBV DNA <400 copies/ml (a secondary outcome) at the end of treatment was 63% for the PEG group, 87% for the PEG + LAM group, and 73% for the LAM group. At end of follow-up (week 72), these proportions were 19%, 20% and 7% in the PEG, PEG + LAM and LAM groups, respectively. Differences between the PEG group and the LAM group were statistically significant ($p=0.001$), as were those between the PEG + LAM and LAM groups ($p=0.001$).

- Lau and colleagues (2004)[35;36] (HBeAg positive patients, unpublished data) employed a response threshold of 100,000 copies/ml. End of treatment responses are not currently available. At follow-up (week 72) response rates were 32%, 34% and 22% for the PEG, PEG + LAM and LAM groups respectively. Differences between PEG + LAM and LAM monotherapy showed statistical significance (p=0.003), as did differences between PEG monotherapy and LAM (p=0.012).

Response rates were higher for patients treated with pegylated interferon alfa-2a in comparison to non-pegylated interferon alfa, although not significantly:

- Cooksley and colleagues[39] measured viral response at <500,000 copies/ml. At follow-up (week 48), 25% of IFN treated patients had responded, in comparison to 36% for all 3 PEG doses combined (p=0.08). Response rates for the PEG groups ranged from 27% (270 µg/wk dose) to 43% (90 µg/wk dose). The difference in response rates between the PEG groups combined vs IFN, and between all 4 treatment groups was not significant.

Changes in HBV DNA levels

Decreases in HBV DNA levels were generally bigger for adefovir dipivoxil in comparison to placebo, and greater decreases were observed with the larger dose:

- The mean reduction in HBV DNA from baseline to week 48 (log_{10} copies/ml) was 3.91 for ADV in comparison to 1.35 for placebo (p<0.001) (Hadziyannis and colleagues[31] Study 438).
  - A conference abstract[40] reported results for 80 patients in this study who received adefovir dipivoxil for 96 weeks. Of the 70 patients included in the analysis, the median change in HBV DNA (log10 copies/mL) was -3.47 (n=70).
  - A second conference abstract[48] reported results for 67 patients treated for 144 weeks. The median change was -3.63.
- The mean change (± SD) in HBV DNA from baseline to 48 weeks (log_{10} copies/ml) was -3.57 ±1.64 (for the 10mg ADV dose), and -4.45 ±1.62 (30mg ADV dose), compared to -0.98 ±1.32 for placebo treated patients (Marcellin and colleagues,[32] Study 437). Differences between both treatment groups and the placebo group were statistically significant (p<0.001).

Decreases in HBV DNA levels were greater for the lamivudine resistant patients who received adefovir dipivoxil in addition to on-going lamivudine, in comparison to those continuing on lamivudine:

- The median change in HBV DNA (log_{10} copies/ml) from baseline level to week 52 was +0.3 (-6.0 to 5.4) for LAM + placebo, compared to -4.6 (-7.3 to 1.5) for LAM + ADV, P<0.001 (Perrillo and colleagues[33]).
  - Additional results are reported in a conference abstract[46], for 78 patients from the original 52 week study with who went on to receive LAM + placebo or LAM + ADV for a further 52 weeks. The median decrease in HBV levels was -6.3 log_{10} copies/ml in the LAM + ADV groups, with no change from baseline in the LAM + placebo group. This difference was statistically significantly different at weeks 100/104.

Decreases in HBV DNA were similar for both lamivudine resistant patients who switched to adefovir dipivoxil, and those who continued with lamivudine with the

addition of adefovir dipivoxil. Both were significantly greater compared to those who continued with lamivudine.

- The mean (± SD) decrease in serum HBV DNA at 48 weeks was significantly greater in both the ADV + placebo and ADV + LAM groups than in the LAM + placebo group (decreases of 4.0, 3.46 and 0.31, respectively, $p<0.001$ in both cases) (Peters and colleagues[37]).

- Sung and colleagues (study 468)[34] reported preliminary results of their on-going study in a conference abstract. The time-weighted averaged change from baseline to week 16 was -4.20 $\log_{10}$ copies/ml for both the ADV + LAM group and the LAM + placebo group. Patients receiving dual therapy showed a greater reduction in HBV DNA from baseline to week 52 (-4.80 $\log_{10}$ copies/ml vs. -5.41 $\log_{10}$ copies/ml for LAM + placebo group). Statistical significance was not reported.

For the two pegylated interferon alfa-2a combination therapy trials, patterns were similar to those observed with HBV DNA response rates. There were similar reductions for pegylated interferon alfa-2a monotherapy and pegylated interferon alfa-2a in combination with lamivudine, and both had greater reductions than lamivudine monotherapy (at end of follow-up). Furthermore, there were larger mean reductions in HBV DNA from baseline to end of treatment than from baseline to end of follow-up. At follow-up, relapse was smallest for PEG monotherapy patients.

- Mean reductions in HBV DNA (log copies/ml) between baseline and end of follow-up (week 72) were -2.3; -2.4 and -1.6 for the PEG; PEG + LAM; and LAM groups, respectively (Marcellin and colleagues (2004)[38], HBeAg negative patients). There was less difference between groups at end of treatment (week 48); the mean change in the PEG + LAM group was -5.0, but mean changes were similar in PEG and LAM monotherapy groups (-4.1 and -4.2, respectively). Statistical significance was not reported.
- Mean reductions in HBV DNA (log copies/ml) between baseline and end of treatment (week 48) were -4.5, -7.2 and -5.8 for the PEG, PEG + LAM and LAM groups, respectively. At end of follow-up (week 72), mean reductions were -2.4; -2.6 and -2.0 for the PEG; PEG + LAM; and LAM groups, respectively. (Lau and colleagues (2004)[35;36] HBeAg positive patients, unpublished data). Statistical significance was not reported.

Reductions in HBV DNA levels were greater with pegylated interferon alfa-2a in comparison to non-pegylated interferon alfa-2a:

- Reductions in HBV DNA from baseline to end of treatment (24 weeks) were greater for all PEG doses than for IFN. Changes were -2.83; -3.5; and -3.14 for the 90, 180 and 270 µg/wk PEG doses respectively, in comparison to -2.2 for IFN treated patients. Figures for the 90 and 270 µg/wk PEG doses were estimated from the graph in the published journal article (Cooksley and colleagues (2003)[39]). Statistical significance was not reported.

Virological response - summary

In terms of HBV response and reductions in HBV DNA:

- Adefovir dipivoxil was significantly more effective than placebo (in both HBeAg positive and negative patients).
- In lamivudine resistant HBeAg positive patients, the addition of adefovir dipivoxil to on-going lamivudine was significantly more effective than maintenance with lamivudine alone. Adding adefovir dipivoxil to on-going lamivudine was of similar effectiveness to switching to adefovir dipivoxil.
- There was little difference between pegylated interferon alfa-2a monotherapy, and pegylated interferon alfa-2a in combination with lamivudine, but both were significantly more effective than lamivudine monotherapy at end of follow-up (both HBeAg positive and negative patients).
- Pegylated interferon alfa-2a was associated with higher response rates than non-pegylated interferon alfa, but the difference was not statistically significant (HBeAg positive patients).
- Following cessation of PEG treatment virological response rates decline.

4.1.2.2 Biochemical response (ALT)

Table 8 and Table 9 present biochemical response for adefovir dipivoxil and pegylated interferon alfa, respectively.

ALT normalisation

The proportion of patients achieving a biochemical response varied across the studies. Response was measured by reductions in ALT to normal levels.

Response rates were significantly higher for patients treated with adefovir dipivoxil in comparison to placebo. A slightly higher response was observed with the 30mg dose:

- 72% of ADV treated patients had normalised ALT levels at week 48 compared to 29% in placebo patients ($p<0.001$) (Hadziyannis and colleagues[31] Study 438).
  - Further results are presented in a conference abstract for 80 patients who received adefovir dipivoxil for 96 weeks[40]. Of the 64 people included in the analysis, 73% (47/64) had normalized ALT.
  - A second abstract reports outcomes after 144 weeks treatment. The proportion with normalized ALT at this time was 88%[42], although another abstract[48] reports this as 69% (43/62).
- The proportion of patients with normalised ALT at 48 weeks was 48% (for the 10mg ADV dose) and 55% (30mg ADV dose) compared to 16% for placebo treated patients ($p<0.001$ for both comparisons) (Marcellin and colleagues[32] Study 437).
  - Additional information is provided in a conference abstract[43]. At week 96 (n=231), 71% of 231 patients who continued to receive 10mg of ADV had normalized ALT levels. At week 144 this figure was 81%, of 84 patients.

Table 8 - Biochemical response ALT (adefovir dipivoxil)

Study, patient type, outcome type **Outcome**	**Treatment arms**			**Difference**
Hadziyannis[31], HBeAg neg, secondary	**ADV 10mg/d (n=116)**	**placebo (n=59)**		
n(%) with normalized ALT levels at 48 weeks	84(72)	17(29)		p<0.001
median decrease from baseline (U per litre) at 48 weeks	55	38		p=0.01
Perrillo[33], HBeAg pos, secondary	**LAM 100mg/d + ADV10mg/d (n=46)**	**LAM 100mg/d + placebo (n=48)**		
ALT change from baseline (IU/L) at 52 weeks Mean (SD) Range	 -90 (160) -793 to 43	 -44 (312) -1643 to 758		
Change from baseline in ALT times the ULN at 52 weeks Median Range	 -1.1 -18.4 to 1.0	 -0.2 -38.2 to 17.6		 P≤ 0.01
ALT normalisation at both 48 and 52 weeks	37%	9%		p=0.003
Sung et al. (2003)[34] UNPUBLISHED DATA	**LAM 100mg/d + ADV 10mg/d (n=55)**	**LAM 100mg/d (n=57)**		
ALT Normalisation W48 & W52 Mean change at week 52	25/52 (48%) -1.80	39/56 (70%) -1.84		p=0.023
ALT Median (× ULN): Baseline W16 W52	 2.79 1.16 0.81	 2.52 0.94 0.55		
Peters[37], HBeAg pos, secondary	**10mg ADV + placebo (n=19)**	**10mg ADV +100mg LAM (n=20)**	**LAM + placebo (n=19)**	
Change in serum ALT level (IU/L) mean ± SD (95% CI) Normalization of serum ALT, n/total (%)	-87.7 ± 121.7 (-143.9, -31.5) 9*/19 (47)	-48.6 ± 82.0 (-84.5, -12.6) 10**/19 (53)	± 30.8 (-4.2, 14.2) 1/19 (5)	 *p=0.004, **p=0.001
Marcellin[32] HBeAg pos, secondary	**10mg ADV (n=171)**	**30mg ADV n=173**	**Placebo (n=167)**	
Change in ALT (IU/Litre) at 48wks Mean ±SD Median 95% CI P Value	 -92.1 ±167.2 -51 -118.8 to –65.3 <0.001	 -74.4±128.4 -54 -95.6 to –53.3 <0.001	 -23±140.7 -17 -45.9 to –0.2	
Normalisation of ALT at 48 wks N/total n§ (%) P Value	 81/168 (48) <0.001	 93/169 (55) <0.001	 26/164 (16)	

Table 9 - Biochemical response (pegylated interferon alfa)

Study, patient type, outcome type	**Treatment arms**			**Difference**
Marcellin[38] HBeAg neg, primary	**PEG 180µg/w (n=177)**	**PEG 180µg/w +LAM 100mg/d (n=179)**	**LAM 100mg/d (n=181)**	
ALT normalization† end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with LAM monotherapy* odds ratio 95% CI‡	 67(38) 30.7 to 45.4 105(59) 51.7 to 66.6 0.004 1.9 (7.2 to 2.8)	 87(49) 41.1 to 56.2 107(60) 52.2 to 67.0 0.003 1.9 (1.2 to 2.9)	 132(73) 65.8 to 79.3 80 (44) 36.8 to 51.8	 *comparison between PEG groups P=0.0915
Lau[35;36] HBeAg pos, secondary UNPUBLISHED DATA	**PEG 180µg/w (n=271)**	**PEG 180µg/w +LAM 100mg/d (n=271)**	**LAM 100mg/d (n=272)**	
ALT normalization at end of follow-up (week 72)	111*(41%)	106** (39%)	76 (28%)	Compared with LAM only: *P=0.002 **P=0.006

Cooksley[39] HBeAg pos	**IFN 4.5 MIU 3 × wk (n=51)**	**PEG 90 µg/w (n=49)**	**PEG 180 µg/w (n=46)**	**PEG 270 µg/w (n=48)**	**All Peg doses**	**Equality of 4 doses p value**	**All Peg vs. IFN p value**
ALT normalisation 24 week follow-up n (%) [95% CI (%, %)]	 13 (25) [14, 40]	 21 (43) [29, 58]	 16 (35) [21, 50]	 15 (31) [19, 46]	 52 (36)	 0.290	 0.153

Response rates were highest for lamivudine resistant patients who received adefovir dipivoxil in addition to on-going lamivudine:

- The proportion of patients with normalised ALT levels at both weeks 48 and 52 was 9% for patients treated with LAM + placebo, compared to 37% for patients treated with LAM + ADV (P<0.003) (Perrillo and colleagues[33]).
  - A conference abstract[46] reported results from 78 patients from the original 52 week study who went on to receive LAM + placebo or LAM + ADV for a further 52 weeks. By 104 weeks, 49% of the LAM + ADV and 10% of the LAM + placebo group had normalised ALT. This difference was statistically significantly different at weeks 100/104.
- The study by Peters and colleagues[37] found that response rates for lamivudine resistant patients who switched to adefovir dipivoxil were similar to those who received adefovir dipivoxil in addition to on-going lamivudine (47%, 53%, respectively). Rates for both groups were significantly higher than for patients who continued with lamivudine (+ placebo) (5%).

- Sung and colleagues reported results from study 468 in a conference abstract[34]. Approximately 70% of the LAM + placebo group had normalized ALT at weeks 48 and 52 compared with 48% of the ADV + LAM group (p=0.023).

Response rates for patients treated with pegylated interferon alfa monotherapy were similar to those treated with pegylated interferon alfa in combination with lamivudine, and both were significantly higher than rates for patients treated with lamivudine monotherapy:

- Marcellin and colleagues (2004)[38] measured ALT normalisation at the end of treatment (week 48), and at the end of follow-up (week 72) in HBeAg negative patients. Patients treated with lamivudine monotherapy had the highest response rates at end of treatment, and the lowest at end of follow-up. Response rates in general were higher at follow-up.
  - The proportion of patients with an ALT response at week 48 was 38%; 49%; and 73% in the PEG; PEG + LAM; and LAM groups, respectively (no significance values reported).
  - The proportion of patients with an ALT response at week 72 was 59%; 60%; and 44% in the PEG; PEG + LAM; and LAM groups, respectively. The differences between the PEG group and the LAM group were statistically significant (p=0.004), as were those between the PEG + LAM and LAM groups (p=0.003).

- Lau and colleagues[35;36] (unpublished data, HBeAg positive patients) report ALT normalisation rates at end of follow-up only:
  - The proportion of patients with an ALT response at week 72 was 41%; 39%; and 28% in the PEG; PEG + LAM; and LAM groups, respectively. Differences between PEG monotherapy and LAM monotherapy were statistically significant (p=0.002), as were those between the PEG + LAM and LAM monotherapy groups (p=0.006).

Response rates were higher for pegylated interferon alfa-2a in comparison to non-pegylated interferon alfa-2a, although not significantly:

- 25% of IFN treated patients had responded at follow-up (week 48), in comparison to 36% for all 3 PEG doses combined (p=0.153). Response rates for the PEG groups ranged from 31% (270 µg/wk dose) to 43% (90 µg/wk dose). The difference in response rates between the 4 treatment groups was not significant (p=0.290) (Cooksley and colleagues[39]).

Changes in ALT levels

Some studies reported mean or median changes in ALT levels between baseline and follow-up, in terms of international units per litre (IU/l), or units per litre (UL). Mean changes in ALT levels were not reported in any of the published pegylated interferon alfa trials.

Decreases in ALT levels were generally greater for adefovir dipivoxil in comparison to placebo, and for the lower dose compared with the higher dose:

- In the study by Hadziyannis and colleagues[31] the median decrease in ALT at week 48 (U/l) was 55 for ADV in comparison to 38 for placebo (p=0.01).
  - Hadziyannis and colleagues report further results in the form of a conference abstract for 80 patients who received adefovir dipivoxil for 96 weeks[40]. Median decrease in ALT (IU/L) was 60.

  - Further results are also reported for open label use up to week 144[49]. The median decrease was 54 by the end of week 144 (n=67).
- In the study by Marcellin and colleagues[32] the mean decrease (± SD) in ALT from baseline to 48 weeks (IU/l) was 92 (±167.2) (for the 10mg ADV dose), and 74 (±128.4) (30mg ADV dose), compared to 23 (±140.7) for placebo treated patients. Both treatment groups showed statistically greater decreases than the placebo group ($p<0.001$ in both cases).

Reductions in ALT were highest for lamivudine resistant patients who received adefovir dipivoxil in addition to on-going lamivudine:
- In the study by Perrillo and colleagues[33] the mean (± SD) change in ALT levels from baseline to week 52 was -44 (± 312) for LAM monotherapy compared to -90 (± 160) for LAM + ADV (not statistically significant).
- Peters and colleagues[37] also found a greater mean reduction in ALT levels in lamivudine resistant patients receiving adefovir dipivoxil (87.7 points) or adefovir dipivoxil added to on-going lamivudine (48.6 points) compared with a mean increase of 3 points in those receiving lamivudine monotherapy. Statistical significance was not reported.

- Sung and colleagues (2003)[34] reported results from study 468 as a conference abstract. The median reduction in ALT was similar for both the LAM monotherapy group (1.84) and the LAM + ADV group (1.80) after 52 weeks treatment. Statistical significance was not reported.

Marcellin and colleagues[38] (HBeAg negative patients) reported marked elevations ("flares") in ALT levels during and after therapy. Flares are often observed prior to a response to treatment.
- Marked elevations in ALT of more than ten times the upper limit of the normal range (or more than 300 IU per litre) were observed in a significantly higher proportion of the PEG monotherapy group than the PEG + LAM or LAM monotherapy groups during therapy (12% vs. 4% ($p=0.007$) and 6% ($p=0.038$), respectively).
- After therapy, the proportion of people with marked elevations in ALT levels was significantly higher in the lamivudine monotherapy (14%, $p=0.03$) or dual therapy (15%, $p=0.02$) groups than in the pegylated interferon alfa monotherapy group (7%). There was a significant association between a marked elevation in ALT during therapy and normalization of ALT levels at week 72 ($P=0.01$).

Biochemical response (ALT) - summary

In terms of ALT response:
- Adefovir dipivoxil was significantly more effective than placebo (both HBeAg positive and negative patients).
- Adefovir dipivoxil added to on-going lamivudine in lamivudine resistant HBeAg positive patients was significantly more effective than continuing with lamivudine.

- There was little difference between pegylated interferon alfa-2a monotherapy, and pegylated interferon alfa-2a in combination with lamivudine, but both were significantly more effective than lamivudine monotherapy (HBeAg negative patients).
- Differences between pegylated interferon alfa-2a and non-pegylated interferon alfa were not effective.

In terms of changes in ALT levels:
- Adefovir dipivoxil was significantly more effective than placebo (both HBeAg positive and negative patients).
- Preliminary conference abstract evidence suggests the two regimens to be of similar efficacy in treatment naïve patients (no significance values reported).

4.1.2.3 Liver histological response

Three studies reported changes in liver histology:
- Study 438 by Hadziyannis and colleagues[31] reported liver histology as a primary outcome measure.
- Adefovir dipivoxil Study 437[32] by Marcellin and colleagues reported histologic improvement as a primary outcome, and other histological assessments as secondary outcomes.
- The pegylated interferon alfa study by Marcellin and colleagues[38] reported histologic response and associated assessments as secondary outcome measures.

Analyses were not ITT, as comparisons were only made where paired biopsy samples were available (shown as a reduced *n*), unless otherwise stated.

Histologic improvement is defined in adefovir dipivoxil Studies 437 and 438[31;32] as a decrease of at least 2 points in the Knodell necroinflammatory score from baseline to week 48, with no concurrent worsening of Knodell fibrosis score. In pegylated interferon alfa Study 241 by Marcellin and colleagues,[38] histologic response is defined as a reduction from baseline of at least 2 points in the modified (Ishak) histologic activity index (HAI). Scores for this index range from 0 to 24, with fibrosis graded from 0 (none) to 6 (cirrhosis), and inflammation graded from 0 (none) to 18 (severe). This study reported histological improvement at end of follow-up (week 72), whereas the two adefovir dipivoxil studies reported the outcome at the end of treatment (week 48). A conference abstract reported outcomes for a subset of patients in Study 438 after 3 years of continuous treatment.

Table 10 - Histologic improvement (adefovir dipivoxil and pegylated interferon alfa)

Study, drug, patient type, outcome type	**Treatment arms**			**Difference**
Outcome				
Hadziyannis[31], ADV, HBeAg neg, primary Study 438	**ADV 10mg/d (n=121)**		**placebo (n=57)**	
Histologic improvement (Knodell score) at end of treatment (week 48)	(n=121) 77 (64%)		(n=57) 19 (33%)	p<0.001; absolute difference (95% CI) 30.0% (15.4 to 45.2).
Marcellin[32], ADV, HBeAg pos, primary Study 437	**10mg ADV (n=168)**	**30mg ADV n=165**	**Placebo (n=161)**	
Histologic improvement (Knodell score) at end of treatment (week 48) n (%) No improvement n (%) Unstratified relative risk 95% CI Stratum-adjusted relative risk 95% CI	 89* (53) 61* (36) 2.1 1.5 to 2.8 2.1 1.6 to 2.8	 98* (59) 47* (28) 2.3 1.7 to 3.1 2.3 1.7 to 3.1	 41 (25) 105 (65)	 *P<0.001 for both groups
Marcellin[38]PEG, HBeAg neg, secondary Study 241	**PEG 180µg/w (n=177)**	**PEG 180µg/w +LAM 100mg/d (n=179)**	**LAM 100mg/d (n=181)**	
Histologic response (Ishak score) at end of follow up (week 72) Improved n (%) 95% CI % No. pts with paired biopsy samples - n. (%) improved - 95% CI %	 85(48) 40.5 to 55.6 143 85(59) 50.9 to 67.6	 68(38) 30.9 to 45.5 143 68(48) 39.1 to 56.1	 72(40) 32.6 to 47.3 125 72(58) 48.4 to 66.4	 P=0.144 overall P=0.101 overall

Table 10 shows histological improvement rates.

- Approximately one third of the placebo group and two thirds of the adefovir dipivoxil group in Study 438 (Hadziyannis and colleagues[31], HBeAg negative patients) experienced histologic improvement, with a statistically significant absolute difference of 30% (p<0.001).
  - Further results for the subset of patients who received continuous adefovir dipivoxil were presented for this study in a conference abstract[42]. The proportion with an improvement in Ishak fibrosis score (defined as a 1 point or greater reduction) after 96 weeks treatment was 53% (10/19). At 144 weeks this figure was 63% (8/12). At weeks 96 and 144, 5% (1/19) and 10% (1/12), respectively, had worsened on this score. The numbers improving or worsening were calculated based on the percentages reported in the conference abstract).
- Adefovir dipivoxil study 437 (HBeAg positive participants) found that both the 10mg and 30mg adefovir dipivoxil groups had a statistically significantly higher rate of histologic improvement than the placebo group (53% and 59% vs. 25%, p<0.001 for both groups). The percentage of participants in Study 437 showing no histological improvement was also greater in the placebo group than in either of

the treatment groups (65% vs. 36% and 28% for placebo, 10mg adefovir dipivoxil and 30mg adefovir dipivoxil groups, respectively).

- The pegylated interferon alfa study[38] reported the proportion of participants showing histologic response both as a percentage of the whole group, treating patients without paired biopsy samples as having no response (i.e. ITT), and as a percentage of participants with paired biopsy samples. Overall tests of treatment effect were not statistically significant in either case, although the PEG group showed a higher percentage of improvers than the PEG + LAM dual therapy group or the LAM group.

Table 11 - Change in Knodell score (adefovir dipivoxil)

Study, drug, patient type, outcome type / **Outcome**	**Treatment arms**			**Difference**
Hadziyannis[31], ADV, HBeAg neg, primary Study 438	**ADV 10mg/d (n=116)**		**placebo (n=59)**	
Change in total Knodell score (week 48) Mean±SD Median Range	(n=112) -3.7±3.1 -4 -11 to 2		(n=55) 0.4±3.7 1 -9 to 8	p<0.001
Change in Knodell necroinflammatory score (week 48) Mean±SD Median Range	(n=112) -3.4±2.9 -3 -9 to 2		(n=55) 0.3±3.2 0 -7 to 8	p<0.001
Change in Knodell fibrosis score at week 48 Mean±SD Median Range	(n=112) -0.3±0.7 0 -3 to 1		(n=55) 0.1±0.9 0 -2 to 2	p=0.005
Marcellin[32], ADV, HBeAg pos, primary Study 437	**10mg ADV (n=150)**	**30mg ADV n=145**	**Placebo (n=146)**	
Necroinflammatory activity- Knodell Score (week 48) Mean ±SD change in score Median change in score Range of scores	 -2.58±3.22 -2 -9 to 6	 -3.17±3.30 -3 -9 to 5	 -0.16±3.06 0 -10 to 7	 P<0.001 for both groups
Fibrosis - Knodell Score (week 48) Mean±SD change in score Median change in score Range of scores	 -0.18*±0.84 0 -2 to 2	 -0.32** ±0.80 0 -2 to 2	 -0.01±0.86 0 -3 to 2	 *P=0.061 **P=0.001

- Change in Knodell score was reported by adefovir dipivoxil studies 437 and 438, but not by the pegylated interferon alfa study (Table 11). The adefovir dipivoxil studies showed a mean reduction in Knodell necroinflammatory score of between -2.58 and -3.4 for treatment arms compared with mean changes in score between +0.3 to -0.16 in placebo arms. The treatment difference compared with placebo was statistically significant for both 10mg and 30mg dosage groups (p<0.001).
- A small change in Knodell fibrosis score was seen for both treatment and placebo groups, ranging from -0.18 to -0.32 for adefovir dipivoxil groups and +0.1 to -0.01 for placebo groups. The treatment difference was statistically significant for the 10mg adefovir dipivoxil group in Study 438 (p=0.005) and the 30mg adefovir

dipivoxil group in Study 437 (p=0.001). In Study 437 changes in Knodell fibrosis score between the adefovir dipivoxil 10mg dose group and the placebo group were not significant.

Table 12 - Ranked assessment of change (adefovir dipivoxil and pegylated interferon alfa)

Study, drug, patient type, outcome type Outcome	Treatment arms			Difference
Hadziyannis[31], ADV, HBeAg neg, primary Study 438	**ADV 10mg/d (n=116)**		**placebo (n=59)**	
Necroinflammatory activity at end of treatment (week 48) Improved No Change Worse Fibrosis at end of treatment (week 48) Improved No Change Worse	 80% 17% 3% 48% 47% 4%		 42% 7% 51% 25% 36% 38%	not reported
Marcellin[32], ADV, HBeAg pos, secondary Study 437	**10mg ADV (n=150)**	**30mg ADV (n=145)**	**Placebo (n=145)**	
Necroinflammatory activity at end of treatment (week 48) n(%) Improved No change Worse Fibrosis at end of treatment (week 48) n(%) Improved No change Worse	 107 (71) 23 (15) 20 (13) 62 (41) 67 (45) 21 (14)	 112 (77) 18 (12) 15 (10) 78 (54) 53 (37) 14 (10)	 59 (41) 37 (26) 49 (34) 35 (24) 72 (50) 38 (26)	 P <0.001 for both groups P <0.001 for both groups
Marcellin[38]PEG, HBeAg neg, secondary Study 241	**PEG 180µg/w (n=143)**	**PEG 180µg/w +LAM 100mg/d (n=143)**	**LAM 100mg/d (n=125)**	
Necroinflammatory activity at end of follow up (week 72) Improved n (%) Worse n (%) Fibrosis Improved n (%) Worse n (%)	 79(55) 16(11) 21(15) 11(8)	 66(46) 23(16) 18(13) 15(10)	 57(46) 21(17) 22(18) 6(5)	

All three studies reported ranked assessments of change (e.g. improved, no change, worse) for participants with paired biopsy specimens at baseline and end of treatment/follow-up (Table 12).

Both adefovir dipivoxil studies reported an improvement in treatment groups compared with placebo in terms of necroinflammatory activity and fibrosis assessments.

- In adefovir dipivoxil Study 438, almost twice as many participants in the adefovir dipivoxil group as in the placebo group showed an improvement in necroinflammatory activity. Only 3% of the adefovir dipivoxil group showed a worsening of necroinflammatory activity, compared with just over half of the

placebo group. Approximately 95% of the adefovir dipivoxil group showed either no change or an improvement in assessment of fibrosis, compared with 61% of the placebo group. Tests of statistical significance were not reported for this outcome.

- Adefovir dipivoxil Study 437 reported statistically significant differences between both treatment groups and the placebo group for all three ranked assessments of necroinflammatory activity and fibrosis ($p<0.001$ for both groups). Approximately one third of the placebo group reported a worsening of necroinflammatory activity, compared with 13% of the adefovir dipivoxil 10mg group and 10% of the adefovir dipivoxil 30mg group. The differences for changes in fibrosis assessment were less marked, with 10% and 14% of the adefovir dipivoxil 30mg and 10mg dose groups, respectively, and 26% of the placebo group experiencing worsening of fibrosis.

Pegylated interferon alfa study 241[38] defined 'improved' and 'worse' as a reduction or increase, respectively, of at least 2 points on the modified HAI scale. Results from this study were broadly similar across the three treatment groups, and no statistical significance values were reported.

- Just over half of the PEG group reported an improvement in necroinflammatory activity, compared with 46% of both the LAM group and the PEG + LAM group.
- Only 11% of the PEG group reported a worsening of necroinflammatory activity compared with 17% of the LAM monotherapy group and 16% of the PEG + LAM.
- Changes in fibrosis were less apparent, with less than 20% of any of the groups showing an improvement in fibrosis and between 5% and 10% of the three groups showing a worsening of fibrosis.

Liver histological response - summary

Two adefovir dipivoxil studies and one pegylated interferon alfa study reported histological outcome measures.

- A statistically significant difference between adefovir dipivoxil groups and placebo groups was seen in terms of histological improvement.
- There was no statistically significant difference in histological improvement between the PEG group, the LAM group and the PEG + LAM group.
- Change in Knodell scores for necroinflammatory activity was significantly better for adefovir dipivoxil compared to placebo. Knodell fibrosis scores were generally better for adefovir dipivoxil compared to placebo, but statistically significant differences were only reported by one study.
- Adefovir dipivoxil was better in terms of ranked assessments of change in necroinflammatory activity and fibrosis than placebo studies did, and this was reported to be statistically significant in one study. Ranked assessments were broadly similar between the pegylated interferon alfa monotherapy group, the lamivudine monotherapy group and the group using adefovir dipivoxil in combination with lamivudine (significance not reported).

4.1.2.4 HBeAg loss/seroconversion

Table 13 and Table 14 present HBeAg loss/seroconversion rates in the included trials (HBeAg positive patients only, by definition) for adefovir dipivoxil and pegylated interferon alfa, respectively.

Table 13 - HBeAg loss/ seroconversion (adefovir dipivoxil)

Study, patient type, outcome type **Outcome**	**Treatment arms**			**Difference**
Perrillo[33] HBeAg pos, secondary N/Total N (%)	**LAM 100mg/d + ADV10mg/d (n=40)**		**LAM 100mg/d + placebo (n=42)**	
HBeAg loss HBeAg seroconversion at week 52	6/40 (15) 3/40 (8)		1/42 (2) 1/42 (2)	
Sung et al. (2003)[34] UNPUBLISHED DATA	**LAM 100mg/d + ADV 10mg/d (n=55)**		**LAM 100mg/d (n=57)**	
HBeAg loss W52	10/53 (19%)		11/54 (20%)	
Marcellin[32] HBeAg pos, secondary	**10mg ADV (n=171)**	**30mg ADV n=173**	**Placebo (n=167)**	
HBeAg Loss at 48 wks N/Total N (%) P Value	41/171 (24) <0.001	44/165 (27) <0.001	17/161 (11)	
HBeAg seroconversion at 48 wks N/Total N (%) P Value	20/171 (12) <0.049	23/165 (14) <0.011	9/161 (6)	
Peters[37], HBeAg pos, secondary	**ADV 10mg/d + placebo (n=19)**	**ADV 10mg/d + LAM 100mg/d (n=18)**	**LAM 100mg/d + placebo (n=19)**	
HBeAg status Neg at week 48 n (%) Rate of seroconversion	3[a] (16) 2 [c] (11)	3 [b] (17) 1 [d] (6)	0 (0) 0 (0)	[a] p=0.075, [b] p=0.067 [c] p=0.152, [d] p=0.304

In the adefovir dipivoxil trials, rates of HBeAg loss and seroconversion were higher in treatment naïve patients than patients who were resistant to lamivudine.

- In the trial by Perrillo and colleagues (HBeAg positive lamivudine resistant patients) the highest rates of loss and seroconversion were in the LAM + ADV group (15% and 8%, respectively), compared to the LAM + placebo group (2% for both). The main trial publication does not mention significance values, although the manufacturer's submission to NICE reports the difference was not statistically significant[24].
    - Perrillo and colleagues[46] reported in a conference abstract results for 78 patients from the original 52 week study who went on to receive LAM + placebo or LAM + ADV for a further 52 weeks. HBeAg seroconversion rates for this sub-group increased slightly, from 6% at year 1 to 9% at the end of year 2 in the LAM + placebo group and from 9% to 12% in the LAM + ADV treatment group. Statistical significance was not reported.

- In the trial by Peters and colleagues (HBeAg positive lamivudine resistant patients) rates of HBeAg loss were marginally higher in the ADV + LAM group (17%) compared to the ADV + placebo group (16%). Seroconversion rates were highest in the ADV + placebo group (11%) compared to the ADV + LAM group (6%). No patients either lost HBeAg or seroconverted in the LAM + placebo group. None of the differences were statistically significant.
- In Study 437 by Marcellin and colleagues, HBeAg loss was highest in patients receiving the 30mg dose of ADV (27%) followed by the 10mg dose (24%), and placebo (11%). Both comparisons with placebo were statistically significant ($p<0.001$). Likewise, HBeAg seroconversion rates were 14%, 12% and 6% respectively. Comparisons with placebo showed statistical significance for the 10mg ADV group ($p<0.049$) and for the ADV 30mg group ($p<0.011$).
  - Additional information was provided in a conference abstract[43]. At week 96, 29% of 231 patients receiving 10mg ADV had seroconverted and 42% had lost HBeAg. At week 144, these figures were 43% and 51%, respectively, based on a total of 84 patients. The abstract reported that patients with confirmed HBeAg seroconversion or HBeAg loss were followed off-treatment in an observational study. This may account for the decreasing number of patients assessed at each follow-up.
  - Chang and colleagues[44] (in a conference abstract) monitored the durability of seroconversion after discontinuation of adefovir dipivoxil (study 481). The study comprised 76 patients (65 of whom were previously enrolled in Study 437). HBeAg seroconversion achieved during ADV treatment was found to be durable in greater than 90% of patients with a median follow-up of 55 weeks. All patients who failed to maintain seroconversion had continued treatment with adefovir for 23 weeks after undergoing seroconversion, compared with 48 weeks for those who maintained seroconversion.
- In the study of treatment naïve patients reported as a conference abstract by Sung and colleagues[34], approximately one fifth of patients in both the LAM monotherapy group and the LAM + ADV group seroconverted.

Table 14 - HBeAg loss/ seroconversion (pegylated interferon alfa)

Cooksley[39] HBeAg pos	**IFN 4.5 MIU 3 × wk (n=51)**	**PEG 90 µg/w (n=49)**	**PEG 180 µg/w (n=46)**	**PEG 270 µg/w (n=48)**	**All Peg doses**	**Equality of 4 doses p value**	**All Peg vs. IFN p value**
HBeAg loss n (%) [95% CI (%, %)]	13 (25) [14, 40]	18 (37) [23, 52]	16 (35) [21, 50]	14 (29) [17, 44]	48 (34)	0.295	0.127
Seroconversion n (%) [95% CI (%, %)]	13 (25) [14, 40]	18 (37) [23, 52]	15 (33) [20, 48]	13 (27) [15, 42]	46 (32)	0.428	0.185

Lau et al[35;36] UNPUBLISHED DATA	**PEG 180µg/w (n=271)**	**PEG + LAM 100mg/d (n=271)**	**LAM 100mg/d (n=272)**	**P compared with LAM monotherapy**
HBeAg Seroconversion (week 48) n (%)	73 (27)	65 (24)	55 (20)	
HBeAg seroconversion (week 72) n (%)	87*(32)	73** (27)	51 (19)	*p <0.001 **P<0.023
HBeAg loss (week 72)	24* (34%)	76** (28%)	57 (21%)	*P<0.001 **p=0.043

Seroconversion rates were higher for pegylated interferon alfa-2a compared with non-pegylated interferon alfa-2a, although not significantly:

- 25% of IFN treated patients had seroconverted (week 48), in comparison to 32% for all 3 PEG doses combined (p=0.185). Rates for the PEG groups ranged from 27% (270 µg/wk dose) to 37% (90 µg/wk dose). The difference in response rates between the 4 treatment groups was not statistically significant (p=0.428) (Cooksley and colleagues[39]).

Seroconversion rates were also higher for pegylated interferon alfa monotherapy-2a in comparison to the combination of pegylated interferon alfa-2a and lamivudine, or lamivudine monotherapy:

- At end of treatment (week 48), 27% of patients in the PEG monotherapy group had seroconverted, compared with 24% of the PEG + LAM group and 20% of the LAM group (Lau and colleagues 2004), unpublished data[35;36]) No significance values are reported. Seroconversion rates at end of follow-up (week 72) had increased to 32%, 27% for the PEG; PEG + LAM groups respectively, but decreased to 19% in the LAM monotherapy group. Differences between the PEG and LAM group and between the PEG + LAM and LAM group were statistically significant (p<0.001 and p<0.023, respectively).

<u>HBeAg loss / seroconversion - summary</u>

- Adefovir dipivoxil was significantly more effective than placebo in treatment naïve patients.
- Unpublished data suggests that HBeAg seroconversion associated with adefovir dipivoxil is durable up to 1 year after discontinuing treatment.
- Differences in HBeAg loss / seroconversion rates between adefovir dipivoxil, adefovir dipivoxil added to lamivudine, or on-going lamivudine in patients with resistance to lamivudine were not significant.

- Differences between pegylated interferon alfa and non-pegylated interferon alfa were not significant.
- Pegylated interferon alfa monotherapy and pegylated interferon alfa in combination with lamivudine were both more effective than lamivudine monotherapy. Pegylated interferon alfa monotherapy was marginally more effective than pegylated interferon alfa in combination with lamivudine.

4.1.2.5 HBsAg loss/seroconversion

HBsAg seroconversion is defined as the loss of HBsAg and the presence of anti-HBs antibodies. All three pegylated interferon alfa studies, and three of the adefovir dipivoxil studies reported HBsAg loss or seroconversion rates, in varying detail (Studies providing tabulated results are reported Table 15). In addition, adefovir dipivoxil study 438 by Hadziyannis and colleagues[31] mentioned HBsAg loss or seroconversion as a secondary outcome, but did not report results in the published paper.

Table 15 - HBsAg loss/ seroconversion at end of follow up (week 72) (adefovir dipivoxil and pegylated interferon alfa)

Study, patient type, outcome type **Outcome**	**Treatment arms**		**Difference**
Marcellin[38], HBeAg negative	**PEG 180µg/w (n=177)**	**PEG 180µg/w +LAM 100mg/d (n=179)**	**LAM 100mg/d (n=181)**
HBsAg loss n (%) P compared with LAM HBsAg seroconversion n (%) P compared with LAM	7 (4) P=0.007 5 (3) P=0.029	5 (3) - 3 (2) -	0 0
Lau[35;36], HBeAg positive UNPUBLISHED DATA	**PEG 180µg/w (n=271)**	**PEG 180µg/w +LAM 100mg/d (n=271)**	**LAM 100mg/d (n=272)**
End of follow up (week 72) HBsAg loss n (%) P compared with LAM HBsAg seroconversion n (%) P compared with LAM	 9 (3) P=0.033 8 (3) P=0.004	 11 (4) P=0.012 8 (3) P=0.004	 2 (<1) 0
Sung et al. (2003)[34] UNPUBLISHED DATA	**LAM 100mg/d + ADV 10mg/d (n=55)**	**LAM 100mg/d (n=57)**	
HBsAg loss W52	0/54	2/55 (4%)	

- The ADV study by Peters and colleagues[37] reported that no participants lost HBsAg during the course of the trial.
- The unpublished study by Sung and colleagues[34] reported that two patients in the LAM monotherapy group lost HBsAg, but no participants in the LAM + ADV dual therapy group did so.
- Perrillo and colleagues[46] reported results in a conference abstract for 78 lamivudine resistant patients from their original 52 week study who went on to receive LAM + placebo or LAM + ADV for a further 52 weeks. Two patients (5%) in the LAM + ADV group lost HBsAg during the second year of treatment, compared to no patients in the LAM + placebo group.

- Marcellin and colleagues found that a small percentage (<5%) of both the PEG monotherapy and PEG + LAM groups lost HBsAg or seroconverted, but that no HBsAg loss or seroconversion was observed in the LAM monotherapy group (Table 15). The difference between HBsAg loss/seroconversion in the PEG group compared with the LAM group was statistically significant (p=0.029). They noted that the HBsAg response observed with pegylated interferon alfa-2a occurred earlier than the response obtained by conventional interferon alfa tends to occur.
- In their study of HBeAg positive patients, Lau and colleagues observed similar results to Marcellin and colleagues. That is, similar proportions of patients in both the PEG monotherapy and dual therapy groups achieved HBsAg seroconversion, and none/few in the LAM monotherapy group.
  - Two patients (<1%) receiving LAM experienced HBsAg loss, compared with nine patients (3%) in the PEG group and 11(4%) in the PEG + LAM group. Differences between both PEG groups compared to the LAM group were statistically significant.
  - No patients receiving LAM experienced HBsAg seroconversion, compared to eight patients (3%) in each of the PEG groups. Results were statistically significant (p<0.01). Differences between both PEG groups compared to the LAM group were statistically significant (p=0.004).
- Cooksley and colleagues did not tabulate results fully, but reported that two patients on PEG cleared HBsAg during the course of the study. Both cleared HBsAg at week 24 and remained negative at the end of follow-up.
- In summary, loss of HBsAg and seroconversion to anti-HBs in the clinical trials was achieved in a small proportion of patients (<5%), both HBeAg positive and negative. The most detailed results show that patients taking pegylated interferon alfa are significantly more likely to respond than patients taking lamivudine.

4.1.2.6 Combined outcomes

Table 16 shows the two studies which measured combined outcomes (both pegylated interferon alfa).

- Marcellin and colleagues (2004)[38] reported results for the combined outcome of ALT normalisation and HBV DNA at both end of treatment (weeks 48), and end of follow-up (week 72). This was further stratified according to level of HBV DNA response (<20,000 copies/ml, and <400 copies/ml). In general, response rates were higher for lamivudine monotherapy at week 48 than for pegylated interferon alfa-2a monotherapy, or for pegylated interferon alfa in combination with lamivudine. However, the reverse was the case by week 72, with response rates in lamivudine monotherapy patients significantly less than the other two treatment groups.
  - Combined response rates at 48 weeks (HBV DNA <20,000 copies/ml) were 36%, 49% and 69% for the PEG, PEG + LAM, and LAM groups, respectively.
  - Combined response rates at 72 weeks (HBV DNA <20,000 copies/ml) were 36%, 38% and 23% for the PEG, PEG + LAM, and LAM groups, respectively. Differences between PEG vs. LAM, and PEG + LAM vs. LAM were statistically significant (p=0.011 and p=0.0002, respectively).
  - Combined response rates at 48 weeks (HBV DNA <400 copies/ml) were 27%, 46% and 60% for the PEG, PEG + LAM, and LAM groups, respectively.

- Combined response rates at 72 weeks (HBV DNA <400 copies/ml) were 15%, 16% and 6% for the PEG, PEG + LAM, and LAM groups, respectively. Differences between PEG vs. LAM, and PEG + LAM vs. LAM were statistically significant (p=0.007 and p=0.003, respectively).

- Cooksley and colleagues (2003)[39] reported results for the combined outcome of HBeAg loss, HBV DNA suppression, and ALT normalisation, at end of follow-up (48 weeks). Response rates were significantly higher in patients treated with PEG than IFN. Amongst the 3 PEG doses response rates were higher in the 180 µg/week dose, marginally followed by the 90µg/week dose (response rates in both these doses were more than two-fold greater than the non-pegylated interferon alfa arm). The difference in response rates between the 4 treatment groups was not statistically significant.

Table 16 - Combined response (pegylated interferon alfa)

Study, drug, patient type, outcome type **Outcome**	**Treatment arms**		
Marcellin et al[38] **HBeAg negative, secondary**	**PEG 180µg/w (n=177)**	**PEG 180µg/w +LAM 100mg/d (n=179)**	**LAM 100mg/d (n=181)**
ALT normalization and HBV DNA <20000 copies/ml end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with LAM monotherapy ALT normalization and HBV DNA <400 copies/ml end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with LAM monotherapy	 63(36) 28.6 to 43.1 63(36) 28.6 to 43.1 P=0.011 47(27) 20.2 to 33.7 26(15) 9.8 to 20.8 P=0.007	 87 (49) 41.1 to 56.2 68(38) 30.9 to 45.5 P=0.0002 82(46) 38.4 to 53.4 29(16) 11.1 to 22.4 P=0.003	 125(69) 61.8 to 75.7 42(23) 17.3 to 30.0 109(60) 52.7 to 67.4 11(6) 3.1 to 10.6

Cooksley et al[39]	**IFN 4.5 MIU 3 × wk (n=51)**	**PEG 90 µg/w (n=49)**	**PEG 180 µg/w (n=46)**	**PEG 270 µg/w (n=48)**	**All Peg doses**	**Equality of 4 doses p value**	**All Peg vs IFN p value**
Combined response of HBeAg loss, HBV DNA suppression, and ALT normalisation. n (%) [95% CI (%, %)]	6 (12) [5, 24]	13 (27) [15, 41]	13 (28) [16, 44]	9 (19) [9, 33]	35 (24)	P=0.088	P=0.036

4.1.2.7 Health related quality of life

The impact of treatment on health related quality of life (HRQOL) was reported in two studies, both of which were for pegylated interferon alfa (Marcellin and colleagues and Lau and colleagues, reported in the manufacturer's submission to NICE[36]). HRQOL was measured using the Short Form 36 of the Medical Outcomes Study (SF-36). The 36-item questionnaire was completed by participants at weeks 12, 24, 48 and 72, and their responses were used in the calculation of scores for:

- physical functioning;
- role physical;
- pain index;
- general health perception;
- vitality;
- social functioning;
- role emotional; and
- mental health index.

Overall component scores (range 0-100) were calculated for physical health (PCS) and mental health (MCS) using the item and scale scores. Higher scores represented better HRQOL. The results were compared with HRQOL data from a study of chronic hepatitis C (CHC) which used the same treatment schedule and methodology (the study is not cited in the manufacturer's submission).

Results for patients treated with pegylated interferon alfa monotherapy:

- During treatment, HBeAg positive CHB patients experienced a mean reduction of one point each in both PCS and MCS values from baseline.
- For HBeAg negative patients, the mean reduction in values was 0.5 and 3 points, respectively.
- For patients with CHC, mean reductions were 2.5 points and approximately 4.5 points, respectively.
- All patients returned to baseline values for both PCS and MCS at follow-up. However, the mean MCS score in the HBeAg negative trial was approximately one point lower and the mean PCS score was approximately one point higher at week 72. In the HBeAg positive trial the PCS score was approximately half a point higher at week 72.
- Similar small increases were experienced by CHC patients at follow-up in both PCS and MCS.
- No statistical significance values were reported for these results.

Comparison with lamivudine:

- In both trials, HRQOL scores for PEG treated patients (with or without lamivudine) returned to levels at least as high as baseline at follow-up.
- For HBeAg negative patients at end of follow-up, differences in two of the SF-36 components were significantly higher (better) in the PEG + LAM dual therapy arm compared with the LAM monotherapy arm ('role emotional', $p<0.01$ and 'mental health' components, $p<0.05$).
- For HBeAg positive patients, reductions in PCS and MCS scores during treatment were generally between 1.0 and 1.5 points greater for the PEG groups than for the LAM monotherapy group. An exception to this was at week 24, when a

difference of 2.7 MCS points was seen between LAM monotherapy and PEG + LAM patients. These differences were reported to be 'clinically insignificant'.

- There was no statistically significant difference in HRQOL between the three treatment arms in the HBeAg positive study over the 72-week trial period.

- In the HBeAg negative study, improvements in HRQOL were found to be greater in virological responders (defined as having normal ALT levels and viral load <20,000 copies/mL) than in non-responders. These differences were statistically significant for MCS, role physical, vitality, social functioning and role emotional ($p<0.01$).

As mentioned, these data were reported in the manufacturer's submission to NICE, and do not yet appear to have been published in a peer-reviewed publication. It is likely that fully published results will emerge in the near future.

4.1.2.8 Sub-group comparisons

Race and genotype

Westland and colleagues[47] reported a pooled sub-group analysis of race and genotype data from adefovir dipivoxil trials 437 and 438 (Table 17). The two trials had different proportions of Asian and Caucasian participants; 59% of Study 437's population (HBeAg positive participants) were Asian, compared with only 30% of participants in Study 438 (HBeAg negative participants). Two thirds of participants in Study 438 were Caucasian, compared with only 36% of participants in Study 437.

Table 17 - Race and genotype data from studies 437 and 438

	Study 437 (n*=510)	**Study 438 (n*=184)**	**Combined (n=694)**
HBeAg status	positive	negative	
Race – Asian	59%	30%	52%
- Caucasian	36%	66%	44%
- Black	3%	3%	3%
- Other	1%	0%	1%
HBV genotype – A	29%	6%	23%
- B	20%	17%	19%
- C	36%	13%	30%
- D	11%	62%	25%
- E	<1%	2%	<2%
- F	1%	<1%	<2%
- G	2%	0%	<2%

* No. pts in whom baseline genotyping was possible

HBV genotype is associated with race (Table 18); therefore the different racial mixes of the two trials should be taken into consideration when viewing the combined percentages by genotype in Table 17. HBV genotypes C, D and A were the most commonly found types in the pooled analysis of studies 437 and 437. 56% of Asian participants were infected with genotype C, and genotypes D and A were found in 53% and 40% of Caucasian participants, respectively (Table 18).

Table 18 - Racial distribution of genotypes

HBV genotype	Asian	Caucasian	Black
A	6%	40%	68%
B	37%	<1%	0%
C	56%	2%	0%
D	1%	53%	14%
E	0%	0%	18%
F	0%	2%	0%
G	0%	4%	0%

Table 19 - Baseline levels of Serum HBV DNA by genotype

	A	B	C	D	E	F	G
HBeAg+ group mean	8.44	8.25**	7.83*	8.47	7.11	7.66	9.49
Pair wise comparisons		**p<0.01 compared with A	*p<0.01 compared with A, B and D				n=11; P<0.05 compared with other major genotypes
HBeAg- group mean	6.44	6.51	6.52	7.16	7.22	6.83	
Pair wise comparisons				P<0.01 compared with A, B and C			

At baseline, serum HBV levels were lower in all HBeAg negative participants than in HBeAg positive participants, with the exception of the 2% of people who had genotype E, where the reverse was found (Table 19). Overall, serum HBV DNA levels were significantly different between genotypes (p<0.001 for HBeAg positive participants, p=0.001 for HBeAg negative participants).

- Among HBeAg positive participants, serum HBV DNA levels were highest in people with genotype G.
- HBV DNA levels were statistically significantly lower in people with genotype B than genotype A, and in people with genotype C compared with genotypes A, B and D (p<0.01 for both groups).
- HBeAg negative people with genotype D had statistically significantly lower HBV DNA levels than those in groups A, B and C (p<0.01).

Table 20 - Reductions in serum HBV DNA (log_{10} copies/ml) by genotype after 48 weeks of ADV therapy

	A (n=43)	B (n=52)	C (n=71)	D (n=96)	E (n=4)	F (n=1)	G (n=2)	Total (n=269)
Mean change	-3.58	-3.42	-3.65	-3.68	-3.6	-4.23	-3.67	-3.61
SD	1.95	1.33	1.35	1.28	0.99	n/a	4.24	1.44

Reductions in serum HBV DNA at week 48 were reported by genotype (Table 20) and by race (Table 21).

- There were no significant differences between patients infected with different HBV genotypes (univariate test: P=0.903; multivariate analysis adjusted for baseline serum HBV DNA and ALT levels: P=0.931).

- There was no significant difference between different racial groups in changes in serum HBV DNA (P=0.182).

Table 21 - Reductions in serum HBV DNA (log_{10} copies/ml) by race after 48 weeks of ADV therapy

	Asian (n=127)	Caucasian (n=129)	Black (n=12)
Mean	-3.58	-3.70	-2.90
SD	1.35	1.50	1.73

The authors reported additional analysis of seroconversion rates, but stated that the number of patients available for analysis after genotype stratification may not provide sufficient statistical power to detect small differences in these. Seroconversion rates ranged from 7% to 20% among people receiving 10-mg adefovir dipivoxil who had major genotypes A to D, but rates were not significantly different (p=0.25).

Cooksley and colleagues[39], in their evaluation of pegylated interferon alfa-2a, reported additional analyses by genotype. They found that response rates across treatment groups were significantly higher in patients with genotype B than genotype C:

- Combined response rates (loss of HBeAg, suppression of HBV DNA and normalization of ALT) were 31% in patients with genotype B, compared with 17.5% in those with genotype C ($p<0.05$).
- Combined response rates were higher in patients treated with pegylated interferon alfa (33% for genotype B and 21% for genotype C) compared with standard interferon alfa (25% and 6% for Genotype B and C, respectively).

Cirrhotic patients

- Cooksley and colleagues[39] reported suppression of HBV DNA for a sub-group of 13 patients with cirrhosis or transition to cirrhosis who were treated with pegylated interferon alfa. Of this group, seven (54%) lost HBeAg and seroconverted, 6 (46%) had undetectable HBV DNA and 5 (38%) had normalised ALT. None of the four patients treated with standard interferon alfa had a response in any of the outcome measures at the end of follow-up.

Baseline ALT

- Cooksley and colleagues[39] reported a sub-group analysis of combined response for 'difficult to treat' patients with low baseline ALT (<2×ULN) and high pre-treatment HBV DNA. A combined response was observed in 6 (27%) of 22 patients treated with pegylated interferon alfa and 1 (11%) of the nine patients treated with standard interferon alfa.
- Lau and colleagues also reported HBeAg seroconversion rates by baseline ALT sub-group, including results for the sub-group with low baseline ALT (≤ 2×ULN). Of the 92 people in this group who were treated with pegylated interferon alfa monotherapy, 27 (29%) seroconverted. In the LAM + PEG dual therapy group, 19 of the 93 patients (20%) seroconverted. Similarly, 19 (20%) of the 96 patients in the LAM monotherapy group seroconverted.

Sub-group comparisons - summary

- Reductions in serum HBV DNA levels after 48 weeks of adefovir dipivoxil therapy were not significantly different when comparing participants by genotype or race.
- Overall response rates were greater for participants with genotype B than with genotype C in a study which compared pegylated interferon alfa with conventional interferon alfa.
- Pegylated interferon alfa groups with genotypes B and C showed significantly higher response rates than standard interferon alfa groups with these genotypes.
- Pegylated interferon alfa was more effective than standard interferon alfa in treating people with cirrhosis or transition to cirrhosis.
- People with low baseline ALT responded better to treatment with pegylated interferon alfa than to treatment with standard interferon alfa. PEG monotherapy was also found to be better than LAM monotherapy or PEG + LAM dual therapy in this patient group.

4.1.2.9 Treatment resistance

Three of the fully published RCTs reported data on treatment resistant mutations:

- At week 48 in the study by Marcellin and colleagues[38], YMDD mutations were detected in 32 people in the LAM group (18%) and 1 person in the PEG + LAM group (<1%). This difference was statistically significant ($p<0.001$).
  - Additional information is provided for this study in the form of conference abstracts[43;44]. Two patients receiving adefovir dipivoxil (3.1%) developed resistance by 144 weeks.
- In the study by Hadziyannis and colleagues[31], samples were obtained at baseline and week 48 from 117 patients with detectable serum HBV DNA levels. Analysis found that four different novel substitutions occurred at conserved sites in the HBV polymerase in three placebo group patients. In vitro phenotypic analyses showed that viruses with the mutations remained fully susceptible to adefovir dipivoxil treatment.
  - Additional information is provided for this study in the form of a conference abstract[41]. Two HBeAg patients (out of a total group of 124) developed rtN236T mutation at 96 weeks, which confers reduced susceptibility to adefovir dipivoxil but remains susceptible to lamivudine. Further results are presented for this study in another conference abstract[42]. The overall incidence of ADV resistance mutations was 3% at week 96 (n=19) and 5.9% at week 144 (n=12).
- Perrillo and colleagues[33] reported YMDD mutations in lamivudine resistant HBeAg positive patients treated with ongoing LAM or ADV + LAM (Table 22). At baseline, 100% of both groups had detectable YMDD mutants, but by week 52, a significantly lower proportion of people in the ADV + LAM group had detectable YMDD mutations (62% vs. 96%, $p<0.001$).

Table 22 - YMDD mutations reported by Perrillo and colleagues[33].

Outcome	LAM 100mg/d + ADV 10mg/d (n=44)	LAM 100mg/d + placebo (n=48)	Difference
No (%) with detectable YMDD mutant at baseline	44/44 (100)	47/47 (100)	
No (%) with detectable YMDD mutant at week 52	26/42 (62)	44/46 (96)	P<0.001
No (%) with YMDD mutant not detectable at week 52	16/42 (38)	2/46 (4)	
HBV DNA negative (%)	14/42 (33)	2/46 (4)	
Wild type (%)	2/42 (5)	0 (0)	

The manufacturer of adefovir dipivoxil, in their submission to NICE[24], report an overview of resistance rates, summarised from 5 studies (including RCTs and observational studies, comprising a mixture of pre- and post- liver transplant patients, and patients co-infected with HIV). The key results are:

- A total of 629 patients from the five studies were monitored for up to four years (a total of 1201 patient-years).
- A total of 22 patients developed resistance to adefovir dipivoxil during this time, which equates to a cumulative risk of resistance of 0% in year one, 2.05% in year two, 7% in year three and 14.5% in year four.
- The annual risk of resistance was calculated as 0%, 2.05%, 5.10% and 8.06% for years one, two, three and four, respectively.
- Study 438 in HBeAg-negative patients had higher resistance rates than the averages across the five studies. After two years of treatment, 3% of patients developed resistance; 10.3% developed resistance during three years of treatment, and 17.5% did so during four years of treatment.

Sung and colleagues 2003[34] reported interim results from their ongoing Phase II (Study 468) as a conference abstract.

- Results showed that 20% of the LAM group, and 2% of the ADV + LAM group developed YMDD mutation (p<0.003), and a similar proportion experienced breakthrough of HBV DNA.

Although we did not systematically review clinical trials of lamivudine (notwithstanding those which included adefovir dipivoxil or pegylated interferon alfa) we report pooled data on lamivudine resistance, as discussed in a submission to NICE by the manufacturer of adefovir dipivoxil[24]. This provides an indirect comparison of resistance rates between the two drugs:

- Lai and colleagues[50] combined four RCTs and calculated the overall proportion of patients with YMDD variants after one year of therapy to be 24%, rising to a cumulative rate of 42% after two years, 53% after three years and 70% after four years. The annual risk was calculated to be approximately 26% per year.
- Lok and colleagues[51]combined seven trials, and calculated that 16% of patients would have developed M204V/I mutations after one year, rising to 36%, 56%, 75% and 80% after two, three, four and five years, respectively.

In summary, resistance rates are generally five fold lower with adefovir dipivoxil than lamivudine. After four years treatment cumulative rates were 14.5% and 70%, respectively

4.1.2.10 Adverse events

Table 23 - Adverse Events in adefovir dipivoxil studies

	Hadziyannis *et al*.[31]		**Perrillo *et al*[33]**		**Marcellin *et al*[32]**			**Peters *et al*[37]**		
	ADV 10mg/d (n=123)	**placebo (n=61)**	**LAM 100mg/d + placebo (n=42)**	**LAM 100mg/d + ADV 10mg/d (n=40)**	**10mg ADV n=171**	**30mg ADV n=173**	**Placebo N=167**	**100mg LAM + placebo (n=19)**	**10mg ADV + placebo (n=19)**	**10mg ADV+100mg Lam (n=20)**
Dose discontinuation for any AE / safety reasons	0	0	NR	NR	2%	3%	<1%	0(0)	0(0)	0(0)
Dose discontinuation for other reasons			NR	NR	5%	5%	7%			
At least one AE n(%)	94(76)	45(74)	40 (83%)	36 (82%)				19 (100)	18(95)	18(90)
At least one severe (grade 3 or 4) AE n(%)	7(6)	6(10)	NR	NR	10%	9%	8%			
At least one serious AE n(%)	4 (7)	4 (3)	NR	NR				1 (5)	3 (16)	0
Headache n(%)	29(24)	10(16)	NR	NR	43 (25)	45 (26)	37 (22)	5(26)	5(26)	6(30)
Pharyngitis n(%)	23(19)	14(23)	NR	NR	44 (26)	70 (40)	54 (32)	6 (32)	5 (26)	1 (5)
Asthenia n(%)	16(13)	10(16)	NR	NR	42 (25)	45 (26)	32 (19)	6(32)	9(47)	10(50)
Influenza-like syndrome n(%)	13(11)	13(21)	NR	NR	28 (16)	32 (18)	31 (19)			
Back pain n(%)	12(10)	4(7)	NR	NR	11 (6)	17 (10)	11 (7)	3(16)	2(11)	3(15)
Pain n(%)	10(8)	6(10)	NR	NR	19 (11)	13 (8)	21 (13)	4(21)	2(11)	4(20)
Insomnia n(%)	6(5)	4(7)	NR	NR				2(11)	4(21)	0(0)
Arthralgia n(%)			NR	NR				3(16)	2(11)	1(5)
Rhinitis n(%)	6(5)	1(2)	NR	NR				5(26)	1(5)	2(10)

Rash n(%)			NR	NR				4(21)	4(21)	0(0)
Fever n(%)			NR	NR				1(5)	3(16)	0(0)
Sinusitis n(%)			NR	NR				5(26)	3(16)	1(5)
abdominal pain / upper abdominal pain n(%)	18(15)	3(5)	NR	NR	31 (18)	38 (22)	32 (19)	5(26)	4(21)	6 (30)
Decreased appetite/ anorexia n(%)			NR	NR	6 (4)	18 (10)	9 (5)			
Diarrhoea n(%)			NR	NR	23 (13)	25 (14)	13 (8)	6(32)	1(5)	2(10)
Dyspepsia n(%)	6(5)	2(3)	NR	NR	15 (9)	19 (11)	14 (8)			
Nausea n(%)			NR	NR	17 (10)	31 (18)	23 (14)	1(5)	2(11)	4(20)
Flatulence n(%)			NR	NR	13 (8)	18 (10)	10 (6)			
Gastroenteritis n(%)			NR	NR				3(16)	1(5)	0(0)
Cough / increased cough n(%)	10(8)	4(7)	NR	NR	11 (6)	19 (11)	21 (13)	3(16)	2(11)	0(0)
Dizziness n(%)			NR	NR	9 (5)	18 (10)	13 (8)			
Infection n(%)			NR	NR				1(5)	1(5)	3(15)
Bacterial infection n(%)			NR	NR				0(0)	0(0)	3(15)

NR= Not reported

Adverse events for adefovir dipivoxil studies are reported in Table 23. Only one study[32] reported any dose discontinuations, and these were similar across treatment groups. Discontinuations for safety reasons were low, but marginally higher in the ADV 30mg group than in the ADV 10mg group or the placebo group. No dose modifications were reported.

With the exception of the study by Marcellin and colleagues[32], which did not report the overall number of participants experiencing adverse events, the majority of trial participants reported at least one adverse event. Within trials, similar numbers of participants in each treatment group reported at least one adverse event.

Two trials reported the number of participants experiencing at least one severe (grade three or four) adverse event[31;32]. Fewer participants in the ADV group than in the placebo group reported these (6% vs. 10%) in the study by Hadziyannis and colleagues, whereas the rates of reporting were similar across groups in the study by Marcellin and colleagues[32] (10% in 10mg ADV group, 9% in 30mg ADV group and 8% in placebo group). The serious adverse events reported by Peters and colleagues were not thought to be related to study medication.

The conference abstract published by Sung and colleagues,[34] which reported the 52 week results of an ongoing 104 week trial, stated that both the lamivudine monotherapy and the lamivudine/adefovir dipivoxil dual therapy regimes were well tolerated with similar safety profiles. Four serious adverse events were reported in the lamivudine monotherapy group (7%) and one (2%) in the LAM + ADV group.

Commonly reported adverse events in studies of adefovir dipivoxil include: pharyngitis; headache; abdominal pain; asthenia and influenza-like symptoms. Other adverse events were experienced by higher percentages of participants in the study by Peters and colleagues[37], but this study had very few participants ($n \leq 20$ in each arm), so small differences in actual numbers inflate reported percentages. None of the studies reported statistical tests for significance of results.

- Two trials reported higher rates of pharyngitis in placebo groups compared with 10mg ADV groups, but one of these also reported a higher rate in the 30mg ADV group than in the placebo group. The small study by Peters and colleagues[37] reported this adverse event for six people in the LAM group, five people in the ADV group and one person in the ADV+LAM therapy group.
- Reporting of headaches was higher in both 10mg ADV groups and the 30mg ADV group than in the placebo groups in ADV studies 437 and 438[33;37], but rates of reporting were broadly similar across groups in the small study by Peters and colleagues.
- Reports of abdominal pain varied, with one of the trials' 10mg ADV groups reporting higher incidences than the placebo group (15% vs. 5%), and another trial reporting similar levels across groups (18%, 22% and 19% in 10mg ADV, 30mg ADV and placebo groups, respectively). Peters and colleagues reported similar rates across treatment groups in their small study.
- Reports of asthenia were also mixed, with one trial[31] reporting a higher rate in the placebo group than in the 10mg ADV group (16% vs. 13%) and one trial reporting a lower rate in the placebo group (19%) than in either the 10mg or 30mg ADV groups (25% and 26%, respectively).

- Influenza-like syndrome was reported by a higher percentage of placebo group participants than those in any of the adefovir dipivoxil groups, although this difference was small in some cases.

Adverse events for pegylated interferon alfa studies are reported in Table 24. With the exception of the study by Marcellin and colleagues[38], tests of statistical significance were not reported. Very few deaths were reported by any of the studies. The three deaths reported in the dual therapy arm of the study by Lau and colleagues were due to accidents not CHB or drug treatment.

Discontinuations for safety reasons were generally very low, but were higher in pegylated interferon alfa groups than in lamivudine or interferon alfa groups. Marcellin and colleagues[38] reported a significant difference between pegylated interferon alfa (overall treatment effect) and lamivudine groups. Dose discontinuations for other reasons were also rare, with no significant difference reported between pegylated interferon alfa and lamivudine groups by Marcellin and colleagues.

Dose modifications for laboratory abnormality were reported in two studies[38;39].

- In the study by Marcellin and colleagues[38], ALT elevation and thrombocytopenia were more common problems in the pegylated interferon alfa monotherapy group than in the PEG + LAM dual therapy group, whereas neutropenia was more frequently seen in the dual therapy group. Dose reductions for any adverse event were also more common in the dual therapy group than in the pegylated interferon alfa monotherapy group. It should be noted that some participants had their doses reduced due to both laboratory abnormalities and adverse events. No dose modifications for laboratory abnormalities or adverse events were reported in the lamivudine monotherapy group.
- In the study by Cooksley and colleagues[39], dose modifications for laboratory abnormalities were approximately two to three times higher in pegylated interferon alfa groups than in the standard interferon alfa group. The most common laboratory abnormalities were neutropenia and ALT elevation.

The number of participants experiencing at least one adverse event was significantly higher in the pegylated interferon alfa groups than in the lamivudine monotherapy group in the study by Marcellin and colleagues[38]. Although no statistical tests were reported, the same pattern is seen in the unpublished study by Lau and colleagues. The total number of participants experiencing at least one adverse event is not reported by Cooksley and colleagues[39]. Serious adverse events were infrequent, but were generally higher in the pegylated interferon alfa groups than in the lamivudine monotherapy group in the study by Marcellin and colleagues. Again, the same pattern was seen in the study by Lau and colleagues. Slightly higher percentages of serious adverse events were reported by the pegylated interferon alfa 180μg and 270μg groups than by the non-pegylated interferon alfa group, although numbers are probably too low to make any meaningful comparison between the groups.

Table 24 - Adverse Events in pegylated interferon alfa studies

	Lau et al.[35;36]			**Marcellin**[38]			**Cooksley**[39]			
	PEG 180µg/w (n=271)	**PEG + LAM 100mg/d (n=271)**	**LAM 100mg/d (n=272)**	**PEG 180µg/w (n=177)**	**PEG 180µg/w +LAM 100mg/d (n=179)**	**LAM 100mg/d (n=181)**	**IFN 4.5 MIU 3 × wk (n=50)**	**PEG 90 µg/w (n=48)**	**PEG 180 µg/w (n=48)**	**PEG 270 µg/w (n=45)**
Discontinuation for safety reasons †	8 (3)	12 (4)	2 (<1)	13(7)	7(4)	0	4%	2%		
Treatment discontinued prematurely because of a serious adverse event							0	0	1	1
Dose discontinuation for other reasons ‡	9 (3)	6(2)	12(4)	2(1)	3(2)	4(2)				
Dose modification§ for Laboratory abnormality ALT elevation Neutropenia Thrombocytopenia				 65(37) 15(8) 30(17) 34(19)	 64(36) 6(3) 44(25) 22(12)	 0 0 0 0	10%	22-30%		
Dose reduction for any AE				13(7)	23 (13)	0				
Deaths	0	3§§	1	1(1)	0	0				
At least one AE † n(%)	240 (89)	240 (89)	152 (56)	155(88)	155(87)	86(48)				
At least one serious* AE n(%)	12 (4)	16 (6)	5(2)	9(5)	12(7)	5(3)	2%	1%	4%	5%
Headache n(%)	76 (28)	81 (30)	27 (10)	42(24)	34(19)	14(8)	26%	46%	38%	46%
Back pain n(%)				4(2)	11(6)	6(3)				
Insomnia n(%)				15(8)	15(8)	5(3)	16%	17%	20%	10%
Pyrexia n(%)	133 (49)	148 (55)	12 (4)	105(59)	98(55)	8(4)	72%	52%	58%	71%
Fatigue n(%)	112(41)	107 (39)	38 (14)	74(42)	75(42)	33(18)	28%	29%	22%	27%
Myalgia n(%)	70 (26)	77 (28)	8 (3)	47(27)	49(27)	11(6)	42%	38%	36%	46%

Arthralgia n(%)				27(15)	27(15)	6(3)				
Sore throat n(%)				11(6)	5(3)	8(4)				
Rigors n(%)				10(6)	5(3)	0				
Abdominal pain / upper abdominal pain n(%)				9(5)	12(7)	14(8)				
Nausea n(%)				14(8)	13(7)	9(5)	8%	10%	18%	15%
Diarrhoea n(%)				20(11)	10(6)	5(3)	8%	8%	18%	17%
Decreased appetite/ anorexia n(%)	41 (15)	34 (13)	5 (2)	31(18)	26(15)	6(3)	20%	8%	18%	19%
Upper respiratory tract infection n(%)				9(5)	4(2)	7(4)	8%	23%	13%	8%
Cough / increased cough n(%)				10(6)	5(3)	2(1)	6%	15%	7%	8%
Alopecia n(%)	55 (20)	78 (29)	6 (2)	24(14)	20(11)	1(1)	24%	17%	33%	44%
Pruritus n(%)				9(5)	11(6)	4(2)				
Injection-site reaction n(%)	30 (11)	15 (6)	0	10(6)	21(12)	0				
Dizziness n(%)				15(8)	12(7)	8(4)	10%	19%	16%	15%
Irritability n(%)				12(7)	8(4)	4(2)				
Depression n(%)				6 (3%)	8 (4%)	2 (1%)				

* serious adverse event defined as 'one that presented a clinically significant hazard or resulted in a contraindication or side effect'
† P<0.001 for overall test of treatment effect in Marcellin[38]
‡P=0.913 for overall test of treatment effect in Marcellin[38]
§ Some patients who required a dose modification had both an adverse event and a lab abnormality.

§§ These three deaths were due to accidents not CHB or drug treatment

Commonly reported adverse events in studies of pegylated interferon alfa include headache, pyrexia, fatigue, myalgia and alopecia.

- Headaches were reported by two to three times as many people receiving pegylated interferon alfa compared with those receiving lamivudine monotherapy, and by approximately 50% more people receiving pegylated interferon alfa than by those receiving standard interferon alfa.
- Pyrexia was reported by over half of all participants receiving 90µg or 180µg pegylated interferon alfa monotherapy or PEG + LAM dual therapy, compared with only 4% of people receiving lamivudine monotherapy. Reports of pyrexia reached over 70% in participants receiving either standard interferon alfa or 270µg pegylated interferon alfa.
- Very few people receiving lamivudine monotherapy reported myalgia (6% in Marcellin and colleagues study and 3% in the Lau and colleagues study), whereas over a quarter of people receiving either 90µg or 180µg pegylated interferon alfa monotherapy or dual therapy reported experiencing this. Myalgia was reported by over 40% of people receiving 270µg pegylated interferon alfa or standard interferon alfa.
- Fatigue was reported by approximately 40% of people receiving pegylated interferon alfa, either as monotherapy or dual therapy, but by less than 20% of people receiving lamivudine monotherapy. Reporting of fatigue was similar across all treatment arms of the study by Cooksley and colleagues, ranging from 22% in the 180µg pegylated interferon alfa group to 29% in 90µg pegylated interferon alfa group.
- Alopecia was rarely seen in people receiving lamivudine monotherapy, but was reported by 11-14% of people being treated with pegylated interferon alfa in the study by Marcellin and colleagues and by 20-29% of the pegylated interferon alfa treated patients in the study by Lau and colleagues. Rates of alopecia increased with dose of pegylated interferon alfa from 17% to 44% in the study by Cooksley and colleagues, compared with a reported rate of 24% in the standard interferon alfa group.

<u>Adverse events - summary</u>

- Dose discontinuations for safety reasons were low for people receiving adefovir dipivoxil. The incidence of commonly reported adverse events between treatments was mixed, with some studies showing higher rates in placebo groups, and others showing higher rates for adefovir dipivoxil.
- Dose discontinuations for safety reasons were significantly higher for people receiving pegylated interferon alfa than for people receiving lamivudine monotherapy.
- The most commonly reported adverse events in the pegylated interferon alfa studies were headache, pyrexia, fatigue, myalgia and alopecia. These were all experienced in greater numbers by people receiving pegylated interferon alfa than by people receiving lamivudine monotherapy.
- People receiving non-pegylated interferon alfa or high dose pegylated interferon alfa (270µg) had greater incidences of pyrexia or myalgia than people receiving 90µg or 180µg pegylated interferon alfa.

- Fewer people receiving standard interferon alfa experienced headaches than people receiving pegylated interferon alfa.

4.1.2.11 Evidence from related systematic reviews

Dando and Plosker[52] conducted a systematic review of adefovir dipivoxil used by people with CHB. This was published as a small component of a more wide-ranging review of the drug, including pharmacodynamic and pharmacokinetic properties, and as such the systematic review element was not described as fully as would usually be expected. For example, inclusion criteria and aim of study were not clearly stated and outcome measures were not pre-specified by the reviewers. The reviewers did not state clearly how many studies were retrieved or excluded from the review, and they did not present any formal assessment of trial quality.

The reviewers pooled 48 week data from the two trials by Hadziyannis and colleagues[31] and Marcellin and colleagues[32] for assessment of tolerability of a dose of 10mg/day adefovir dipivoxil (see Appendix 12). The most common adverse events were asthenia, headache and abdominal pain, but these were actually reported in higher numbers by people in the placebo group than by people in the treatment group. With the exception of haematuria levels, higher numbers of laboratory abnormalities were reported in the placebo group than in the adefovir dipivoxil group. The review also identified several non-comparative trials assessing the effects of adefovir dipivoxil in specific patient populations, e.g. patients co-infected with HIV, patients with hepatic decompensation, and pre- and post-liver transplant patients.

4.1.2.12 Effectiveness of treating patients with co-morbidities / co-infections

As mentioned earlier, none of the RCTs included in this review included patients with co-infections or major co-morbidities. However, we identified conference abstracts reporting results of treating such patients.

- Benhamou and colleagues reported up to 4 years of 10mg qd ADV treatment in patients with lamivudine-resistant HBV and HIV co-infection in a series of eight conference abstracts [53-60]. Adefovir dipivoxil was added to the pre-existing anti-retroviral therapy including lamivudine, and key results are shown in Table 25.

Table 25 - Results of adefovir dipivoxil treatment in patients co-infected with HIV

	Week 48 (n=35)	Week 96 (n=30)	Week 144 (n=28)	Week 192 (n=22)
Median change from baseline in serum HBV DNA (log_{10} copies/mL)	-3.97*	-4.80*	-5.55*	-5.62*
HBV DNA <1000 copies/ml	2 (6%)	8(27%)	13 (46%)	13 (59%)
Median serum ALT vs. baseline (102.3 IU/L)	53*	46*	31*	32*
Mean serum ALT vs. baseline (102.3 IU/L)	76.8 p=0.04	60.4 p=0.003	54.0 p<0.0001	Not reported
ALT normalization (%)	19%	37%	64%	67%
Median change from BL in serum ALT (IU/L)	-16.0 (p=0.04)	-44.5 (p=0.02)	-46.0*	-48.0*

* p<0.001 compared with baseline

  - HBV DNA levels decreased significantly throughout the study, with a concurrent rise in the proportion of people achieving undetectable levels of HBV DNA. Results improved only slightly between weeks 144 and 192.
  - At week 72, mean ALT changed from baseline by -48.20 IU/L ($p<0.001$) and mean serum HBV DNA declined by -4.80 over the same time period ($p<0.0001$).
  - Three of the 33 patients who were HBeAg positive at baseline lost HBeAg and two of these had seroconverted by week 72; seroconversion remained durable at week 192.
  - Two patients seroconverted to anti-HBe by week 48.
  - There were no serious adverse events related to ADV throughout the study period.
- Four other abstracts[61-64] mentioned people co-infected with HIV, but did not present detailed results for this patient group.
- In summary, results reported in these conference abstracts suggest that adding ADV to ongoing therapy for CHB patients co-infected with HIV significantly reduces HBV DNA and ALT levels.

4.1.2.13 Treatment for pre- and post-operative liver transplant patients

We did not identify any fully published RCTs evaluating adefovir dipivoxil in pre- and post-liver transplant patients. However, expert opinion suggests it would be unethical to withhold treatment in this group, making controlled studies in this patient group problematic. We therefore examined the observational evidence in this area, some of which is only currently available as conference abstracts:

- A large open label study of ADV (n=324 LAM resistant patients; 128 pre- and 196 post-liver transplant) was published by Schiff and colleagues (Study 435) [65;66]. After 48 weeks of treatment, HBV DNA was reduced to undetectable levels in 81% of the pre-transplant and 34% of the post-transplant cohort. Serum ALT normalized in 76% of pre-transplant patients and 49% of post-transplant patients. One-year survival was 84% for pre-transplant and 93% for post-transplant patients.
- Schiff and colleagues (2004)[67] have also reported what appears to be long term follow-up of the above study in a conference abstract (in 226 pre- and 241 post-liver transplant patients with LAM-resistant HBV). HBV DNA reductions in the first 48 weeks were maintained or improved throughout 144 weeks. Increasing proportions of patients normalised ALT over time. Resistance up to 144 weeks was reported in two patients between weeks 48 and 96; both patients had discontinued LAM prior to emergence of resistance and addition of LAM to ADV resulted in re-suppression of HBV DNA. Survival rates at 144 weeks were 88% (pre-transplant patients) and 83% (post-transplant).
- Perrillo and colleagues conducted an open label evaluation of ADV (10mg/d) in combination with ongoing LAM (100mg/d) for 52 weeks in 40 patients (26 transplant candidates with decompensated liver disease; 14 with recurrent HBV following transplantation). The majority of patients were HBeAg positive (see Appendix 10 for full tabulated details of this study).
  - 92% of patients achieved a HBV DNA response at weeks 48 and 52 (response defined as serum HBV DNA level $\leq 10^5$ copies/ml or ≤ 2 $\log_{10}$ reduction from baseline HBV DNA level at weeks 48 and 52); Median HBV DNA ($\log_{10}$ copies/mL) decreased from 8.6 at baseline to 3.2 at follow-up;

  - Of the 68% who were HBeAg positive at baseline, 30% lost HBeAg at follow-up, and 4% (1 of 27) seroconverted.
  - Median ALT levels (x the upper limit of normal) reduced from 1.9 at baseline to 0.9 at follow-up; and the percentage with ALT normalisation at follow-up was 53%.
- An observational study[68]investigated the incidence of ADV resistance in liver transplantation patients (n=114). After two years of ADV therapy, only two people had the adefovir resistance mutation rtN236T. The addition of LAM therapy resulted in clinical stabilisation in both patients with this mutation.
- Barcena and colleagues[69] reported the results of a retrospective observational study in a conference abstract. The study included 39 transplant patients with HBV resistant to lamivudine who were treated with ADV (mean age 54, 22/39 were HBeAg positive, mean time from transplant to beginning of ADV treatment was five years). Approximately 46% negativized DNA. ALT levels decreased significantly (p=0.002) and 21.4% reached normal ALT ranges (32% in HBV+ patients, without HCV co-infection). No seroconversions, deaths or serious adverse events occurred.
- A number of small observational studies have reported that adefovir dipivoxil therapy is associated with biochemical, virological and clinical improvements in post-liver transplant patients [70-73]. For example:
  - Ahmad and colleagues (2000)[74] reported results for six patients and found that an average of 5 months adefovir dipivoxil treatment decreased HBV DNA levels by a mean of >3 $\log_{10}$ copies/ml. One patient normalised ALT.
  - Foxton and colleagues. (2002)[75] found that ADV significantly suppressed HBV replication in three pre-operative and three post-operative liver transplant patients with lamivudine resistant HBV.
- Several non-systematic reviews have examined the evidence base for treatment of pre- and post- liver transplant patients and have noted that adefovir dipivoxil is a promising treatment for lamivudine-resistant HBV in post-liver transplant patients[70;76-78].
- In summary, the evidence shows that HBV DNA and ALT levels are generally observed to reduce in pre- or post-operative liver transplant patients treated with adefovir dipivoxil. Three year survival rates in the largest of these studies were in excess of 80%.

It is worth noting that there is a wider evidence base on the use of lamivudine and other agents (e.g. Hepatitis B immunoglobin HBIG) in this patient group, although this is outside the scope of this report. Below is a brief summary of review articles and observational studies identified through our searches for studies of adefovir dipivoxil:

- An Australian case series of 32 transplanted patients concluded that LAM and low dose HBIG (400 or 800 IU) were effective at preventing HBV recurrence. At follow-up 31 of the 32 patients were HBsAg negative[79].
- A non-systematic review suggested that combined therapy of Hepatitis B immunoglobulin (HBIG) and lamivudine is more effective in preventing recurrent HBV than either treatment used as monotherapy, decreasing recurrence rates to 0-18% in some studies[77]. Drug resistance led to breakthrough infections in up to 25% of patients.
- Another non-systematic review suggested that post-transplant prophylaxis with HBIG has significantly reduced hepatitis B virus (HBV) recurrence rates, but that

HBIG is ineffective in patients with pre-transplant viraemia[76]. Long-term administration is expensive and potentially associated with emergence of escape HBV mutants.

4.1.2.14 Ethnicity

- One conference abstract was identified which specifically reported on ethnicity. Lim and colleagues (2003)[80] reported the combined results of two RCTs (n=338 HBeAg+, n=184 HBeAg-). Half of the combined study participants were Asian and 46% were Caucasian. At week 48, histological improvement was seen in 60% of the Caucasian ADV group and in 26% of the Caucasian placebo group ($p<0.001$). Among Asian patients, 56% of the ADV group and 39% of the placebo group showed histological improvement ($p<0.001$). Change in HBV DNA from baseline was also similar for both groups: -3.9 and -3.7 $\log_{10}$ copies/ml in Caucasian and Asian patients, respectively. 35% of Caucasian patients and 39% of Asian patients had undetectable HBV DNA (<400 copies/ml) at week 48. 63% of Asian and 64% of Caucasian people achieved ALT normalization at week 48.

4.1.2.15 Clinical effectiveness: summary

This section summarises the clinical effectiveness results from the previous sub-sections. Note that differences in response thresholds, timing of measurements, and treatment comparators makes it difficult to compare results across studies.

The majority of the fully published RCTs report outcomes measured at the end of 48 weeks treatment (for the pegylated interferon alfa studies results are also presented 24 weeks after end of treatment, i.e. week 72). Some of the adefovir dipivoxil studies are on-going with treatment up to 5 years. Interim results are currently only available as conference abstracts. In general, the active treatments were effective in terms of a range of outcomes in relation to placebo. In relation to each other, results were mixed.

<u>HBV DNA</u>

Reductions in HBV DNA to low or undetectable levels were associated with all active treatments. In general, adefovir dipivoxil was significantly more effective than placebo (21% to 51% compared to 0, respectively), and when added to lamivudine in patients with lamivudine resistance it was more effective than on-going lamivudine 35% to 85% compared to 0-11%, respectively).

In the two pegylated interferon alfa trials, the general trend was for pegylated interferon alfa monotherapy and PEG + LAM dual therapy to be of similar efficacy, and both were significantly superior to lamivudine monotherapy. For HBeAg positive patients, end of follow-up HBV DNA response rates were 32%, 34% and 22%, respectively (based on unpublished data). For HBeAg negative patients, end of follow-up HBV DNA response rates were 43%, 44% and 29%, respectively. HBV DNA levels tended to decrease between cessation of treatment and 24 week follow-up.

Response rates were also higher for all doses of pegylated interferon alfa in comparison to non-pegylated interferon alfa (24 weeks after 24 weeks of treatment). However, this difference was not statistically significant.

Biochemical (ALT) response

Reductions in ALT to normal levels were observed in all studies, to varying degrees. Response rates for adefovir dipivoxil monotherapy after a year's treatment were in the range 48% to 72% in comparison to 16% to 29% for placebo (statistically significant). In lamivudine resistant patients, significantly higher response rates were observed for patients given adefovir in addition to lamivudine, compared to those who continued with lamivudine (37% vs 9%). Response rates for lamivudine resistant patients who switched to adefovir dipivoxil (+ placebo), were significantly higher than rates in patients who continued on lamivudine (+ placebo).

For the two pegylated interferon alfa studies, pegylated interferon alfa monotherapy and PEG + LAM dual therapy were of similar efficacy, and both were superior to lamivudine monotherapy. For HBeAg positive patients, end of follow-up response rates were 41%, 39% and 28%, respectively (based on unpublished data). For HBeAg negative patients, end of follow-up response rates were 59%, 60% and 44%, respectively. In one of these studies, ALT response rates increased between end of treatment and follow-up in both pegylated interferon alfa monotherapy and dual therapy treated patients, but decreased in lamivudine monotherapy patients.

ALT response rates (measured 24 weeks after 24 weeks of treatment) were also higher for all doses of pegylated interferon alfa-2a in comparison to non-pegylated interferon alfa. However, this difference was not statistically significant.

Liver histological response

Only three of the included studies reported liver histology results (two adefovir dipivoxil studies – one with HBeAg positive and one with HBeAg negative patients, and one pegylated interferon alfa – HBeAg negative patients). All three studies reported improvements in liver histology following treatment, expressed in terms of changes in Knodell and Ishak scores.

Adefovir dipivoxil was more effective than placebo in terms of histologic improvement (where the proportion of patients treated with adefovir dipivoxil was generally double that of placebo treated patients), mean changes in histology scores (necroinflammation and fibrosis), and ranked assessment of change (e.g. improved, no change, worsened).

In the pegylated interferon alfa study, histologic improvements were observed for all three treatments (in the range 48% to 59% based on paired biopsy samples), with no significant differences between groups. Similarly, there were improvements in terms of ranked assessment of change although differences did not appear to be statistically significant.

HBeAg seroconversion

Seroconversion rates across the trials of HBeAg positive patients varied according to characteristics of the patients, the treatment duration, and regimen. Rates reached as high as 14% for adefovir dipivoxil and 37% for pegylated interferon alfa.

In treatment naïve patients, adefovir dipivoxil was significantly more effective than placebo (12% to 14% compared to 6% placebo). In patients with lamivudine resistance, switching patients to adefovir dipivoxil, or adefovir dipivoxil to lamivudine, was more effective than continued lamivudine, although significance levels are not reported.

Significantly higher rates were observed for pegylated interferon alfa monotherapy, and pegylated interferon alfa in combination with lamivudine therapy compared to lamivudine monotherapy (32%, 27% and 19%, respectively. Based on as yet unpublished data). Rates increased between end of treatment and follow-up (but not for lamivudine monotherapy where there was a slight decrease).

Seroconversion rates were higher for all doses of pegylated interferon alfa in comparison to non pegylated interferon alfa. However, differences were not significant.

HBsAg seroconversion

The level of detail reported on changes in this outcome varied. Up to 5% of patients seroconverted (varying according to characteristics of the patients, the treatment duration, and regimen).

In the two pegylated interferon alfa combination therapy trials (HBeAg positive and negative patients), seroconversion rates were similar for patients treated with pegylated interferon alfa monotherapy and dual therapy with lamivudine monotherapy (in the range 2% to 3%). No patients treated with lamivudine monotherapy seroconverted in either trial. Differences between mono and dual PEG therapies compared to lamivudine were significant.

Combined outcomes

Two studies employed combined measures of effect, both of them evaluating pegylated interferon alfa.

In one study, rates of both ALT normalisation and HBV DNA levels <20,000 copies/ml at end of follow-up (week 72) varied between 23% and 36%. Rates were similar between patients treated with pegylated interferon alfa monotherapy and with the combination of pegylated interferon alfa with lamivudine. Rates in both groups were significantly greater than lamivudine monotherapy. A similar pattern was observed when the HBV DNA threshold was lowered to 400 copies/ml.

In the other study, rates of HBeAg loss, HBV DNA suppression and ALT normalisation were significantly higher for pegylated interferon alfa treated patients compared to non-pegylated interferon alfa (24% vs 12%, p=0.03).

Health related quality of life

Quality of life was reported as an outcome in only two of the included trials, both of them on pegylated interferon alfa combination therapy (in the manufacturer's submission to NICE). The SF-36 questionnaire was completed by patients in the trials. HRQOL scores tended to decrease during treatment, but returned to their approximate baseline values at follow-up. Between baseline and follow-up there was no significant difference in HRQOL between patients treated with pegylated interferon alfa and patients treated with lamivudine.

During treatment, CHB patients experienced lower mean reductions in physical and mental health values than did patients with chronic hepatitis C (based on an indirect comparison). Therefore, pegylated interferon alfa does not appear to reduce quality of life in CHB patients to the same extent as observed in CHC patients. Fully published results are anticipated.

Adverse events

Dose discontinuations for safety reasons were low for patients receiving adefovir dipivoxil. The majority of participants in each trial reported at least one adverse event, and proportions tended to be similar across trial arms. Adverse events included: pharyngitis; headache; abdominal pain; asthenia and influenza-like symptoms. In some studies, incidence of events was greater in placebo groups; in others it was greater in adefovir dipivoxil treated patients.

In the pegylated interferon alfa studies, treatment discontinuation due to safety and dose continuations was relatively low (<7%), but tended to be higher for pegylated interferon alfa than for lamivudine. Likewise, incidence of adverse events (including serious adverse events) in patients treated with pegylated interferon alfa tended to be greater than in those treated with lamivudine (e.g. headache, pyrexia, fatigue, myalgia and alopecia). Incidence of pyrexia and myalgia was greatest in high dose pegylated interferon alfa and non-pegylated interferon alfa.

Patient sub-groups

Data on sub-groups of treated patients were limited. In terms of genotype, results were mixed. One pooled analysis of two adefovir dipivoxil trials found no significant difference in treatment effects according to genotype. Another study (evaluating pegylated versus non-pegylated interferon alfa) reported significantly higher response rates for genotype B than C.

Race did not appear to be associated with changes in HBV DNA.

The effects of treatment on a small sub-group of cirrhotic patients was reported in one trial (pegylated interferon alfa). Response was only observed in pegylated interferon alfa treated patients (as opposed to non-pegylated interferon alfa) and rates at follow-up varied between 38% and 54%, depending on outcome measure.

Response rates (including HBeAg seroconversion) in patients with 'difficult to treat' low baseline ALT levels were in the range 20-29% depending on regimen used (e.g. pegylated interferon alfa with and without lamivudine).

For patients co-infected with HIV the addition of adefovir dipivoxil to existing anti-retroviral therapy (including lamivudine) significantly reduces HBV DNA and ALT levels. This is based on data presented in conference abstracts.

Pre- and post-liver transplant patients

A number of observational studies have evaluated the effectiveness of treating patients before and after liver transplant to prevent the recurrence of HBV infection. The largest study reported that adefovir dipivoxil administered pre- and post-transplant was associated with reductions in HBV DNA, ALT, and three year survival rates in excess of 80%.

5 ECONOMIC ANALYSIS

5.1 Introduction

The aim of this section is to assess the cost-effectiveness of pegylated interferon alfa and adefovir dipivoxil compared to existing treatments (conventional interferon alfa and lamivudine) or best supportive care in adults with chronic hepatitis B in England and Wales. The economic analysis comprises:

- a systematic review of the literature on the cost-effectiveness of pegylated interferon alfa and of adefovir dipivoxil (Section 5.2);
- a review of the manufacturer submissions (cost-effectiveness section) to NICE (Sections 5.3 and 5.4);
- presentation of our economic model and cost-effectiveness evaluation (Section 6).

5.2 Systematic review of the literature

5.2.1 Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations comparing pegylated interferon alfa and/ or adefovir dipivoxil to existing treatments (conventional interferon alfa and lamivudine) or no treatment (best supportive care) in adults with chronic hepatitis B. The details of the search strategy are documented in Appendix 3. The manufacturers' submissions to NICE were reviewed for additional studies.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by a health economist. Economic evaluations were eligible for inclusion if they reported on the cost-effectiveness of pegylated interferon alfa and/ or adefovir dipivoxil versus existing treatments (conventional interferon alfa and lamivudine) or no treatment (best supportive care) in adults with chronic hepatitis B. Studies reporting the economic evaluation of comparator treatments were also

identified. We reviewed these to identify key methodological issues in economic evaluation of treatment for chronic hepatitis B.

5.2.2 Results of the systematic review: cost-effectiveness

A total of 1951 publications relating to cost-effectiveness in hepatitis B were identified through our searches. None of these was a fully published economic evaluation of either drug. No additional publications were identified from the manufacturer submissions and further discussion with the industry teams confirmed that no full reports of economic evaluation of pegylated interferon alfa or adefovir dipivoxil have been published. One conference abstract reporting a cost-effectiveness study of the use of adefovir dipivoxil as a salvage strategy for chronic hepatitis B patients who have developed lamivudine-resistance was identified and is reviewed in outline below (NB. During finalisation of our report we became aware that this abstract had just been fully published. We provide the reference so that readers may refer to the full publication if they wish[81]).

Kanwal F and colleagues 2004 (Conference Abstract)[82]
Recognising the high cost of adefovir dipivoxil, in contrast to lamivudine, this USA based analysis considered a hybrid strategy that would take advantage of the comparatively low cost and durable on-treatment effectiveness of lamivudine and that would be responsive to the high level of resistance observed with long-term lamivudine therapy. A Markov model was used to estimate the cost-effectiveness of this "salvage strategy" compared to current practice of either interferon alfa or lamivudine therapy alone for a cohort of 40 year old patients with chronic hepatitis B with raised ALTs, but without cirrhosis. Unlike other cost-effectiveness analyses published to date this evaluation was not limited only to patients with HBeAg positive CHB, but also included patients with HBeAg negative CHB (as 23% of the cohort analysed in the base case analysis).

The three treatment strategies evaluated were:

1) 5 million units of interferon alfa, three times per week, for 6 and 12 months for HBeAg positive and HBeAg negative patients respectively;
2) 100 mg of lamivudine daily continued until sustained virological response was achieved;
3) 100 mg of lamivudine daily continued until resistance develops at which point treatment swaps to 10 mg of adefovir dipivoxil daily (salvage therapy).

The abstract reports that transition probabilities were derived from a systematic review of the literature and that treatment and health state costs were obtained from Medicare and the Red Book. There is insufficient detail in the abstract to enable us to critique the study or to determine the validity of the model structural assumptions, parameter inputs or costings.

Undiscounted lifetime costs for the three treatment strategies were $18,607, $ 20,915 and $28,362 for interferon alfa, lamivudine and adefovir dipivoxil salvage respectively, while the undiscounted outcomes in terms of life years were 34.7, 37.2 and 38.9. The salvage strategy produced improvements in outcome, but at a substantially increased cost. When costs and outcomes were discounted at 3% the incremental cost-effectiveness ratio for the salvage strategy was $14,204 per life year

gained. Sensitivity analysis showed that adefovir dipivoxil salvage became the dominant strategy if adefovir dipivoxil costs were halved (or alternately lamivudine costs doubled) and where greater than 60% of the treatment cohort consisted of people with HBeAg negative CHB.

5.2.2.1 Hepatitis B Anti-Viral Therapy: published economic evaluations

In the absence of published economic evaluations of pegylated interferon alfa and adefovir dipivoxil this section presents a brief review of economic evaluations of other anti-viral therapies for the treatment of chronic hepatitis B. We present an overview of methods used to model disease progression, estimate benefits/ outcome and to estimate costs.

5.2.2.2 Summary of Methods

Six fully published economic evaluations of anti-viral interventions for chronic hepatitis B were found,[16;83-87] although two of these[84;87] report analyses using the same model and differ only in that there is more long term evidence of treatment effectiveness in the second publication. All the fully published economic evaluations for anti-viral therapy (conventional interferon alfa and lamivudine) have presented models for disease progression in patients with HBeAg positive disease and have excluded those with HBeAg negative CHB from their analysis. As a result of this the principal treatment endpoint has been HBeAg seroconversion and the effect of this on disease progression – although one evaluation adopted a wider definition of response also including loss of HBV DNA, ALT normalisation and histological improvement[83]. In all evaluations the effect of this has been to reduce the rate of progression to compensated cirrhosis, due to the lower transition probability from the HBeAg seroconverted state to compensated cirrhosis compared to that from active CHB (i.e. prior to seroconversion) to compensated cirrhosis. This applies to all the anti-viral agents being evaluated – though the estimates for the exact proportion of patients seroconverting and the durability of seroconversion vary between studies and between agents that have been evaluated.

There may also be benefits from HBeAg seroconversion through a lower transition probability to hepato-cellular carcinoma[88], though not all evaluations have taken this into account. Two evaluations[83;84] did not allow the transition from the HBeAg seroconverted state to hepatocellular carcinoma, while the other maintained the same risk of developing hepatocellular carcinoma from CHB and HBeAg seroconversion, but applied a substantially lower risk for HBsAg seroconverted patients[16].

Evaluations of lamivudine[84-87] have identified additional benefits in a reduced rate of progression to cirrhosis after 1 year of treatment for HBeAg positive patients who do not seroconvert. Pooled results from three clinical studies showed that progression to cirrhosis at 1 year for lamivudine treated patients was 1.8% compared to 7.1% for placebo and 9.5% for interferon alfa. Where evaluations have included this effect, it has been assumed to occur only after the first year of treatment; after that lamivudine provided no benefit against progression to cirrhosis.

All published evaluations have assumed that patients who stop therapy, do not respond or who do not achieve a sustained response follow the same course of disease as those who were untreated.

None of the evaluations discussed in the following section used prospectively collected cost data from clinical trials or observational studies of patients with chronic hepatitis B. Where studies have been concerned with the effect of short-term biochemical and virological end-points (measured in clinical trials) on longer term outcomes (such as disease progression, life expectancy and QALYs) state transition models have been developed and estimates of health state costs have been incorporated into these models to provide estimates of the costs of managing disease progression in a cohort of patients. For this purpose protocols were developed identifying resources used by patients in each health state and the frequency of use of those resources. In most cases this was limited to identifying hospital attendances, whether these be for inpatient or outpatient care.

Separate exercises have been undertaken in each of the evaluations to cost the interventions being investigated. Studies have differed in the comprehensiveness of these costings. Most included estimates of both the cost of drugs and monitoring patients while on treatment,[16;83;84;86;87] though they vary substantially in the detail provided to enable comparison of their assumptions in costing treatment; one study limited their costings of the interventions to drug costs only[85].

Direct comparisons of the cost of interventions are not appropriate as they relate to a number of different countries with varying clinical practice and have been undertaken over a period of years (1995-2002).

In general, sensitivity analyses showed that study results were more sensitive to variation in variables that impacted on the effectiveness of interventions (eligibility for treatment and rate of progression to cirrhosis [84;86;87]) rather than to those which impacted on the costs of interventions.

In the next section we describe in more detail the methods and assumptions used in each of these economic evaluations. Their results are not discussed.

5.2.2.3 Economic Evaluations – modelling disease progression, outcomes and costs

Wong and colleagues (1995) - Cost-effectiveness of Interferon alfa 2b Treatment for Hepatitis B e Antigen-Positive Chronic Hepatitis B

Wong and colleagues[16] in the US developed a decision analytic model to synthesise evidence on the natural history of chronic hepatitis B and the effect of a 16-week course of interferon alfa compared to standard care. Patients entered the model aged 35 with chronic hepatitis and both HBeAg and HBsAg, without cirrhosis, and the progression of their disease was modelled using a cycle length of 1 year. The principal outcome of interferon alfa treatment modelled was HBeAg loss, described as equivalent to loss of HBV DNA. Patients with HBeAg negative CHB were excluded

from the model as were patients with co-infection with hepatitis C or hepatitis D virus.

The annual spontaneous rate of HBeAg loss, based on a review of the literature, was assumed to be 10% except for the first year of the model where a value of 9.1% was used. This was derived from the authors' own meta-analysis of nine randomised trials of interferon alfa 2b and corresponds to the proportion of untreated patients with loss of HBeAg. The effect of a 16-week course of interferon alfa 2b estimated in the meta-analysis was that 45.6% of treated patients would achieve HBeAg loss. In applying this effect in the model they assumed that the randomised trials included in the meta analysis had reported their results on an intention to treat basis and that these would therefore include patients with dose reductions and who discontinued treatment due to side effects. The rates for loss of HBsAg were also derived from the authors' meta-analysis with the same rate applied to treated and untreated patients. A higher rate was applied for patients in the year after losing HBeAg irrespective of whether this was treatment induced or spontaneous. Patients who lost HBeAg could reactivate (i.e. regain HBeAg, lose anti-HBe), at a high rate of 7% in the year after HBeAg loss or subsequently at a lower baseline rate of 2.9%. Patients who did not lose HBeAg within one year of treatment were assumed to follow the same course of disease as untreated patients.

Screening for hepatocellular carcinoma was excluded from the model, due to uncertainty over the benefits of screening in a North American population.[89] Despite this, screening for HCC remains a core component of clinical guidelines for monitoring CHB patients during and post-treatment[3;90;91]. Liver transplantation was also excluded on the assumption that few decompensated patients could benefit given the then limited supply of donor organs, but also due to the high risk of re-infection with CHB. Subsequent research using lamivudine and adefovir dipivoxil as prophylaxis for patients undergoing liver transplantation suggests that these agents can significantly reduce the risk of re-infection for patients on immunosuppression and, while transplants for liver disease resulting from viral infection are not common, they are an established component of the treatment pathway

The principal benefit of modelled HBeAg loss, either spontaneous or treatment-related, was a reduced rate of progression to compensated cirrhosis (1% for those who lost HBeAg compared to 12.1% for those who did not). Since patients could only progress to decompensated disease (which has a substantial excess mortality risk of 39%) after first developing compensated cirrhosis, reducing the transitions to the compensated cirrhosis health state provides a large benefit in terms of life expectancy. Additionally, given that the health state utilities applied for decompensated disease differed markedly from those for compensated cirrhosis and CHB (0.54 compared to 0.92 and 0.94 respectively) a disproportionate QALY gain would be expected by reducing this transition, even in the absence of mortality differences.

Health state utility values adopted in this evaluation were derived from an expert panel of clinicians assessing their own utilities for each of the health states identified in the model (these are reported later in Section 5.2.3). The report states that the values used were an average of valuations derived using standard gamble and time trade-off techniques, but does not indicate how the health states were described nor exactly how these values were elicited.

The costs of interferon alfa therapy were based on a treatment course of 10 million units, three times per week, for sixteen weeks. Total costs of treatment were made up of the cost of the drug itself and costs for office visits and laboratory fees, with interferon alfa comprising 82% of the total cost of treatment. Unit costs were not specified, nor was a schedule of the frequency of office visits or of laboratory tests provided so it is difficult to assess the validity of this estimate.

The health state costs for the model were developed using estimates of the frequency of hospitalisation, outpatient visits and medications from an expert panel. Hospitalisations and outpatient attendance within the chronic hepatitis B and compensated cirrhosis states were assumed to vary by serological status so that patients who had seroconverted HBeAg and HBsAg were assumed to use fewer resources than those who had not seroconverted. Patients with decompensated cirrhosis and a proportion with hepatocellular carcinoma were assumed to receive daily medication (furosemide, spironolactone, norflaxacin and lactulose) and these were included in the health state cost. Health state costs increased with disease progression, being least for chronic hepatitis B and greatest for decompensated cirrhosis. The unit costs applied for hospitalisation due to compensated and decompensated disease were the same and the difference in annual cost between the health states (approximately $4,000 for CC and $18,000 for DC) was due to the assumed frequency of hospitalisation (once every two years for CC and once every 5 months for DC). The annual cost for the hepatocellular state was lower than for decompensated cirrhosis due to a lower unit cost for hospitalisation despite a slightly higher frequency of hospitalisation (once every 4 months for HCC compared to once every 5 months for DC).

A sensitivity analysis was performed on costs during which the cost of interferon alfa treatment was increased by 13%; the report states that this did not change the decision but does not indicate how influential any of these cost variables are on the final result.

Dusheiko and Roberts (1995). Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal.

In a UK evaluation, Dusheiko and Roberts[83] estimated the response to interferon alfa therapy in patients who had not developed cirrhosis, using the results of a published meta-analysis of 15 RCTs of interferon alfa to estimate the treatment effect. Response in this analysis was defined as clearance of HBeAg, seroconversion to anti-HBe, normalisation of ALT, loss of HBV DNA and histological improvement of chronic hepatitis to minimal or no hepatitis. They estimated the initial response at 40%, but with a relapse rate of 12.5%, leading to a final response rate of 35% for CHB patients treated with interferon alfa.

A natural history state transition model was used to determine outcomes for two cohorts (one treated, one untreated) each of 1000 patients with treatment non-responders exposed to risks of developing cirrhosis, decompensation and death from liver disease. Since no background mortality was included the model time horizon was set to 30 years. Treatment responders effectively left the model, as the treatment effect was assumed to be durable over the model time horizon, though studies of the natural history of CHB suggest that disease may reactivate after seroconversion in 20-

30% of cases[3]) and that patients in the seroconverted state may also develop hepatocellular carcinoma. Mortality from liver disease, in the model, only occurred from the decompensated cirrhosis health state in this model, whereas current opinion would suggest that excess mortality should be modelled for the compensated cirrhosis state and possibly also the chronic hepatitis B state, though at a substantially lower rate than for decompensation[3;92;93]. Health gains, in terms of years of life saved, were converted to QALYs using health state valuations derived using clinical judgements. However the authors state that the weightings adopted were essentially arbitrary and should not be applied uncritically by other researchers.

The rate of progression from CHB to compensated cirrhosis was modelled at two rates: a low rate of 0.0105 per year and a high rate of 0.0221 per year. These rates are substantially lower than those used by Wong and colleagues,[16] and an annual progression rate of 5% per annum was estimated at a recent consensus meeting[3]. The annual rate of progression from compensated cirrhosis to decompensated cirrhosis was 5%. Mortality from decompensation was estimated at two rates, a low value of 5% and a high value of 13%. These rates are low compared to those adopted in other evaluations which have excess mortality rates for decompensation at 39% and 56% for hepatocellular carcinoma.

The model took no account of spontaneous responses in the untreated cohort. All patients in the untreated cohort remained in the chronic hepatitis B health state in the model of disease progression. Studies of the natural history of the disease suggest that HBeAg seroconversion occurs spontaneously at a mean annual rate of 8-15% in Western countries and at a lower rate of 2-5% in Asian children.

The costs of interferon alfa therapy were estimated based on a treatment course of 10 million units, three times per week, for sixteen weeks. Total costs of treatment were made up of the cost of the drug itself, costs for patients' initial presentation and evaluation, an overnight stay for first interferon alfa injection and training in administering the drug, and for eight follow up visits. Costs for untreated patients were based on two out-patient visits per year, the first of which was a comprehensive work-up equivalent to the initial presentation visit for treated patients. Interferon alfa comprised 72% of the additional costs of treating patients in the first year.

Health state costs were based on a schedule of routine monitoring based on good practice guidelines agreed by an international expert panel of hepatologists attending a consensus conference and, for patients with decompensated disease, an assumption that they would be hospitalised once per year. Apart from the year in which interferon alfa treatment was provided, treated and untreated patients were monitored identically and the frequency of follow-up was assumed to increase with disease progression. Patients with CHB without cirrhosis were seen twice yearly, those with cirrhosis quarterly and those with decompensation (including HCC) were seen every two months. The assumptions underlying the health state costs for this model are generally less resource intensive that those adopted by Wong and colleagues, particularly for the most severe stages of disease where outpatient attendances were assumed to be monthly and 2 - 3 inpatient admissions were expected for decompensated patients.

An additional analysis was presented including assumed values for patient-borne costs (both direct costs in terms of travel and indirect costs due to time taken off work) and value of lives lost (assuming a value of life of £1.4 million).

Brooks and colleagues (2001) - Economic evaluation of lamivudine compared with interferon alfa in the treatment of chronic hepatitis B in the United States.

A decision tree model was developed to determine the costs and outcomes of interferon alfa and lamivudine in treating patients with chronic hepatitis B over a one year time horizon[85]. The aim of the study was stated as determining "the more successful treatment for chronic hepatitis B given a fixed drug budget", adopting the perspective of a third party payer. Two key endpoints were evaluated in this study:

- HBeAg seroconversion, defined as loss of HBeAg from the patient's bloodstream combined with development of antibodies to HBeAg (i.e. gain of anti-HBe) and loss of detectable serum HBV DNA;
- the number of patients progressing to cirrhosis.

HBeAg seroconversion rates were taken from an RCT comparing lamivudine monotherapy with interferon alfa therapy and with lamivudine and interferon alfa combination therapy[94]. The rates used, 17.5% for patients receiving lamivudine and 18.8% for patients receiving interferon alfa, were those observed 52 weeks after starting treatment. The spontaneous HBeAg seroconversion rate for untreated patients was based on a pooled analysis of patients in two placebo-controlled trials of lamivudine[95;96] by combining the numbers of patients who seroconverted while on placebo. Three out of seventy placebo-treated patients in one trial[95] and four out of sixty nine in the other[96] seroconverted, giving a combined seroconversion rate of 5.0%. A pooled analysis of all three trials was undertaken to determine the rate of progression to cirrhosis for patients who do not seroconvert; for lamivudine treated patients this was 2.2%. The rates of progression to cirrhosis in the combined trial populations was 12.1% (4 out of 33 patients) for interferon alfa and 7.4% (7 out of 94) for placebo. Due to the small numbers of patients in this analysis and a lack of statistically significant difference between the two populations a weighted average of 8.7% for both interferon alfa and no treatment was used in the model.

Given the time horizon for the evaluation was defined at the outset to be one year no model of the natural history of CHB progression was developed, and no estimates of gain in life expectancy or quality adjusted life expectancy were reported. The study report is not explicit regarding categories of patients included in the analysis. However, the use of HBeAg seroconversion and the rate of progression to cirrhosis as prime endpoints suggests that patients with HBeAg negative CHB were excluded as were patients who had already developed cirrhosis. One assumption underlying this comparison is that the treatment effects of interferon alfa and lamivudine are equally durable. Durability of seroconversion for lamivudine has been estimated between 60% and 80% and between 80% and 90% for interferon alfa. [3] A recent meta-analysis of patient-level data on long term follow up (up to three years) for patients treated with lamivudine or interferon alfa reported a relative risk of relapse of 4.6 for lamivudine compared to interferon alfa [97].

The only costs included in this evaluation were the direct costs of a treatment course of 10 million units, three times per week, for sixteen weeks of interferon alfa

($5,589.10), and fifty two weeks of a regimen of lamivudine at 100 mg per day ($1,580.80). The purpose of this study was to determine the proportion of patients that could be treated, within a fixed budget, with either of the two interventions and for convenience the budget was set at a figure sufficient to treat 100 patients with interferon alfa ($558,910). Simple arithmetic shows that this same budget would fund a year's lamivudine treatment for 353 patients and the bulk of the evaluation was concerned with estimating the short term outcomes (in terms of HBeAg seroconversion and progression to cirrhosis) for this hypothetical cohort of patients. No health state costs were estimated as the evaluation was not concerned with disease progression beyond the year of treatment nor with long-term outcomes.

Orlewska (2002) The cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B in Poland

Orlewska[86] developed a decision tree model to estimate the cost and outcome of four treatment scenarios for populations of patients with CHB. In the first two scenarios interferon alfa and lamivudine were available and only varied according to whether interferon alfa or lamivudine was the first choice treatment for eligible patients. In the third only interferon alfa was available. The final scenario was one where no anti-viral treatment was available and patients' disease would progress according to the natural history with treatment provided when sequelae of CHB develop. The outcomes estimated in the model were HBeAg seroconversion (defined as loss of HBeAg and appearance of HBeAb) and non-progression to cirrhosis. The model had a one year time horizon and adopted the perspective of a third party payer. Patients entering the model were all assumed to be HBeAg positive (patients with HBeAg negative CHB were excluded), aged between 30 and 50, with moderately raised ALT levels, but had not progressed to cirrhosis. Sixty percent of the population was female and all patients were assumed to be interferon alfa naïve.

Rates of seroconversion for lamivudine (18%) and interferon alfa (19%) were taken from a randomised controlled trial comparing lamivudine monotherapy with interferon alfa therapy and with lamivudine and interferon alfa combination therapy[94]. The spontaneous seroconversion rate was based on the rate for untreated patients in a placebo controlled trial of lamivudine. The annual probability of progression to cirrhosis was based on an adjustment to a pooled analysis of data from three clinical trials[98]. The reported proportions of 1.8%, 7.1% and 9.5% for lamivudine, placebo and interferon alfa respectively (which included both seroconverted and non-seroconverted patients in the denominators) were adjusted upward to 2%, 8%, 12% to provide estimates of rates of progression for non-seroconverted patients based on the observation that no patients in the three trials who seroconverted progressed to cirrhosis by 52 weeks (regardless of whether they were in treatment or placebo arm). The difference in the rate of progression between interferon alfa and placebo was not regarded as significant and the value for interferon alfa was applied to rate of progression of cirrhosis for both interferon alfa treated and untreated patients, partly due to the similarity of this estimate to that presented by Wong[16].

In addition to estimating key transition rates related to treatment the model required estimates of the population of patients eligible for each anti-viral treatment. An expert panel of Polish hepatologists estimated that 60% of patients would be eligible for treatment with interferon alfa and 90% eligible for lamivudine.

To estimate the impact of treatment on patient life expectancy, the annual probability of dying from cirrhosis was estimated to be 0.1127, based on a published 5 year survival rate of 55% for patients with CHB and cirrhosis. This is significantly greater than the usual values for compensated disease. The reduction in life expectancy due to cirrhosis was calculated using a life table approach. First, male and female life expectancies were estimated for individuals aged 30 and 50 by applying age and sex-specific death rates. Then life expectancy with cirrhosis was estimated after adding the estimate of the disease-specific excess mortality and then adding in this estimate of the disease-specific excess mortality. The average reduction in life expectancy was calculated by taking a weighted average of the age and sex-specific reductions in life expectancy, assuming that 60% of the affected population was female.

The life expectancy estimates based on outcomes assessed at the end of the year of treatment may be an underestimate by ignoring evidence of the efficacy of longer term lamivudine treatment. A greater danger of bias in the study results from assuming that the treatment effect estimated at one year is durable. Relapse from HBeAg seroconversion to active CHB has been estimated to occur spontaneously in around 3% of cases annually[16], and at a higher rate in the year following seroconversion for patients treated with anti-viral agents[99]. The durability of HBeAg seroconversion following lamivudine treatment appears to be lower than in interferon alfa treated patients[97].

The drug cost for interventions in this evaluation were estimated based on a treatment course of 5 mIU of interferon alfa, three times per week, for twenty four weeks (which was the usual clinical practice in Poland) and fifty two weeks of a regimen of lamivudine at 100 mg per day. In addition to the drug costs, total costs of treatment were made up of costs for patients' assessment and monitoring by hospital specialists (including laboratory tests and investigations) while on treatment and, for interferon alfa only, an initial 10 day hospitalisation and 72 ambulatory visits for parenteral administration of the drug. The schedule of consultations, investigations and procedures was developed for costing purposes, based on responses to a questionnaire sent out to Polish hepatologists, which was further discussed at a consensus meeting. Patients treated with interferon alfa were more intensively monitored, requiring eleven specialist consultations during the year in which treatment occurred, compared to lamivudine treated patients who required eight specialist consultations during the first year of treatment. Patients not receiving any anti-viral therapy were assumed to have the same schedule of specialist consultations as the lamivudine treated patients. For both interventions drugs represented the majority of the costs of anti-viral therapy. Drug costs comprised 70% of the total cost of interferon alfa treatment and 79% of the total cost of lamivudine treatment.

The only health state cost estimated was for patients progressing to cirrhosis during the year of treatment. This cost was based on patients having a liver biopsy, laboratory tests and comparatively low cost medication. It was assumed that patients developing cirrhosis would not experience more specialist consultations than non-cirrhotic patients during the year.

An extreme scenario sensitivity analysis was performed varying the cost of the drug component of interferon alfa therapy and the non-drug costs of both interferon alfa

and lamivudine separately. To test sensitivity to the interferon alfa drug cost a dosage of 10 million units for four months (the dose and treatment duration used in all the other economic evaluations) was used, but had very little impact on the results. To test sensitivity to the non-drug cost for each intervention, the cost of hospitalisation was removed from interferon alfa treatment and was added to lamivudine treatment, again with little impact on the results. Overall the study results were most sensitive to variation in variables that impacted the effectiveness of interventions, particularly the proportions of patients eligible for either treatment and in the rate of progression to cirrhosis for non-seroconverted patients, and least sensitive to variation in cost.

Crowley and colleagues (2000; 2002) Cost-effectiveness analysis of lamivudine for the treatment of chronic hepatitis B/ Introduction of lamivudine for the treatment of chronic hepatitis B: expected clinical and economic outcomes based on 4-year clinical trial data.

Crowley and colleagues [84;87] developed a two stage decision analytical model to compare three treatment scenarios for patients with chronic hepatitis B in Australia. The treatment options included in the three scenarios were as follows:

- scenario 1 included treatment with either interferon alfa or lamivudine;
- scenario 2 included only treatment with interferon alfa;
- scenario 3 included no anti-viral therapy and best supportive care was provided. This consisted of monitoring the patient's condition and drug and hospital treatment for the effects of progressive disease.

The evaluation incorporated a one year decision tree model evaluating outcomes, in terms of HBeAg seroconversion and progression to cirrhosis, under each of the three scenarios. In a second stage of the analysis the longer term outcomes from the treatment scenarios were modelled using a six state Markov model. The six states included in the model were HBeAg seroconversion (defined as loss of HBeAg and gain of anti-HBeAg), chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and death. HBsAg seroconversion and liver transplant states were excluded from the model due to their infrequent occurrence.

The population of patients entered into the model were 70% male with an average age of 30, were HBeAg positive (patients with HBeAg negative CHB were excluded, as were patients who had progressed to cirrhosis or who had been previously treated with interferon alfa) and had ALT levels greater than or equal to twice the upper limit of normal. The model structures adopted in both publications[84;87] are identical as are the input data, other than the second paper contains trial-based HBeAg seroconversion rates for up to four years of lamivudine treatment whereas only three years of data were available for the original publication.

The study estimated the cost-effectiveness of treatment scenarios for patients with ALT levels greater than or equal to twice the upper limit of normal and, therefore, did not base their estimates of treatment effects on the trial reports for all patients. The clinical trials from which the key transition values for HBeAg seroconversion were derived were the same trials as used by Brooks and colleagues[85] and Orlewska [86]. However Crowley used a pooled analysis which only included patients with ALT levels greater than or equal to twice the upper limit of normal, reported as comprising

60% of trial participants. These patients were selected as being the group in which durable response to anti-viral therapy is most likely to occur.

The HBeAg seroconversion rates applied in the one year model were 28.7% for lamivudine and interferon alfa (a weighted average of the observed seroconversion rates of 30% and 24% for lamivudine and interferon alfa respectively) and 9% for untreated patients. As with the other evaluations described here the spontaneous seroconversion rate is based on the pooled results from the two placebo-controlled lamivudine trials. The seroconversion rates for lamivudine at two, three and four years of used in the model were 18.7%, 39.6% and 22.9% respectively. These were based on the longer term results of patients in the clinical trials meeting the ALT inclusion criterion and correspond to cumulative rates of 42%, 65% and 73%. Continued treatment with lamivudine after year 4 was assumed to confer no additional benefit in terms of seroconversion, so that the spontaneous rate of 9% was applied to patients treated beyond that time. The authors do not discuss the clinical rationale for maintaining non-seroconverted patients on a treatment that was predicted to offer no benefit in terms of seroconversion or reduced risk of progression to cirrhosis.

It was assumed that 15% of patients who seroconverted, either spontaneously or following treatment with either interferon alfa or lamivudine, reactivated disease within a year of seroconverting, returning to the active CHB health state, but that after this time no further reactivation occurred. This was based on a review of the literature on the durability of seroconversion. This contrasts with the model developed by Wong who estimated a high reactivation rate within 12 months of seroconversion (7%), but also applied a baseline reactivation rate of 3% to all seroconverted patients over the model time horizon. This accords with studies of the natural history of disease [3;100;101] and long term follow up of lamivudine treated patients [102;103] which show reactivation of CHB in a proportion of patients who seroconvert.

Pooled data from the three lamivudine trials were also used to derive estimates of the effect of lamivudine on the rate of progression to cirrhosis for the sub-group of patients with raised ALTs. In the year 1 model it was assumed that no patients who seroconverted would progress to cirrhosis and for non-seroconverted patients the appropriate rates were 2% and 14% for lamivudine and interferon alfa/ no treatment respectively. In the long term model lamivudine treatment was assumed to have no beneficial effect on the rate of progression to cirrhosis and non-seroconverted patients faced a transition rate of 12.1% (based on the value used by Wong). For seroconverted patients an annual progression rate of 1% was assumed based on two natural history studies with 3 year follow-up.

Other transitions used in the model were based on a review of studies of the natural history of CHB and were not affected by the choice of treatment. An annual transition rate of 5% was assumed from compensated to decompensated cirrhosis. The rate of development of HCC is dependent on progression of liver disease with higher rates observed once cirrhosis has developed. A transition rate of 0.4% was assumed from CHB to HCC and of 2.5% from cirrhosis, but it was assumed that no individuals in the seroconverted state develop HCC; this differs from other evaluations (Wong) and natural history studies which suggest that this risk exists and may be as great as for patients with CHB without cirrhosis.

The final set of progressions in the model was related to excess mortality for a number of health states defined within the model. Population all-cause mortality rates were applied to all health states in the model and no excess mortality was included for the seroconverted and CHB states. Annual excess mortality rates for compensated cirrhosis were 5.1%, 39% for decompensated cirrhosis and 84.3% for hepatocellular carcinoma.

One scenario omitted from this analysis was the option to use lamivudine as a second line treatment for patients who fail to seroconvert when treated with interferon alfa. The authors also assumed that patients who seroconverted and then relapsed to chronic hepatitis B would not be retreated. However, discussion with UK specialists suggests that it is normal practice to re-initiate treatment in patients whose disease reactivates. The meta-analysis by van Nunen and colleagues[97] suggests that patients who have previously reactivated disease after seroconverting are less likely to achieve a durable response when re-treated, though the effect was not a statistically significant predictor in the analysis.

Drug costs were based on a treatment course of 10 MU, three times per week, for sixteen weeks of interferon alfa and a variable length regimen of lamivudine at 100 mg per day. Lamivudine treatment was ceased on progression to seroconversion. Additional costs arose from the assessment and monitoring of patients by hospital specialists (including laboratory tests and investigations) with a higher intensity of monitoring assumed during the first six months of the one year model. The schedule of consultations, investigations and procedures was based on discussion with an expert panel of six Australian hepatologists and responses to a questionnaire sent out to a further 30 hepatologists.

Patients treated with interferon alfa were more intensively monitored, requiring ten specialist consultations during the year in which treatment occurred compared to lamivudine treated patients who required only seven. The protocol stated that interferon alfa-treated patients were seen weekly for the first month, then monthly for the remaining course of active treatment and reviewed two months after treatment ceased whereas lamivudine-treated patients were seen monthly for the first four months of treatment then reviewed at six months. Patients not receiving any anti-viral therapy were assumed to have the same schedule of specialist consultations as the lamivudine treated patients. For the second six months of year one all patients were seen every three months. For both interventions drugs were the largest single component of the costs, comprising 66% of the total cost of interferon alfa treatment and 50% of the total cost of lamivudine treatment. The next largest components were laboratory tests and pathology at 20% of the total for interferon alfa and 32% of the total for lamivudine treatment.

Health state costs for the model were developed using responses to the hepatologists questionnaire and were based on estimates of the frequency of specialist and primary care consultations, investigative tests and hospitalisation for patients in each of the health states. Health state costs increased with disease progression, being least for seroconverted patients and greatest for hepatocellular carcinoma. The unit costs applied for hospitalisation due to compensated and decompensated disease were the same and the difference in annual cost between the health states (approximately $3,000 for compensated cirrhosis and $13,500 for decompensated cirrhosis) was due

to the assumed frequency of hospitalisation (once every two years for compensated cirrhosis and three times per year for decompensated cirrhosis).

Both papers report a summary of the deterministic sensitivity analyses which state that variation in the drug and disease management costs had no significant effect on the study outcome.

Published economic evaluations – summary of methods

- A systematic review of cost-effectiveness studies identified only one economic evaluation (unpublished). This was a USA Markov model comparing adefovir dipivoxil as salvage therapy to interferon alfa or lamivudine. The incremental cost-effectiveness ratio for adefovir dipivoxil salvage therapy was $14,204 per life year gained.
- The systematic review also identified six fully published economic evaluations of current treatments for CHB, namely interferon alfa and lamivudine. Their methods were reviewed to set the context for our own economic evaluation.
- The evaluations were published between 1995 and 2002 and were conducted in the USA, UK, Poland and Australia. The principal treatment outcome modelled was HBeAg seroconversion, though progression to compensated cirrhosis was also included as a secondary outcome.
- Most of the evaluations employed state transition models to estimate long term outcomes extrapolated from short term endpoints. None were based on prospective clinical evaluations. Time horizons ranged from 1 year to patients' lifetimes. Many of the evaluations excluded liver transplantation from their scope.
- Baseline cohorts generally comprised people in their 30s without cirrhosis who had not previously received anti-viral treatment. None included patients with HBeAg negative CHB.
- A number of treatment scenarios were modelled, including interferon alfa and lamivudine (as first or second line therapies) and supportive care.
- Costing methods varied in terms of comprehensiveness, but most included drug costs and costs associated with monitoring during treatment. Some used expert panels of hepatologists to estimate resource use.
- There was some variability in assumptions used. For example, transition rates from CHB to compensated cirrhosis varied substantially between two evaluations.
- In summary, whilst the published economic evaluations were similar, in that most employed state transition models to estimate long term effects of HBeAg seroconversion, there were differences in time horizon, assumptions, costs and resource use estimates and transition probabilities.

5.2.3 Health related quality of life for patients with chronic hepatitis B

We undertook a literature search to identify studies reporting health state values/ utilities associated with chronic hepatitis B (see Appendix 3 for details of the search strategy). The literature search identified one published study reporting on health state values/utilities for patients with CHB[104], discussed in Section 5.2.3.1. There is little information in general on quality of life for patients with CHB, and that reported tends to be a minor component of surveys based on liver clinic patients which are principally concerned with HCV. In the cost-effectiveness literature, reviewed earlier,

all studies have derived QALYs based on health state utility weights estimated by expert panels of clinicians. Table 26 reports the values used in previous economic evaluations and, for comparison, health state values for stages of progressive liver disease that were used in the Mild Hepatitis C Trial[105].

Table 26 - Health state utilities used in previous economic evaluations in CHB

Health state	Wong et al‡	Dusheiko and Roberts‡	Crowley et al‡	Mild Hepatitis C Trial†
HBeAg Seroconverted	0.931	0.90	0.783	NA
Chronic hepatitis		0.80		NA
No treat	0.893		0.692	
Treat IFN	0.777		0.467	
Treat LAM			0.611	
Compensated cirrhosis	0.874	0.50	0.561	0.55
Decompensated cirrhosis	0.540	0.20	0.150	0.45
Hepatocellular carcinoma	0.490	0.20	0.118	0.45

Note references marked ‡ derived utilities based on clinician opinion whilst reference marked † used patient data on health state classification using EQ-5D and tariff values from the general population[106].

5.2.3.1 Health State Values/Utilities

Owens and colleagues[104] derived utility scores for asymptomatic, mildly symptomatic and severely symptomatic hepatitis B virus (HBV) states using ratings expressed by medical staff in the medicine, paediatrics and surgical departments at Stanford University Medical School in an anonymous questionnaire. The questionnaire assessed physicians' knowledge of occupational risks from HIV and HBV as well as containing a section to assess quality of life associated with different HIV and HBV states. The authors expected physicians to rank asymptomatic states higher than symptomatic and mildly symptomatic higher than severely symptomatic. They also expected HBV states to be rated higher than similar HIV states.

Utilities were assessed using what the study authors refer to as a form of time trade-off technique where a description of each health state was followed by the statement "this scenario is equivalent to _____ months of healthy life". The physicians' stated equivalent months in good health were divided by 12 to give a utility value ranging from 0 to 1. This is approach does not follow the principles of the time trade-off technique as described by Torrance and colleagues[107].

Response rate to the questionnaire was 64%. The mean and median utilities for HIV and HBV health states declined, as expected, with increasing severity and were lower for HIV than for equivalent HBV states, except that the mean utility for HBV with severe symptoms was lower than for AIDS (the most severe HIV state) though the difference was non-significant and the medians were identical). Utility values for HBV were 0.812 for the asymptomatic state (defined as being asymptomatic, but with the potential to transmit the disease), 0.670 for mildly symptomatic (defined as mild fatigue and malaise that did not interfere with work) and 0.218 for severely symptomatic states (defined as cirrhosis, ascites and gastrointestinal bleeding). In this

study no comparable utilities from other studies of quality of life for hepatitis B states were presented.

Owens himself has subsequently questioned the validity of these utilities when writing a commentary on a published report of quality of life in chronic hepatitis C and chronic hepatitis B patients recruited in the liver clinic at St Mary's Hospital[108]. This paper (reviewed below) suggested that chronic hepatitis B patients differed from population-based controls only on the mental health and general health perception subscales of the SF-36. Owens argued that clinician-derived utility weights may over-estimate the negative impact of health states when compared to utility values for similar states derived from patients.

5.2.3.2 Supporting information on quality of life associated with chronic hepatitis B

Two studies have reported on health-related quality for chronic hepatitis B patients who were not on anti-viral therapy, using a generic quality of life instrument (SF-36). Foster and colleagues[15] investigated sequential chronic hepatitis C and hepatitis B patients attending out-patient clinics at St Mary's Hospital, London. Patients with cirrhosis or other significant chronic conditions were excluded as were any patients who were on anti-viral medication (or had been within six months). Seventy-six HCV and 30 HBV patients were recruited and scores for each dimension of the SF-36 were compared with published population norms.[109] Scores for HCV patients were significantly reduced compared to the general population norms. Scores for patients with HCV and HBV were compared to determine whether the reduction in quality of life was due to chronic hepatitis infection or was specifically due to HCV. Values for patients with HBV were lower than for the general population but only differed significantly ($p<0.01$) on general health and mental health dimension and showed no significant reductions for physical dimensions. Compared with HCV, patients with HBV scored significantly better on social functioning, physical role limitation and energy and fatigue dimensions. No correlations were found between SF-36 scores and ALT scores, indicating that severity of hepatitis does not influence quality of life.

Pojoga and colleagues[17] investigated 66 consecutive patients with chronic viral hepatitis within six months of referral to tertiary centres in Romania who were not receiving anti-viral treatment. Patients with cirrhosis or alcoholic liver disease were excluded from the study population, which consisted of 27 patients with CHB, 38 patients with hepatitis C and one patient with both CHB and hepatitis C. Scores on the SF-36 for all hepatitis patients were compared to scores for healthy volunteers and also for each type of hepatitis. Items concerning bodily pain were excluded as they were not thought to be relevant to hepatitis B or C. Independent sample t-tests showed significant differences in scores between hepatitis patients and controls ($p<0.0001$). Within the chronic hepatitis group CHB patients scored significantly higher on general health, social functioning and mental health. As with the Foster and colleagues study[15] and other studies concerned with quality of life in chronic viral hepatitis[110;111], no significant correlations were found between patients' transaminase levels and quality of life as assessed by the SF-36.

These studies suggest economic evaluations of interventions for CHB need to take account of the reduction in patients' quality of life when modelling outcomes in progressive disease states, but that severity of hepatitis infection (as assessed by aminotransferase levels or level of viraemia) does not impact on quality of life. The limited evidence available suggests that the impact on quality of life for CHB infection is not as great as for hepatitis C, when in the asymptomatic state. However, there is no evidence of a difference in the impact of CHB and HCV on quality of life once patients have progressed to cirrhotic and decompensated disease.

5.3 Review of Roche submission to NICE (pegylated interferon alfa-2a)

The introduction to the economic analysis in the submission states that it is concerned with assessing the cost-effectiveness of pegylated interferon alfa-2a relative to current available treatments for patients with chronic hepatitis B, relating the clinical benefits and the drug acquisition costs of the alternative treatment options. The analysis presented in the submission differs from the evaluations reviewed in the previous section by including all patients with CHB, i.e. patients with HBeAg negative CHB are not excluded. The comparators are clearly identified as conventional interferon alfa, lamivudine, adefovir dipivoxil and best supportive care (termed no treatment in the submission). All these interventions are included in a series of pair-wise comparisons for the treatment of patients with HBeAg positive chronic hepatitis B, while only lamivudine and best supportive care are included as comparators for patients with HBeAg negative CHB.

The perspective of the analysis is clearly stated as being that of the NHS, capturing direct costs and benefits only. Health benefits to sexual partners and family members of treated patients were excluded from the analysis. This exclusion applied to all interventions included in the evaluation and is therefore not likely to introduce a bias in the results.

5.3.1 Estimation of benefits

5.3.1.1 Model structure/ structural assumptions

Separate state transition models were developed to model disease progression and treatment effects in HBeAg positive and HBeAg negative chronic hepatitis B. These were structurally similar to models used in previous economic evaluations that have included long term models of disease progression (2165}, Crowley [84;87]) and are consistent with published studies of the natural history of chronic hepatitis B infection[3;92;100].

The structure of the models for the two disease variants was identical, in terms of the definition of progressive stages of liver disease associated with CHB (compensated/ decompensated cirrhosis and hepatocellular carcinoma with condition-specific excess mortality risks), but differed in the definition of response to treatment. As with previous economic evaluations of anti-viral treatment for chronic hepatitis B the primary therapeutic aim modelled for patients with HBeAg positive disease was HBeAg seroconversion. Since this endpoint is, by definition, not achievable by patients with HBeAg negative disease the therapeutic aim modelled for these patients was termed "response" and was defined as normalisation of ALT and suppression of HBV DNA below 20,000 copies/mL. The benefits of treatment are assumed to result

only from changes in patients' viral, biochemical or serological status, in that transition rates to progressive disease are lower for the seroconversion/ response states than for the chronic hepatitis B health state. No short-term effect of anti-viral therapy on progression to compensated cirrhosis, such as that estimated in recent economic evaluations of lamivudine (Orlewska [86]; Crowley [84;87]), has been included. The models do not take any explicit account of lamivudine or adefovir dipivoxil resistance. However, it is assumed that by taking seroconversion rates from long-term follow up (which show reducing denominators over time) some of the effects of drug resistance, as indicated by reduced seroconversion rates, will have been captured.

The models differ from those used in previous economic evaluations of treatments for CHB by including liver transplantation. Wong and colleagues and Crowley and colleagues excluded liver transplantation from their models due to uncertainty over outcomes for this sub-group of patients, and the comparatively small numbers of CHB patients progressing to this treatment. Given that liver transplantation is now an established component of the treatment pathway, with anti-viral prophylaxis improving outcomes for patients undergoing transplantation, it is appropriate to include this group of patients in the evaluation. In contrast to the evaluation by Wong and colleagues, but in common with Crowley and colleagues, HBsAg seroconversion has been excluded from the model due to the comparatively small number of patients who achieve this. This exclusion is unlikely to have a significant impact on comparisons between pegylated interferon alfa and other anti-viral agents.

A number of assumptions are common to the two models. Patients who do not respond to treatment (or reactivate disease following an initial response) follow the pattern of disease progression as described by the natural history model. Patients who maintain their response are indistinguishable from healthy individuals and have the same life expectancy and quality of life as that observed in the general population. Patients in either of the response categories may reactivate disease and this was assumed to occur at a baseline, spontaneous, rate in the natural history model. Treated patients who achieve a response face a higher reactivation rate in the year following response, but then relapse to the baseline rate in subsequent years. Lamivudine and adefovir dipivoxil treated patients who respond are maintained on consolidation therapy for six months and then receive no further drug treatment as long as they remain in that state; this is consistent with current clinical guidelines.

The impact of adverse events was excluded from the model on the basis that recorded events were generally comparable for conventional and pegylated interferon alfa and relatively inexpensive to treat, with none of the main side effects requiring hospitalisation. While the exclusion of costs of treating side effects from the model may be reasonable, Table 23 in the submission shows considerably higher proportions of pegylated interferon alfa treated patients reporting side effects which are likely to impact on patients' quality of life (e.g. pyrexia, fatigue and headache) than those treated with lamivudine in the Phase III trial[35]. An adjustment to the quality of life scores for patients while on treatment, similar to those adopted in previous economic evaluations involving interferon alfa [16;84;87] could have been adopted in the sensitivity analysis.

The lifetime horizon adopted in the models was appropriate given that the evaluation is concerned with treatments for a chronic disease which seek to delay, and possibly

avoid, sequelae that result in significant impacts of patients' quality of life and also substantial excess mortality. The cycle length of one year is also appropriate given the comparatively slow rate of progression of disease.

5.3.1.2 Supporting data

The majority of the transition probabilities included in the natural history model are taken from the previous economic evaluations by Wong and colleagues [16] and Crowley and colleagues[84;87]. Both of these evaluations excluded liver transplantation, hence a third source[112] was used to derive transition probabilities for patients with decompensated cirrhosis undergoing liver transplantation and for condition-specific excess mortality for patients in the liver transplantation state. As the previous evaluations had excluded HBeAg negative patients a review of natural history studies was undertaken to assess the validity of applying these transition rates to this group of patients. Other than the obvious observation that these patients cannot achieve HBeAg seroconversion, the only differences that were applied in the two models were for transitions from chronic hepatitis B to compensated cirrhosis (0.06 and 0.09 for HBeAg positive and negative patients respectively) and from chronic hepatitis B to decompensated cirrhosis (0.004 and 0.006) to reflect the more rapid progression of disease observed in HBeAg negative patients.

The submission reports eight comparisons for HBeAg positive patients: these are discussed in turn below:

Pegylated interferon alfa and conventional interferon alfa

Three comparisons of pegylated interferon alfa and conventional interferon alfa are reported:

- The first uses seroconversion rates for pegylated interferon alfa and conventional interferon alfa reported by Cooksley and colleagues[39] (as we discussed earlier in Section 4.1) based on 24 weeks of treatment with each agent.
- The second uses the seroconversion rate and treatment duration reported by Lau and colleagues[35] (see Section 4.1) for pegylated interferon alfa against those for conventional interferon alfa reported by Cooksley and colleagues[39]. The seroconversion rates for pegylated interferon alfa are almost identical (hence life expectancy/QALYs are almost identical as are the costs of treating disease progression). The only difference is that, due to an extra 24 weeks of treatment, pegylated interferon alfa costs double. The purpose of this comparison appears to be to provide an evaluation of pegylated interferon alfa at its licensed dosage and treatment duration.
- An additional comparison uses a 9 mega unit dose of conventional interferon alfa for 24 weeks, but uses the seroconversion rate reported by Cooksley and colleagues[39], against the seroconversion and treatment duration for peginteferon reported by Lau and colleagues[35]. This simply increases the cost of conventional interferon alfa therapy and therefore reduces the ICER for pegylated interferon alfa. The purpose of this comparison appears to be to provide an evaluation of pegylated interferon at its licensed dosage and treatment duration against the normal dosage and duration of treatment on conventional interferon alfa in the treatment of HBeAg positive CHB.

The probability of relapse from HBeAg seroconversion for both pegylated and conventional interferon alfa was taken from a recent meta-analysis of patient-level data on the durability of seroconversion following treatment[97]. However, the meta-analysis did not contain any patients treated with pegylated interferon alfa. It was conservatively assumed that the same probability should apply to both forms of interferon alfa treatment.

Pegylated interferon alfa and lamivudine

Two comparisons are made between pegylated interferon alfa and lamivudine:

- the first was based on seroconversion rates observed 24 weeks after the end of 48 weeks of treatment as reported by Lau and colleagues[35];
- the second extends the treatment period for lamivudine to four years, by applying HBeAg seroconversion rates reported in the literature[113].

The seroconversion rates used for years 2 – 4 in the longer term analysis are comparatively low. Cumulative rates for HBeAg seroconversion on lamivudine therapy are typically quoted in the range of 27%-35% at two years, and above 40% at three years. The seroconversion rates used by Crowley and colleagues in their cost-effectiveness study were substantially higher – 28.7% at one year, 42% at two years, 65% at three years and 73% at four years. These rates apply to CHB patients with ALT levels at greater than or equal to twice the upper limit of normal and were estimated for a subset of patients from included in clinical trials of lamivudine[94-96].

A probability of reactivation of CHB of 0.35, based on the meta-analysis by van Nunen and colleagues[97], was applied to the seroconversion rate observed for 48 weeks of treatment. This is likely to represent an overestimate given that the seroconversion rate used in the analysis was that observed 24 weeks after treatment had ended. A lower reactivation rate of 25% was applied in the four year model. This was done on the basis that longer term lamivudine treatment provides a more durable response. But it appears that this value has been applied only to the cumulated stock of seroconverted patients at year 5, in contradiction to the stated assumption that the excess seroreversion rates are applied in the year following seroconversion. The analysis presented has been conducted as if assuming that all patients were treated for the full four years – including those who seroconverted. However, the model assumptions state that seroconverted patients were maintained on a consolidation treatment of lamivudine for six months, then ceased therapy (provided they remained in the seroconverted state).

Pegylated interferon alfa and adefovir dipivoxil

Two comparisons are made between pegylated interferon alfa and adefovir dipivoxil:

- the first was based on the seroconversion rate observed after 48 weeks of adefovir dipivoxil treatment in a placebo controlled clinical trial[32] compared to that in the RCT of pegylated interferon alfa reported by Lau and colleagues[35];
- the second comparison extended the treatment period for adefovir dipivoxil to four years, by applying reported HBeAg seroconversion rates for adefovir dipivoxil derived from the literature[43] (this is a conference abstract reporting long-term follow-up of patients in study 437).

Only three years of data are available for adefovir dipivoxil so that the seroconversion rate for the fourth year of treatment was assumed to be the same as that for lamivudine. No attempt was made to model the effect of adefovir dipivoxil resistance in this comparison. It was assumed that a proportion of the patient drop out in the long

term studies of adefovir dipivoxil reflected resistance. The durability of seroconversion with adefovir dipivoxil was assumed to be the same as for conventional and pegylated interferon alfa (92%).

Pegylated interferon alfa and best supportive care

The final comparison uses the seroconversion rate for pegylated interferon alfa reported by Lau[35] compared to best supportive care (termed "no treatment" in the submission). The documentation of the submission states that HBeAg seroconversion rates were "set to zero for the no treatment strategy". Given that a spontaneous seroconversion rate of 9% was assumed in each of the comparisons of anti-viral therapy it is unclear why no spontaneous rate was assumed for this comparison. Otherwise the natural history model of disease (as stated earlier, largely based on those outlined by Wong and colleagues and Crowley and colleagues) was used to estimate disease progression in this scenario.

5.3.1.3 Health-Related Quality of life

The utility values used in the submission are principally based on those reported by Wong and colleagues[16], which were averages of values elicited using time trade-off and standard gamble techniques from an expert panel of clinicians. Using the valuations reported by Wong and colleagues for chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma the reduction in utility for these health states, relative to the HBeAg seroconverted health state, was calculated by subtracting the health state's weight from that derived for the HBeAg seroconverted state (0.99) – hence the reduction in utility for chronic hepatitis B, without cirrhosis, was calculated as 0.04, based on a weight for CHB of 0.95.

Since liver transplantation was excluded from the scope of the Wong and colleagues study, as discussed earlier, values reported in another economic evaluation (Bennett and colleagues[112] decision analysis on interferon alfa treatment for chronic hepatitis C) for the year in which the transplant took place and for quality of life in years following transplantation were used. As for the other health states the difference in utility from HBeAg seroconversion was calculated by subtracting the reported value from 0.99.

Table 27 - Age-specific utilities for healthy population, state-specific decrements and estimated health state utilities

Age	Utility	HBeAg	CHB	CC	DC	HCC	LT	PostLT
		-0.00	-0.04	-0.07	-0.45	-0.50	-0.49	-0.29
0 - 44	0.91	0.91	0.87	0.84	0.46	0.41	0.42	0.62
45 - 54	0.85	0.85	0.81	0.78	0.40	0.35	0.36	0.56
55 - 64	0.80	0.80	0.76	0.73	0.35	0.30	0.31	0.51
65 - 74	0.78	0.78	0.74	0.71	0.33	0.28	0.29	0.49
75 +	0.73	0.73	0.69	0.66	0.28	0.23	0.24	0.44

Notes: HBeAg = HBeAg seroconverted; CHB = chronic hepatitis B; CC = compensated cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma; LT = liver transplant; PostLT = post-liver transplantation.

For the cost-effectiveness analysis, age-specific utility weights reported by Kind and colleagues[114] were used for the seroconverted and combined response (in HBeAg negative patients). Utilities for each of the other health states were calculated by subtracting the previously calculated state-specific decrements in life expectancy from the age-specific values – see Table 27.

5.3.2 Estimation of costs

The costs applied in the submission were made up of two components. As in the published evaluations discussed in the preceding section, the costs of anti-viral treatment were estimated separately from the health state costs used to estimate the lifetime costs of the medical management of chronic hepatitis B.

The drug costs for interferon alfa-based interventions were based on a treatment course of 4.5 mega unit/0.5ml three times per week (giving a weekly cost of £67.80), for 24 weeks of conventional interferon alfa and 180 microgram/0.5 ml per week (giving a weekly cost of £132.00) for either 24 or 48 weeks for pegylated interferon alfa 2a. Drug costs for lamivudine were based on either a 48 or 208 week regimen at 100 mg per day (weekly cost £19.52). On progression to seroconversion patients continued on lamivudine for a six-month consolidation treatment. Drug costs for adefovir dipivoxil were based on a dose of 10 mg per day (weekly cost £73.50) for either a fixed period 48 or 208 weeks. There is no indication in the submission whether adefovir dipivoxil-treated patients who seroconvert stop treatment immediately, continue to the end of the fixed treatment period or receive consolidation treatment.

The submission contains no estimate of any additional costs arising from the assessment and monitoring of patients (including laboratory tests and investigations) during treatment. The evaluations we reviewed in Section 5.2.2 costed a higher intensity of monitoring during the first six months of treatment and while drug costs were, in all cases, the majority of the costs of therapy medical costs accounted for an additional 20-50% of total costs. Previous evaluations, and clinical advice sought in developing our own evaluation suggests that conventional interferon alfa and pegylated interferon alfa treatment require a higher intensity of medical management than do lamivudine or adefovir dipivoxil and such costs should be included in any comparison.

Health state costs for the submission were developed using a combination of methods, including assumption, bottom-up costing using protocols based on expert opinion and extrapolation from costs developed for previous submissions. The assumption that the HBeAg seroconverted state or "response" state for HBeAg negative patients have zero costs does not correspond with current clinical guidelines that would suggest that patients in these categories should be reviewed every six to twelve months during which time their serological status/ HBV DNA should be assessed and a screen for hepatocellular carcinoma should be undertaken. A protocol-based costing similar to that developed for the chronic hepatitis B health state may have been a more appropriate option for these states.

Table 28 - Health state costs from Roche submission

State	Value	Source
HBeAg	£0.00	Assumption
Response[a]	£0.00	Assumption
CHB	£1,038	Bottom-up costing by assumption
CC	£3,228[b]	
DC	£7,855	
HCC	£7,980	NICE Hep C HTA report, 2003
Liver transplant	£46,551	NICE Hep C HTA report, 2003
Post-liver transplant	£1,677	Bottom-up costing by assumption

[a] "response" in Roche submission refers to patients who have both normalised ALT and have DNA levels below 10^5 copies
[b] includes £1007.64 annual cost of lamivudine

One anomalous component of the protocol-based costing for the compensated cirrhosis health state is the inclusion of lamivudine given that this is one of the comparator interventions.

5.4 Review of Gilead submission to NICE (adefovir dipivoxil)

The objective stated for the economic analysis in the submission is to assess the cost-effectiveness of first and second-line use of adefovir dipivoxil relative to current available treatments for patients with chronic hepatitis B. The analysis presented in the submission differs from the published evaluations we reviewed in Section 5.2.2 in that patients with HBeAg negative CHB are included. The comparators in the evaluation are clearly identified as lamivudine and best supportive care (termed no treatment in the submission). The interventions were evaluated as a series of sequential treatment strategies:

- no specific anti-viral treatment (best supportive care)
- lamivudine first-line with no second-line treatment
- lamivudine first-line with adefovir dipivoxil as second-line treatment
- adefovir dipivoxil as first-line with lamivudine as second-line treatment.

Interferon alfa was not considered in this submission. It was assumed that the estimated 1.3% of patients who receive and respond to interferon alfa were excluded from the scope of this evaluation.

The perspective of the analysis is clearly stated as being that of the NHS, capturing direct costs and benefits only. Mention is made of the probable lost productivity for patients with advanced liver disease, such as decompensated cirrhosis or hepatocellular carcinoma.

The model time horizon was the patient's lifetime, which is appropriate given that the progression of chronic disease is being modelled. The model uses a one year cycle length, partly due to the fact that the clinical trials reviewed report data at annual intervals. This is appropriate given the comparatively slow progression of chronic liver disease. Monte Carlo methods to simulate individual patients were adopted for this evaluation, primarily to overcome the Markovian assumption and allow patients to carry treatment history through the model. A particular application was to record

whether patients had become HBeAg negative during the simulation or had developed drug resistance. The submission states that these complications mean that the disease cannot be modelled within a decision tree framework, at least not without the use of additional health states. While it is true that multiple additional states are required in decision tree-based Markov models where cohort members need to carry history, it is also the case that purpose designed software for such modelling may enable a more efficient solution than methods requiring the simulation of several thousand individual patients.

5.4.1 Estimation of benefits

5.4.1.1 Model structure/ structural assumptions

A single Markov state transition model was developed to model disease progression and treatment effects. This was structurally similar to models used in previous economic evaluations that have included long term models of disease progression [16;84;87], and was consistent with published studies of the natural history of chronic hepatitis B infection[3;92;100]. The model has twelve health states incorporating an immunotolerant state which precedes the active CHB state. The immunotolerant state has not been included in other evaluations, which have taken the starting state for the evaluation as chronic hepatitis B as this is the health state in which patients would present for anti-viral treatment. The other state included in this model that was not present in previous evaluations is labelled "viral suppression", although in the model this is defined by normalisation of ALT levels rather than by HBV DNA levels. This is the health state indicating response to treatment for patients with HBeAg negative disease.

As with previous economic evaluations of anti-viral treatment for chronic hepatitis B, response among HBeAg positive patients is defined by HBeAg seroconversion. ALT normalisation and transition to the "viral suppression" state also occurs with these patients, with a benefit in terms of a reduced risk of progression to cirrhosis. The main difference between the HBeAg seroconversion health state and "viral suppression" is that the majority of patients in the latter state will revert to active CHB if they do not continue anti-viral treatment.

One problem with using a single model for this analysis is that no account appears to have been taken of the different ages at which patients with HBeAg positive and negative disease are likely to present. Age at presentation with HBeAg positive disease is typically 24 to 36 years (median 31) whereas for HBeAg negative disease the range is 36 to 45 years (median 40)[92].

The decision to populate the initial states of the model based on the distribution of patients attending a liver clinic requires further discussion. An assumption appears to have been made that these prevalent cases already in contact with specialist services are representative of new cases expected to present for treatment. If it was desired to model the cost-effectiveness of treatment for a typical distribution of patients at initial presentation in normal practice the distribution derived from the audit of the liver clinic could have been contrasted with published indications of the distribution of patients at initial presentation[92].

5.4.1.2 Supporting data

A systematic review was conducted to identify relevant clinical-effectiveness studies for adefovir dipivoxil and lamivudine. The principal benefits of treatment result from changes in patients' viral, biochemical or serological status, in that transition rates to progressive disease are lower for the seroconversion/ "viral suppression" states than for the chronic hepatitis B health state. No short term effect of anti-viral therapy on progression to compensated cirrhosis, such as that estimated in the published economic evaluations of lamivudine [84;87;115], has been included.

The estimates of treatment effects after one year of treatment with lamivudine were taken from two placebo-controlled clinical trials[95;96], which showed a relative risk of HBeAg seroconversion of 3 to 3.7 and of 2.7 to 4.1 for ALT normalisation among patients with HBeAg positive disease. An additional RCT included in the review showed a relative risk for ALT normalisation among patients with HBeAg negative CHB of 11.3. The estimates of treatment effects after one year of treatment with adefovir dipivoxil for patients with HBeAg positive disease were taken from a placebo controlled clinical trial[32] (study 437, as discussed in Section 4.1) which showed a relative risk of HBeAg seroconversion of 2 and relative risk for ALT normalisation of 3. A slightly lower relative risk for ALT normalisation of 2.5 was calculated for patients with HBeAg negative disease using data from a placebo controlled clinical trial in this group of patients[31] (study 438, as discussed in Section 4.1).

Health states in which patients are deemed suitable for treatment are:

- "viral suppression"
- active CHB
- compensated cirrhosis
- decompensated cirrhosis
- hepatocellular carcinoma
- liver transplant

If the patient has developed drug resistance they are deemed ineligible for treatment, even if they are in one of the treated health states. In the model the baseline transition probabilities are multiplied by the relative risks of HBeAg seroconversion or ALT normalisation to estimate the effects of treatment with either drug. This is used in each year that the patient is eligible to receive treatment, assuming a constant treatment effect over time and equal effectiveness for each drug. The validity of these, implicit, assumptions is not discussed in the submission. The published economic evaluations modelling the cost-effectiveness of long term lamivudine treatment used values for HBeAg seroconversion derived from long term follow up of clinical trial subjects. These varied substantially year on year and assumed no benefit for treatment after four years (the limit of follow up of the clinical trial patients). A discussion of the effects of these extrapolations on the cost-effectiveness estimates could have been included in the submission.

5.4.1.2.1 Methodology note

Transition probabilities in the model are estimated independently, based on the mean baseline values (with minimum and maximum values specified) and multiplied by an estimated relative risk (with mean, minimum and maximum values specified). Where no treatment effect is assumed the relative risk is unity. As the sum of these simulated transition probabilities rarely equals one a re-scaling is performed (by dividing each simulated value by the sum of the simulated values, to ensure they sum to unity) before applying them in the model. While this ensures logical consistency in the sum of the transition probabilities in the model it may mean that the properties of the simulated distributions for the transitions probabilities bear little relation to those that were assumed a priori. This procedure also takes no account of likely correlation between effects. For example, baseline HBeAg seroconversion and ALT normalisation probabilities are sampled separately, as are the relative risks for treatment effects for each of these, though it may be expected that these are correlated both in terms of spontaneous and treatment-related effects.

The model uses normal distributions for all variables being simulated; the generation of illogical values (such as probabilities outside the range 0 – 1) is precluded by specifying limits to the sampled values. However, the use of normal distributions for probabilities and utilities is not in line with normal practice for sampling these types of data, where beta or possibly logistic distributions might be more appropriate. The use of normal distributions for cost variables is also not in line with current practice, where gamma distributions are recommended to allow for asymmetry and long right hand tails. One likely effect of using truncated normal distributions (i.e. normal distributions, but with limits set at specified values) for sampling probabilities and utilities is that the tails are likely to be over-represented and the sampled values are likely to have greater dispersion than would be the case with distributions more commonly used for these types of data.

5.4.1.3 Health-related quality of life

The utility values used in the submission are derived from a range of sources, including published economic evaluations which used health state valuations based on ratings by expert panels of clinicians and from quality of life studies using valuations derived directly from patients with chronic viral hepatitis. The majority of the valuations adopted for the less progressive stages of liver disease (HBeAg seroconversion, ALT normalisation and CHB) were based on those reported by Wong and colleagues[16] for chronic hepatitis B, derived from ratings by a clinical expert panel. For compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma the health state utilities used are those derived for the Mild Hepatitis C trial[105] which used the EQ-5D health state questionnaire and values from a published tariff[106]. Finally the health state values used for the liver transplant state are taken from a study reporting on quality of life three months after liver transplantation, which used the EQ-5D health state questionnaire.[116]

5.4.2 Estimation of costs

The costs used in the model consist of two components; costs have been estimated for each of the health states included in the model, with drug costs added if the health is

one in which anti-viral therapy is indicated. The health state costs were derived by a combination of costing by assumption (based on disease management protocols indicating frequency of contact with health services and associated tests and investigations) and adoption of published costs derived through literature review.

For the bottom-up costing exercise the frequency of out-patient attendance was determined by discussion with UK consultant hepatologists and hepatology nurses along with the frequency of serology, liver function tests and DNA assays associated with these attendances. Additionally, the annual frequency of liver biopsy, tests of renal function and screening for hepatocellular cancer (by abdominal ultrasound and α-fetoprotein) were determined. These formed the bases of the health state costs for the immunotolerant, HBsAg and HBeAg seroconverted, "viral suppression" and chronic hepatitis B health states. The costs for health states associated with more advanced liver disease (compensated cirrhosis, decompensated cirrhosis and HCC) were based on those reported for the economic appraisal of treatment for mild hepatitis C [105] – these costings were conducted at three UK centres. The costs of liver transplantation and post-transplant follow-up were based on data collected in a national Department of Health-funded study into liver transplantation[117].

The drug costs for adefovir dipivoxil were based on a dose of 10 mg per day (£315.00 per 30-tablet pack or £3835.13 per patient-year) and for lamivudine were based on a dose of 100 mg per day (£83.97 per 28-tablet pack or £1095.36 per patient-year). No time-limited course was assumed for the interventions. It was assumed that on progression to seroconversion patients would cease treatment. For patients who developed drug resistance the base case assumed that they stopped treatment immediately, while this assumption was varied in sensitivity analysis with up to 50% of resistant patients continuing therapy.

The submission contains no estimate of any additional costs arising from the assessment and monitoring of patients during treatment the early stages of treatment. As discussed in Section 5.2.2.1 previous evaluations costed a higher intensity of monitoring during the first six months of treatment. While drug costs were, in all cases, the majority of the costs of therapy, medical costs accounted for an additional 20-50% of total costs. Since both the drugs included in this analysis are well tolerated and do not require substantially greater patient monitoring in the early stages of treatment this omission is unlikely to produce a bias.

5.5 Comparison of cost-effectiveness results presented in industry submissions

Table 29 presents the cost-effectiveness results reported in the Roche submission to NICE for pegylated interferon alfa-2a. A number of scenarios are modelled, the majority for HBeAg positive patients, including an indirect comparison between pegylated interferon alfa and adefovir dipivoxil.

Table 29 – Cost effectiveness of pegylated interferon alfa (Roche submission)

HBeAg positive patients		
Comparison	**Outcome**	**Incremental cost/QALY**
1. PEG 24 vs IFN 24	HBeAg seroconversion	£2,663
2. PEG 48 vs IFN 24	HBeAg seroconversion	£13, 921
3. PEG 48 vs LAM 48	HBeAg seroconversion	£5, 281
4. PEG 48 vs LAM 208	HBeAg seroconversion	£5, 948
5. PEG 48 vs ADV 48	HBeAg seroconversion	£1, 439
6. PEG 48 vs ADV 208	HBeAg seroconversion	Cost saving / dominant
7. PEG 48 vs no treatment	HBeAg seroconversion	£2, 790
HBeAg negative patients		
8. PEG 48 vs LAM 48	Combined ALT and HBV DNA response	£3, 209
9. PEG 48 vs LAM 208	Combined ALT and HBV DNA response	£1, 886
10. PEG 48 vs no treatment	Combined ALT and HBV DNA response	£1, 467

Table 30 presents the cost-effectiveness results reported in the Gilead submission to NICE for adefovir dipivoxil, based on a number of scenarios comparing drug switching regimes following development of treatment resistance.

Table 30 - Cost-effectiveness of adefovir dipivoxil (Gilead submission)

Comparison	**Cost/QALY**
1. lamivudine first line, no treatment second line (LAM-NT) vs no treatment (NT)	£3, 109
2. lamivudine first line, adefovir dipivoxil second line (LAM-AD) vs no treatment (NT)	£6, 651
3. adefovir dipivoxil first line, lamivudine second line (AD-LAM) vs no treatment (NT)	£8, 185
4. lamivudine first line, adefovir dipivoxil second line (LAM-AD) vs lamivudine first line, no treatment second line (LAM-NT)	£9, 201
5. adefovir dipivoxil first line, lamivudine second line (AD-LAM) vs lamivudine first line, no treatment second line (LAM-NT)	£11, 435
6. adefovir dipivoxil first line, lamivudine second line (AD-LAM) vs lamivudine first line, adefovir dipivoxil second line (LAM-AD)	£29, 359

The cost per QALY estimates are generally highest when adefovir dipivoxil is used as first line therapy.

The two submissions differ in terms of the drug comparisons made, and hence their conceptualisations of clinical practice. Roche have compared pegylated interferon alfa-2a as first line treatment against interferon alfa, lamivudine, and adefovir dipivoxil. In contrast, Gilead have omitted interferon (pegylated or otherwise) from their model. They assumed a proportion of patients would receive interferon alfa as first line treatment, and that only those failing to respond would then receive lamivudine or adefovir dipivoxil. Expert clinical opinion suggests that not all of these drugs would be used as first line treatment in all patients. Although there may be variation in practice it would appear that interferon alfa (and likely pegylated interferon alfa) would be used in a specific group of relatively healthy patients as a first 'hit' to induce HBeAg seroconversion and transition to the low or non-replicative state. Lamivudine and adefovir dipivoxil would then be used in patients who had not responded or who had relapsed.

6 SHTAC COST-EFFECTIVENESS ANALYSIS

6.1 SHTAC Cost-effectiveness model

6.1.1 Statement of the decision problem and perspective for the cost-effectiveness analysis

We developed a model to estimate the cost-effectiveness of pegylated interferon alfa 2a and of adefovir dipivoxil compared to conventional interferon alfa, lamivudine and best supportive care in a UK cohort of adults with chronic hepatitis B. The perspective of the cost-effectiveness analysis is that of the NHS and personal social services.

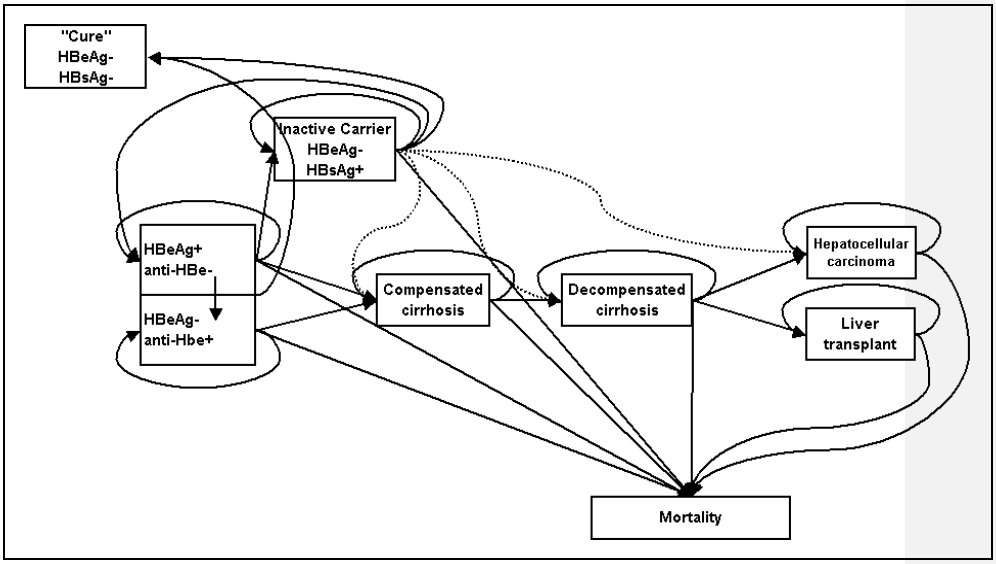
6.1.2 Strategies/ comparators

The scope for the appraisal, as issued by NICE, states that the interventions to be considered are adefovir dipivoxil and pegylated interferon alfa-2a. The comparators for these interventions are current standard practice, (non-pegylated) interferon alfa-2a/2b, lamivudine, and non-drug treatment strategies, all of which are indicated for patients with chronic hepatitis B and compensated liver disease. Interferon alfa-based treatments are not indicated for patients with decompensated disease and the comparison for these patients will be restricted to adefovir dipivoxil as the intervention, and lamivudine and best supportive care as comparators.

6.1.3 Model type and rationale for the model structure

Clinical trial data relating to the effectiveness of interventions included in this appraisal are limited to measurements of short term serological, virological and histological changes. In order to estimate the impact of these intermediate effects on final outcomes for patients a natural history model for chronic hepatitis B was required. A Markov state transition model was constructed, informed by a systematic search of the literature to identify source material on the natural history, epidemiology and treatment of chronic hepatitis B (see Appendix 4 for details of the search strategy). In particular this review sought to identify key determinants of morbidity and mortality associated with the disease. The state transition diagram describing the eight health states within the model and the allowable transitions between these states is shown in Figure 3. This description of the model was informed by discussions with clinicians involved in the care and treatment of patients with CHB to ensure its comprehensiveness and clinical validity.

Figure 3 - State transition diagram for natural history model in chronic hepatitis B



The state transition model indicates that within the natural history of the disease patients with chronic hepatitis B may:

- remain in that state
- move on to more progressive stages of liver disease (such as cirrhosis or hepatocellular carcinoma)
- clear the disease spontaneously, either through HBeAg seroconversion to what has traditionally been termed the "inactive carrier" state or through HBsAg seroconversion, where the patient is effectively cured.

HBsAg seroconversion is assumed to be a permanent condition with no possibility of reactivating chronic hepatitis B and very low risk of developing progressive liver disease. In contrast, HBeAg seroconversion is not assumed to be permanent and patients may reactivate to the chronic hepatitis B state. For patients with HBeAg negative disease it has been assumed that patients may spontaneously move into remission (with normalisation of ALT and low serum DNA) but it is uncommon for spontaneous remission to be sustained[92;118].

The diagram indicates that individuals may progress to hepatocellular carcinoma from any of the health states, but this occurs at different rates. The lowest risk is for HBsAg seroconverted patients and the greatest risk is for those with cirrhosis. By contrast, it is assumed that individuals can only progress to decompensated liver disease if they have first developed compensated liver disease.

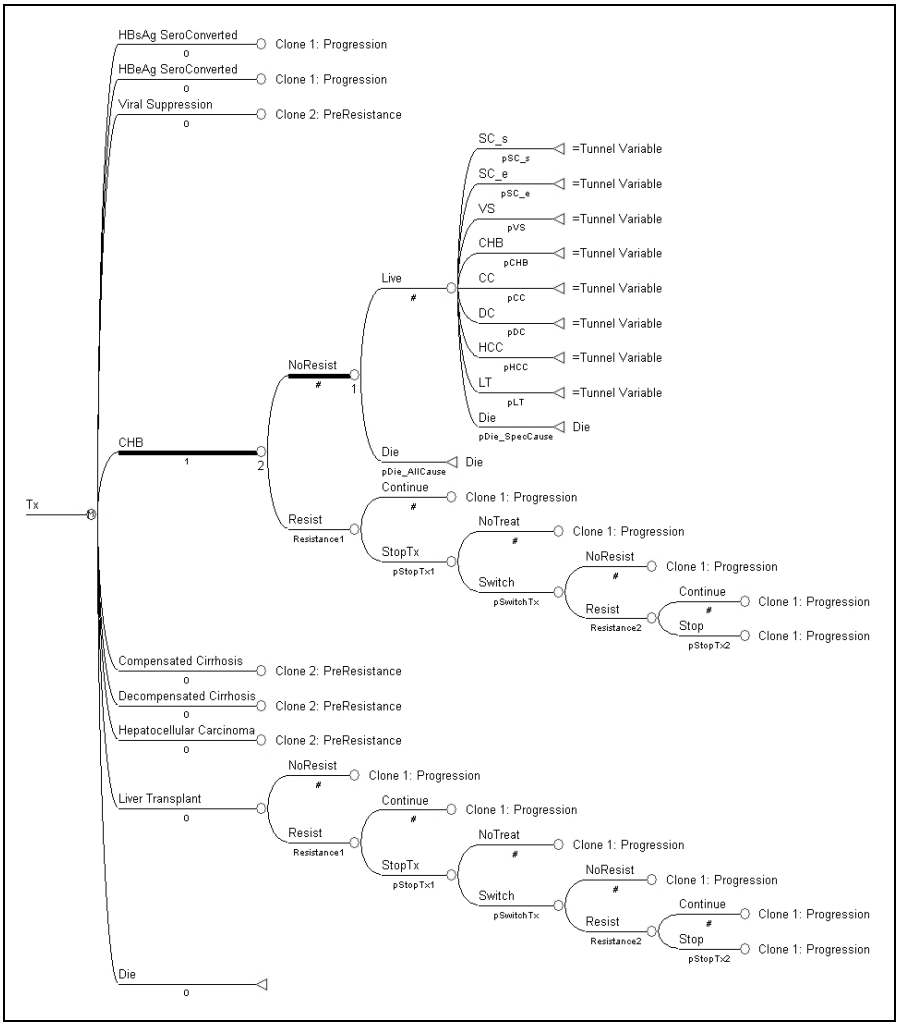
All individuals within the model are assumed to be exposed to a background mortality risk from all causes. The diagram indicates which states are assumed to have an excess mortality risk with transitions indicated into the box marked "mortality". This includes an excess mortality risk for individuals with chronic hepatitis B without cirrhosis; previous evaluations have not included an estimate of excess mortality risk

for chronic hepatitis B. However, natural history studies have estimated that this risk may be as high as 2%[3].

A Markov state transition model has been used to conduct the cost-effectiveness analysis. A decision tree representation of the model is shown in Figure 4. To simplify the presentation, only one full branch of the tree (for patients with CHB who do not develop drug resistance) is shown. The tree was developed with a fixed structure that would be capable of modelling costs and outcomes for the range of relevant intervention strategies as described above. For the best supportive care comparator no anti-viral drug treatment is modelled, so that only natural history transition probabilities and health state costs are applied in the cycle tree. For the evaluation of each of the anti-viral drug therapies, the natural history transition probabilities are modified to take account of treatment effects described in Section 6.1.5.1 (Effectiveness data) and intervention costs as described in Section 6.1.5.5 (Intervention costs) are included. As stated earlier, the principal effect of anti-viral treatment is to change patients' serological, biochemical, histological or virological status to place them in health states where they are less likely to develop progressive liver disease.

The model has a lifetime horizon and a cycle length of one year, with a half-cycle correction applied. The sub-tree labelled 1 (named "progression") shows the possible states that an individual can progress to in the next cycle of the model. Initially, general mortality associated with the ageing of the cohort is estimated by applying age-specific all-cause mortality rates. The survivors at each cycle are then exposed to the state-specific risks of seroconversion, remission (i.e. ALT normalisation) and disease progression (including the state-specific excess mortality risk). Not all of the destination states shown in this sub-tree are accessible from each starting state. For example, individuals with CHB are assumed not to progress directly to decompensated disease while an individual with HBeAg negative CHB will not be able to undergo HBeAg seroconversion. In these cases the transition probability for any non-allowable transition is set to zero within the tree. This structure has been developed to allow copies of the sub-tree to be attached to other locations in the tree as shown in Figure 4. These copies of sub-trees are labelled as clones in the figure with the number and name indicating which cloned sub-tree has been attached at which node. The advantage of using cloned sub-trees is that only one "master" copy needs to be maintained rather than requiring maintenance of numerous identical sub-trees.

Figure 4 - Markov tree used to model patient outcome and treatment costs



Moving to the left of the "progression" sub-tree, a second sub-tree labelled 2 (named "PreResistance") shows different management options for individuals who develop resistance. Patients who do not develop resistance during the cycle follow the branch marked "NoResist" and have outcomes evaluated as described in the previous paragraph by following the progression sub-tree.

The treatment options open to patients who have become resistant are that they may continue on treatment, though no therapeutic benefits are assumed from continued treatment, or they may cease treatment on the drug to which they have developed resistance. The latter group of patients may stop all anti-viral treatment (receiving best supportive care from then onwards) or, if other anti-viral agents are available, they may switch to another drug for active treatment.

If patients switch drugs there is a possibility that they may develop resistance to the second treatment. In the model, developing resistance to a second treatment is independent of the fact that the patient has already developed resistance to their first treatment. This accords with clinical evidence on lamivudine and adefovir dipivoxil, the two anti-viral agents in which resistance has been shown to develop. There is no evidence of resistance developing in patients treated with interferon alfa[3].

If patients develop resistance to the second drug it is assumed that they either continue on treatment, though there are no therapeutic benefits assumed from continued treatment, or stop all anti-viral treatment (receiving best supportive care from then onwards). The "pre-resistance" sub-tree is cloned to each of the health states in which patients are eligible to receive active anti-viral treatment (compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and liver transplantation) as shown in Figure 4.

Given that patients with HBeAg positive and HBeAg negative disease were expected to have different distributions of age at diagnosis and to differ in some of the transition probabilities between health states these groups of patients needed to be kept separate in the analysis. However, the structural assumptions underlying the state transition model described in Figure 3 apply to both groups of patients, which suggests that the structural assumptions of the model are equally applicable. Hence a common modelling structure was adopted for both groups of patients, but required a mechanism to keep the two groups separate within the model and apply appropriate ages for the start of treatment and to maintain separate transition probabilities.

Each of the eight states in the model, other than death, consists of, up to 12 tunnel (or temporary) states in order to track history within the simulated patient cohort. This is to determine whether individuals have HBeAg positive or HBeAg negative disease (given the difference in cohort age, hence age-specific mortality rates, and also that transition probabilities are not all the same for both forms of disease) or have developed drug resistance.

Tunnel states are commonly used in Markov models to take account of mortality and quality of life differences between similar health states that logically occur in sequence. For example, chronic viral hepatitis disease progression models will usually include a liver transplantation health state which needs to distinguish between mortality and quality of life for patients in the year in which transplantation takes place and for subsequent years post-transplant. One solution to this problem is to create two separate states: one for the year in which the liver transplant occurs (which patients only occupy for one year), and a second into which patients transit and remain following the year of transplantation. However, this can lead to a substantial increase in the number of states defined making the problem less tractable. Specialist decision tree software provides the ability to define tunnel states, which can be used as a means to avoid the Markov assumption of no memory. The approach taken in this analysis is slightly different in that the tunnels do not define different risks that are applied to the same group of patients at different points in time (as is the case with the liver transplantation example above), but uses the tunnel states to track different groups of patients as described below, and summarised in Table 31.

Separate tunnels were defined for HBeAg positive and HBeAg negative patients which were then further subdivided to allow maintenance of history regarding the development of drug resistance. Since this appraisal includes two drugs which are suitable for long term therapy (i.e. lamivudine and adefovir dipivoxil) and in which drug resistance has been observed, tunnel states were defined for HBeAg positive and HBeAg negative patients to show whether they were resistant to either drug and whether they were continuing or had stopped therapy.

Table 31 - Defining characteristics of tunnels within health states in Markov cycle tree

Tunnel within health state	Tunnel characteristics (based on patient characteristics of type of chronic hepatitis B and drug resistance status)
1	HBeAg positive, non-resistant
2	HBeAg positive, resistant to first (non-interferon alfa) drug, but continue treatment
3	HBeAg positive, resistant to first (non-interferon alfa) drug and stop anti-viral treatment
4	HBeAg positive, resistant to first drug and switch to second (non-interferon alfa) drug
5	HBeAg positive, resistant to first drug and second drug, but continue treatment
6	HBeAg positive, resistant to first drug and second drug and stop treatment
7	HBeAg negative, non-resistant
8	HBeAg negative, resistant to first (non-interferon alfa) drug, but continue treatment
9	HBeAg negative, resistant to first (non-interferon alfa) drug and stop anti-viral treatment
10	HBeAg negative, resistant to first drug and switch to second (non-interferon alfa) drug
11	HBeAg negative, resistant to first drug and second drug, but continue treatment
12	HBeAg negative, resistant to first drug and second drug and stop treatment

6.1.4 Baseline cohort of adult chronic hepatitis B patients

Baseline characteristics of chronic hepatitis B patients at the time of diagnosis are taken from natural history studies:

- patients with HBeAg positive disease have an age range at diagnosis of 24 to 36 years (median 31) and a male-to-female ratio of 1.5 to 4.9;
- patients with HBeAg negative disease have an age range at diagnosis of 36 to 45 years (median 40) and male-to-female ratio of 3.9 to 17.

For the purposes of this assessment the median ages will be used and it will be assumed that 70% of HBeAg positive and 90% of HBeAg negative patients are male. For the baseline analysis it was assumed that all patients have chronic hepatitis B, but have not progressed to cirrhosis.

6.1.5 Data Sources

6.1.5.1 Effectiveness data

We have reported on the findings from our systematic review on the clinical-effectiveness of pegylated interferon alfa-2a and adefovir dipivoxil (Section 4) and also the findings of a review of natural history models and clinical effectiveness data used in economic evaluations of interventions included as comparators in this appraisal (Section 5.2).

Table 32 and Table 33 report the transition probabilities adopted in the natural history model for this economic evaluation. They represent the complete set of transition probabilities for the best supportive care comparator, and also indicate which

transitions probabilities are modified due to the treatment effects discussed below in each of the treatment models.

Table 32 - Transition probabilities for natural history model for patients with HBeAg positive chronic hepatitis

# indicates a residual probability (i.e. one minus the sum of all the other probabilities at the node. Typically the residual probabilities are those for remaining in the current health state.

Health state		Transition probability		Treatment effect
From	To	Value	Source	
HBsAg	HBsAg	#		
	HCC	0.00005	Wong et al[16]	
HBeAg	HBsAg	0.02	EASL[3]	
	HBeAg	#		
	CHB	0.03[a]	Wong et al[16]	
	CC	0.01	Fattovich et al[100], Liaw et al[119], Crowley et al[84;87]	
	HCC	0.001	Wong et al[16]	
CHB	HBsAg	0.0175	Wong et al[120] and Wong et al[16]	
	HBeAg	0.09	Wong et al[16], Crowley et al[84], Fattovich[92]	Yes
	CHB	#		
	CC	0.05	Fattovich et al[100], EASL[3], Liaw et al[119]	Yes[b]
	HCC	0.005	Wong et al[16], DiBisceglie et al[121]	
	Die	0.0035	Gilead submission	
CC	HBeAg	0.09	Wong et al[16], Crowley et al[84]	Yes
	CC	#		
	DC	0.05	Crowley et al[84], Fattovich et al[100]	Yes
	HCC	0.025	Wong et al[16], Crowley et al[84]	
	Die	0.051	Crowley et al[84;87], Lau et al[122]	
DC	DC	#		
	LT	0.03	Bennett et al[112], Shepherd et al[123]	
	HCC	0.025	Assume same as CC	
	Die	0.39	Wong et al[16], Crowley et al[84]	Yes
HCC	HCC	#		
	LT	0		
	Die	0.56	Wong et al[16], Lavanchy[124],	
LT	LT	#		
	Die	0.21	Bennett et al[112]	Yes
LT	LT	#		
	Die	0.057	Bennett et al[112]	Yes

Full health state names: : HBeAg = HBeAg seroconverted; CHB = chronic hepatitis B;
CC = compensated cirrhosis; DC = decompensated cirrhosis; HCC = hepatocellular carcinoma;
LT = liver transplant; PostLT = post-liver transplantation

Notes: [a] a higher rate for reversion to CHB applies in the year immediately following seroconversion in the treatment models. The exact value of this higher reversion rate depends on the treatment being evaluated.

[b] this effect has only been demonstrated for lamivudine and applies only in the first year of treatment[84;86;98]

Table 33 - Transition probabilities for natural history model for patients with HBeAg negative chronic hepatitis

Health State		Transition probability		Treatment Effect
From	To	Value	Source	
HBsAg	HBsAg	#		
	HCC	0.00005	Wong et al[16]	
Respond	HBsAg	0.0175	Wong et al[120] and Wong et al[16]	
	CHB	0.029		
	CC	0.01	Assume same as HBeAg SC - > CC	
	HCC	0.005	Assume same as CHB - > HCC	
	Die	0.0035	Assume same as CHB - > Die	
CHB	HBsAg	0.005	Fattovich[92]	
	Respond	0.14	Lai[50]	Yes
	CHB	#		
	CC	0.09	EASL[3]	
	HCC	0.005	Wong et al[125], DiBisceglie et al[121]	
	Die	0.0035	Gilead submission[24]	
CC	CC	#		
	DC	0.05	Crowley 2000, Lavanchy[124], Fattovich et al[126]	Yes
	HCC	0.025	Wong et al[16], DiBisceglie et al[121], Crowley et al[84]	
	Die	0.051	Crowley et al[84;87], Lau et al[122]	
DC	DC	#		
	LT	0.03	Bennett et al[112], Shepherd et al[123]	
	HCC	0.025	Assume same as CC	
	Die	0.39	Wong et al[16], Crowley et al[84]	Yes
HCC	HCC	#		
	LT	0.0		
	Die	0.56	Wong et al[16], Lavanchy[124]	
LT	LT	#		
	Die	0.21	Bennett et al[112]	Yes
LT	LT	#		
	Die	0.057	Bennett et al[112]	Yes

Table 34- Effectiveness of treatment (HBeAg positive patients)

Transition	**Conventional interferon**	**Pegylated interferon**	**Lamivudine**	**Adefovir dipivoxil**
CHB to HBeAg seroconverted	25%	32%	18%	18%
CHB to compensated cirrhosis	This effect occurs applies first year of treatment		2%	
HBeAg seroconverted to CHB	9%	9%	25%	9%
	Effect only applies in the year following on-treatment seroconversion			
Compensated cirrhosis to decompensated cirrhosis			1.8%	1.8%
Decompensated cirrhosis to death			19.5%	19.5%
Liver transplant to death			2.1%	2.1%
Post-liver transplant to death			0.6%	0.6%

Table 34 summarises the treatment effects that replace the natural history transition probabilities for HBeAg positive patients indicated in Table 32, within the treatment models. HBeAg seroconversion rates for up to one year of treatment with pegylated interferon alfa-2a (32%) were taken from the Phase III RCT[35] and from a randomised Phase II study for conventional interferon alfa[39] (see Section 4). HBeAg seroconversion rates for lamivudine and adefovir dipivoxil were based on seroconversion rates from the Phase III RCTs[32;35] and from reports of seroconverted patients in studies with up to four years of follow up[113;127;128] and three years of follow up on clinical trial patients for adefovir dipivoxil[43]. It was assumed that the same seroconversion rate applied for patients with and without compensated cirrhosis within the natural history model.

The durability of HBeAg seroconversion was estimated using Kaplan-Meier estimates of the cumulative relapse rates for treated patients.[97] The estimated relapse rate for lamivudine treated patients was 25% and for interferon alfa monotherapy was 9%. These relapse rates were only applied to patients who underwent seroconversion while on treatment and are only applied in the year immediately following seroconversion, after which the relapse risk reverts to the spontaneous reactivation rate. For adefovir dipivoxil the proportion not maintaining HBeAg seroconversion (9%) was taken from the conference abstract reviewed in Section 4.1.2.4[44]. In the absence of information in the durability of HBeAg seroconversion following treatment with pegylated interferon alfa-2a, the value for reactivation for conventional interferon alfa (9%) was used. For non-seroconverted patients receiving lamivudine the transition rate from chronic hepatitis B to compensated cirrhosis was reduced to 2% from the baseline level of 5% for the first year of treatment only, based on the pooled analysis of three clinical trials of lamivudine[98].

Table 35- Effectiveness of treatment (HBeAg negative patients)

Transition	Conventional interferon	Pegylated interferon	Lamivudine	Adefovir dipivoxil
CHB to response	50%	59%	73%	72%
CHB to compensated cirrhosis	This effect occurs applies first year of treatment		2%	
Relapse to CHB from treatment response	60%	25%	80%	80%
	Effect only applies in the year after treatment ceases			
Compensated cirrhosis to decompensated cirrhosis			1.8%	1.8%
Decompensated cirrhosis to death			19.5%	19.5%
Liver transplant to death			2.1%	2.1%
Post-liver transplant to death			0.6%	0.6%

For HBeAg negative patients the proportion of patients normalising ALT were taken from Phase III RCTs[31;38] for pegylated interferon alfa-2a (59% at end of follow up), lamivudine (73% at end of treatment) and adefovir dipivoxil (72% at end of treatment). Review articles have reported biochemical response rates for conventional interferon of 50%[118;124;129]and relapse following end of treatment of 60-70%. For lamivudine and adefovir it is assumed that treatment continues until resistance develops, at which point reactivation occurs for the majority of patients. Based on long-term follow up of lamivudine-treated patients an 80% reactivation rate is applied

in the year in which resistance develops and effective treatment ceases[130-132]. In the absence of long-term follow up data on adefovir dipivoxil in this group of patients, the same assumptions as for lamivudine were applied. For pegylated interferon alfa-2a reactivation of CHB in the year following treatment is assumed to occur in 25% of patients who showed an initial response to treatment. This is the value used in the Roche submission and is substantially higher than that for conventional interferon alfa. The impact of this estimate on the cost-effectiveness of pegylated interferon will be tested in sensitivity analysis. Response in patients with compensated cirrhosis is assumed to be the same as for patients with CHB without cirrhosis.

6.1.5.2 Health state values/ utilities

A systematic search of the literature was undertaken (see Section 5.2.3) which identified one study reporting health state utilities for asymptomatic and symptomatic chronic hepatitis B. Due to methodological weaknesses in this study[104] it was decided not to use the values reported. We believe this remains an area of uncertainty.

Given the limitations in the empirical literature it was assumed, in our model, that patients who HBsAg or HBeAg seroconvert have the same level of health-related quality of life as healthy individuals. Consequently, published age-specific quality of life weights for healthy populations were applied to patients in these health states. Utility values for other health states are estimated relative to these values. Using values adopted in the economic evaluation by Wong and colleagues[16] the quality of life weight for the chronic hepatitis B health state is 0.04 less than the equivalent age-specific value for a healthy individual. Using values derived from a population of patients with chronic hepatitis C and liver transplant patients, whose health state utilities were determined using the EQ-5D[105;133], the following decrements to the age-specific health state utilities for healthy individuals were developed:

- -0.44 for compensated cirrhosis;
- -0.54 for decompensated cirrhosis and hepatocellular carcinoma;
- -0.55 for patients undergoing liver transplant
- -0.32 for post-transplant patients.

The validity of applying health state valuations developed for chronic hepatitis C patients to chronic hepatitis B patients was discussed with clinical advisors to the project. This approach was considered appropriate, since only the more progressive stages of disease were being valued in this way. In addition our literature review on chronic viral hepatitis and health-related quality of life had not found any studies suggesting that aetiology of liver disease had any impact on quality of life with progressive liver disease.

6.1.5.3 Discounting of future benefits

A discount rate of 1.5% has been applied to future benefits. This is the current convention in UK cost-effectiveness analysis, and is in line with present guidance from NICE. Other discount rates have been applied in sensitivity analyses (3.5%).

6.1.5.4 Cost data

Costs in the model were developed in two stages. First the additional resource use, in terms of laboratory tests, diagnostic tests and outpatient visits, required for monitoring patients while on treatment were identified based on clinical guidelines and discussion with hepatologists/ specialist nurses at Southampton General Hospital Trust. These are described below as intervention costs. The same approach to identifying the resource use for routine monitoring of untreated patients in the seroconverted and chronic hepatitis B health states was used to develop health state costs. Secondly, literature describing the costs of the progressive liver disease health states was reviewed and appropriate estimates applicable to the UK setting were extracted and used in the analysis.

6.1.5.5 Intervention costs

The frequency and intensity of monitoring of patients being treated with conventional interferon alfa, pegylated interferon alfa-2a, lamivudine and adefovir dipivoxil was identified based on clinical guidelines and discussion with hepatologists/ specialist nurses at Southampton General Hospital Trust. Additional costs for patient management, including the initial evaluation of a new patient with HBV, further investigations required to assess suitability for treatment, costs of clinical decision-making regarding choice of treatment and final tests prior to commencing treatment were also identified. These additional costs (described in full in Appendix 14) were applied in full to patients who were being evaluated prior to initiation of treatment, whilst for patients receiving best supportive care only the initial costs of evaluation of a new HBV patient were included. Protocols for frequency of patient monitoring during treatment and for untreated patients are included in Appendix 15.

Patients in the active CHB health state who receive no active treatment were closely monitored, being seen four times a year. Two of these (occurring at month 3 and month 9 in the annual management cycle) were described as “standard” examinations which are primarily concerned with monitoring of patients’ liver function and blood counts. These are conducted by specialist nurses and were assumed to last 30 minutes. The remaining two consultations (occurring at month 6 and month 12 in management cycle) were detailed examinations involving assessment of HBeAg and HBsAg serology and screening for hepatocellular carcinoma using abdominal ultrasound and α-fetoprotein test. They differ only in the proportion of patients having HBV DNA assessed at the 6-month consultation and in the likelihood of the assessment being performed by the consultant. All 12-month assessments for patients not receiving active anti-viral therapy were performed by the consultant while there was an equal probability of assessment by consultant or hepatology nurse specialist at the 6-month assessment. A lower intensity of monitoring was assumed for patients who seroconverted, who undergo a single, detailed, assessment annually.

Patients on conventional interferon alfa would be seen ten times during a twenty four week treatment period. This corresponds to weekly visits for the first month of treatment, then fortnightly for the second month and then monthly visits. Full blood counts, liver function tests, urea and electrolytes and blood clotting tests are assessed at each consultation. Every three months a more detailed assessment is undertaken during which HBeAg and HBsAg serology, HBV DNA and thyroid function is assessed. During the detailed assessments patients are also screened for hepatocellular

carcinoma using abdominal ultrasound and α-fetoprotein. Standard consultations are assumed to take 30 minutes whereas the detailed assessments require one hour of clinical time. All assessments for treated patients are assumed to be performed by specialist nurses.

In addition to the excess costs of health service contacts for patients undergoing treatment with conventional interferon alfa, the costs of drugs also need to be assessed. Drug costs were calculated for a dosage of 9 million unit pre-filled syringe, self-administered by patients three times per week (unit cost £45.19) for HBeAg positive patients and 4.5 million unit pre-filled syringe, self-administered by patients three times per week (unit cost £22.60) for HBeAg negative patients. Unit costs were taken from the British National Formulary, number 49 (March 2005). This corresponds to a weekly cost of £135.57 and a total drug cost of £3,253.68 for a 24 week course of treatment for HBeAg positive patients. For HBeAg negative patients the corresponding costs are £67.80 and £3,254.40 for a 48 week course.

Patients on pegylated interferon alfa would be seen sixteen times during a forty eight week course of treatment, corresponding to weekly visits for the first month of treatment, then fortnightly for the second month and then monthly for the remainder of treatment. As for conventional interferon alfa, full blood counts, liver function tests, urea and electrolytes and blood clotting tests are assessed at each consultation with more detailed assessments being undertaken every three months, during which HBeAg and HBsAg serology, HBV DNA and thyroid function is assessed as well as screening for hepatocellular carcinoma using abdominal ultrasound and α-fetoprotein. Standard consultations are assumed to take 30 minutes whereas the detailed assessments require one hour of clinical time. All assessments for treated patients are assumed to be performed by specialist nurses. Drug costs were calculated for a dosage of 180 microgram/0.5ml, self-administered by patients once per week. This corresponds to a weekly cost of £132.06 or a total drug cost for a 48 week course of treatment at £6,338.88.

Patients on lamivudine or adefovir dipivoxil are seen eleven times during a year of treatment, corresponding to monthly visits, but with no visit during month eleven. As for interferon alfa-treatment, full blood counts, liver function tests, urea and electrolytes and blood clotting tests are assessed at each consultation. At weeks 13 and 39 more detailed assessments are undertaken, during which HBeAg and HBsAg serology, HBV DNA are assessed with screening by α-fetoprotein test, and at weeks 26 and 52 a full assessment is conducted at which all these tests are undertaken with the addition of screening for hepatocellular carcinoma using abdominal ultrasound. All consultations are assumed to take 30 minutes of clinical time and are assumed to be performed by specialist nurses. Drug costs for lamivudine were calculated for a dosage of 100 mg, self-administered by patients daily giving a weekly cost (based on a unit price of £78.09 for a 28-tablet pack) of £20.99 or a total drug cost for a patient-year of treatment of £1,095.36. Drug costs for adefovir dipivoxil were calculated for a dosage of 10 mg, self-administered by patients daily giving a weekly cost (based on a unit price of £315.00 for a 30-tablet pack) of £73.50 or a total drug cost for a patient-year of treatment of £3835.13.

6.1.5.6 Health state costs

Health state costs adopted in the economic evaluation were a combination of values estimated specifically for this assessment, based on treatment protocols developed with expert advisors to the project and costed with the assistance of the finance department at Southampton University Hospitals Trust, and published cost estimates for the progressive stages of liver disease. The previous section describes the schedule and content of consultations for patients in the chronic hepatitis B and seroconverted health states for patients receiving each of the anti-viral interventions and for the best supportive care comparator. Health state costs for compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma have been taken from the observational study conducted during an HTA funded trial in mild hepatitis C [105] with costs for liver transplantation and post-liver transplantation taken from a Department of Health funded study of the costs of liver transplantation[117].

Table 36 - Health state costs adopted for the economic evaluation

Health State	Cost
HBsAg seroconverted	£0
HBeAg seroconverted	£267
ALT normalisation	£537
Chronic Hepatitis B	£537
Compensated cirrhosis	£1,138
Decompensated cirrhosis	£9,120
Hepatocellular carcinoma	£8,127
Liver transplant	£36,788
Post-liver transplant	£1,385

6.1.5.7 Discounting of future costs

A discount rate of 6% has been applied to future costs. This is the rate that is used by convention in economic evaluations in the UK, and is in line with current guidance from NICE. Other discount rates have been applied in sensitivity analyses (3.5%).

6.1.5.8 Presentation of results

We report findings on the cost-effectiveness of interventions based on analysis of a cohort of patients having age and sex characteristics as reported in the literature, and discussed earlier, including patients with both wild-type chronic hepatitis B and HBeAg negative CHB. For the interventions being assessed in this report comparisons are made to their closest comparator (for pegylated interferon alfa this is to conventional interferon alfa, for adefovir dipivoxil this is to lamivudine) and all interventions and comparators are evaluated against the best supportive care option.

In addition, the cost-effectiveness of a series of more clinically meaningful treatment scenarios are modelled. For example, a typical treatment strategy would be interferon alfa used as first-line treatment with lamivudine or adefovir dipivoxil reserved as second-line treatment for those patients who fail to respond to interferon alfa. We report the results of these comparisons in terms of the incremental gain in quality adjusted life years (QALYs) and the incremental costs determined in the cohort analysis. We identify the estimated costs of anti-viral therapy separate from the medical costs incurred by managing progressing liver disease.

6.1.5.9 Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

Parameter uncertainty is addressed using probabilistic sensitivity analysis. Probability distributions are assigned to the point estimates used in the base case analysis. The point estimates for state transitions in the natural history and treatment effects are reported in Table 32, Table 33 and Table 34 and for health state costs in Table 36. Distributions are also assigned to the health state utilities described in Section 6.1.5.2 and these are sampled during the probabilistic analysis. Appendix 17 reports the parameters included in the probabilistic sensitivity analysis, the form of distribution used for sampling each parameter along with the upper and lower limits assumed for each variable.

Deterministic sensitivity analysis is used to address particular areas of uncertainty in the model related to:

- model structure
- methodological assumptions
- transition probabilities around which there is considerable uncertainty or which may be expected, a priori, to have disproportionate impact on study results.

The purpose of this analysis is to identify clearly the impact of this uncertainty and to test the robustness of the cost-effectiveness results to variation in structural assumptions and parameter inputs. Particular attention will be paid to key structural differences between models previously used in studies of the cost-effectiveness of anti-viral therapy and the model adopted for this evaluation.

<u>SHTAC cost-effectiveness model – summary of methods</u>

- We devised a Markov state transition model to estimate the cost-effectiveness of adefovir dipivoxil and pegylated interferon alfa 2a, from the perspective of the NHS and personal social services. This was based on our systematic review of literature on natural history, epidemiology and health-related quality of life in CHB, as well as clinical effectiveness and cost-effectiveness of anti-viral treatment.
- The model includes eight health states (CHB, HBeAg seroconversion/ remission, HBsAg seroconversion, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and death). 12 "tunnel" states take into account previous treatment history (e.g. switching drugs when resistance develops).
- A cohort of patients passes through these states at different rates. The baseline cohort comprises patients with HBeAg positive disease, who have a mean age of 32 and 75% of whom are male, and HBeAg negative disease, who have a mean age of 40 years and are 90% male.
- The model has a lifetime horizon, with a cycle length of one year (with half cycle correction applied).
- Short term outcomes include HBeAg seroconversion (for HBeAg positive patients) and ALT normalisation (for HBeAg negative patients).
- Published age-specific quality of life weights for healthy populations were used to estimate utility values for patients who HBsAg or HBeAg seroconvert. Utility

values for other health states are estimated relative to these values, based on published literature.

- To assess costs associated with the management of CHB, resource use was estimated from clinical guidelines and advice from clinical practitioners. Drug costs were taken from the BNF. Health state costs for advanced disease were obtained from the published literature.
- Costs were discounted at 6% and benefits at 1.5%.

6.2 Cost-effectiveness results

Cost-effectiveness findings are presented for two separate groups (i) patients with HBeAg positive CHB and with HBeAg negative CHB, and (ii) for an overall cohort of CHB patients having the age and sex characteristics reported in the literature and described in Section 6.1.4. Discounted costs, identifying the contribution to total costs of anti-viral medication and supportive care for patients' liver disease, are presented along with life expectancy and quality-adjusted life expectancy for patients in the cohort. Findings are presented for the incremental cost per life year gained and for incremental cost per QALY. Clinical advisors to the project have emphasised differences in the action of interferons and the nucleoside/ nucleotide analogues. Hence the cost-effectiveness analysis will only compare treatments to their closest comparator. For conventional interferon the closest comparator is best supportive care while for pegylated interferon the comparator is conventional interferon. For lamivudine the comparator is best supportive care while for adefovir the comparator is lamivudine.

Costs and outcomes modelled for a cohort containing patients with HBeAg positive and HBeAg negative disease for each of the interventions are presented in Table 37. Additionally incremental cost per QALYs ratios are shown for each intervention relative to their closest comparator. Costs are discounted at 6% and health outcomes discounted at 1.5%.

Table 37 – Cost-effectiveness of interventions and comparators (all patients)

	Costs (£)	Discounted years of life expectancy	Discounted QALYs	Incremental cost-effectiveness ratio (£)
Best supportive care	8,555	22.29	17.07	
Conventional interferon alfa	12,609	22.98	17.75	5,994[a]
Pegylated interferon alfa	15,745	23.51	18.26	6,119[b]
Lamivudine	12,286	23.36	18.08	3,685[c]
Adefovir dipivoxil	29,918	24.55	19.15	16,569[d]

Notes:
[a] comparing conventional interferon alfa to best supportive care
[b] comparing pegylated interferon alfa to conventional interferon alfa
[c] comparing lamivudine to best supportive care
[d] comparing adefovir dipivoxil to lamivudine

These comparisons are based on a 24-week course of treatment with non-pegylated interferon alfa for patients with HBeAg positive disease and non-pegylated interferon alfa for 48 weeks for patients HBeAg negative disease. A course of treatment with pegylated interferon alfa is 48 weeks for both HBeAg positive and HBeAg negative

patients, whereas there is no fixed treatment course for lamivudine and adefovir (though the EASL guideline recommends at least one year of treatment[3]). In the model we assumed that treatment with lamivudine or adefovir, once started, is continued until HBeAg seroconversion occurs, drug resistance develops or the patient dies. Patients who undergo HBeAg seroconversion with lamivudine or adefovir treatment are maintained on consolidation therapy for six months.

Table 38 and
Table 39 report the modelled costs and outcomes for each intervention for HBeAg positive and HBeAg negative patients separately. The tables illustrate clearly the lower life expectancy for patients with HBeAg negative disease. This is just under 16 years lower for HBeAg negative patients receiving best supportive care, compared to HBeAg positive. This more than offsets the eight year difference in mean age between HBeAg positive and negative patients that was assumed for the baseline cohort. In each group of patients adefovir is associated with the greatest costs – typically double that for pegylated interferon and three times the cost for other treatment options. However, these increased costs are associated with substantial health gains – of the order of two QALYs compared to best supportive care and one QALY compared to lamivudine.

Table 38 - Cost-effectiveness of interventions and comparators (HBeAg positive patients)

	Costs (£)	Discounted years of life expectancy	Discounted QALYs	Incremental cost-effectiveness ratio (£)
Best supportive care	7,402	25.27	20.08	
Conventional interferon alfa	11,359	25.78	20.58	7,936[a]
Pegylated interferon alfa	14,704	25.99	20.78	16,166[b]
Lamivudine	10,909	26.32	21.08	3,489[c]
Adefovir dipivoxil	25,224	27.35	22.02	15,289[d]

Notes:
[a] comparing conventional interferon alfa to best supportive care
[b] comparing pegylated interferon alfa to conventional interferon alfa
[c] comparing lamivudine to best supportive care
[d] comparing adefovir dipivoxil to lamivudine

Table 39 - Cost-effectiveness of interventions and comparators (HBeAg negative patients)

	Costs (£)	Discounted years of life expectancy	Discounted QALYs	Incremental cost-effectiveness ratio (£)
Best supportive care	11,247	15.32	10.05	
Conventional interferon alfa	15,524	16.45	11.14	3,922[a]
Pegylated interferon alfa	18,172	17.72	12.36	2,162[b]
Lamivudine	15,499	16.46	11.08	4,131[c]
Adefovir dipivoxil	40,870	18.01	12.44	18,620[d]

Notes:
[a] comparing conventional interferon alfa to best supportive care
[b] comparing pegylated interferon alfa to conventional interferon alfa
[c] comparing lamivudine to best supportive care
[d] comparing adefovir dipivoxil to lamivudine

These may not be the most clinically relevant comparisons. Additional intervention strategies have been modelled using interferon alfa as first line intervention with lamivudine or adefovir dipivoxil for those patients who do not respond to interferon alfa. We have also modelled a set of sequential treatment strategies for pegylated interferon as first line with lamivudine or adefovir dipivoxil for those patients who do not respond. The final strategy in each comparison is referred to as adefovir salvage, in which patients receive interferon as first line treatment and lamivudine is provided for those who do not respond to interferon. Patients who develop resistance to lamivudine then have adefovir added to their treatment. The costs of these intervention strategies, their outcomes and incremental cost-effectiveness are reported in Table 40. This table reports results for the overall cohort containing patients with HBeAg positive and negative disease. Tables reporting results for the two groups of patients separately are included in Appendix 16.

Table 40 – Cost-effectiveness of sequential treatment strategies (all patients)

Strategy	Costs (£)	Discounted years of life expectancy	Discounted QALYs	Incremental cost-effectiveness ratio (£)
Best supportive care	8,555	22.29	17.07	
Conventional interferon alfa	12,609	22.98	17.75	5,994
Conventional interferon alfa followed by lamivudine	15,159	23.76	18.45	3,604[a]
Conventional interferon alfa followed by adefovir dipivoxil	27,442	24.81	19.40	8,987[b]
Conventional interferon alfa followed by lamivudine with adefovir salvage	27,740	25.00	19.56	11,402[c]
Pegylated interferon alfa	15,745	23.51	18.26	6,119
Pegylated interferon alfa followed by lamivudine	18,053	24.20	18.88	6,766[d]
Pegylated interferon alfa followed by adefovir dipivoxil	28,907	25.13	19.71	4,649[e]
Pegylated interferon alfa followed by lamivudine with adefovir salvage	28,976	25.28	19.83	4,452[f]

Notes:
[a] comparing conventional interferon alfa followed by lamivudine to conventional interferon alfa alone
[b] comparing conventional interferon alfa followed by adefovir to conventional interferon alfa alone
[c] comparing conventional interferon alfa followed by lamivudine, with adefovir salvage to conventional interferon alfa followed by lamivudine
[d] comparing pegylated interferon alfa followed by lamivudine to conventional interferon alfa followed by lamivudine
[e] pegylated interferon alfa followed by adefovir to conventional interferon alfa followed by adefovir
[f] comparing pegylated interferon alfa followed by lamivudine, with adefovir salvage to conventional interferon alfa followed by lamivudine, with adefovir salvage

As with the comparison of intervention costs in monotherapies, all intervention strategies that include adefovir are substantially more costly than those that do not. However these are also associated with health gain, in the range of 2 to 3 QALYs

when compared to best supportive care, or around one QALY when compared to the interventions including active anti-viral therapy. In all of these cases the incremental cost-effectiveness ratios are well within the range that would conventionally be regarded as being cost-effective.

Separating these results out for patients with HBeAg positive and negative disease reveals different patterns in the cost-effectiveness of these sequential treatment strategies.

For patients with HBeAg positive disease the strategy to provide interferon (non-pegylated or pegylated) followed by lamivudine, with adefovir salvage for patients who develop resistance to lamivudine, has lower total costs than the strategy to provide interferon followed by adefovir. Including adefovir salvage is substantially more costly than using lamivudine-only as second line treatment, but provides substantial additional health gain. Comparing strategies which include pegylated interferon to similar strategies including non-pegylated interferon shows increases in cost of treatment and improved outcomes. However, the incremental cost-effectiveness ratios are substantially higher. This largely reflects the assumption, in the absence of long-term follow-up of patients achieving HBeAg seroconversion after treatment with pegylated interferon, that the durability of HBeAg seroconversion for pegylated interferon would be the same as for non-pegylated interferon.

For patients with HBeAg negative disease a different pattern of relative costs for the non-pegylated and pegylated interferon strategies is revealed. Pegylated interferon provides a substantial health gain over treatment with conventional interferon. Strategies that include second-line anti-viral treatment for patients who fail to respond to interferon alfa treatment also provide substantial health gains, with strategies that include adefovir being cost saving in comparison to conventional interferon. This reflects the assumption in the model that relapse for HBeAg negative patients treated with pegylated interferon alfa is substantially lower than for patients treated with conventional interferon alfa.

6.2.1 Sensitivity analysis

6.2.1.1 Deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around model structure and for variation in certain key parameters that were expected, a priori, to be influential on the cost-effectiveness results. Separate sensitivity analyses were undertaken for the two sets of results presented in Section 6.2 above and these are reported and discussed separately. The method we adopted is univariate sensitivity analysis. That is, varying one parameter at a time, leaving all other variables unchanged. This is to highlight the impact, if any, of each selected parameter alone on the cost-effectiveness results. The effects of uncertainty in multiple parameters was addressed using probabilistic sensitivity analysis, which is reported later in the section.

Table 41 reports the results of the sensitivity analysis for the overall cohort of patients, including those with HBeAg positive and HBeAg negative disease, for the comparison of each drug reported in Table 38 in Section 6.2. The table is divided to

distinguish between analyses undertaken due to uncertainties in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values. A particular concern in performing the analysis of structural assumptions was to consider the impact of state transitions that have been omitted in previous economic evaluations of anti-viral therapy for chronic hepatitis B on the cost-effectiveness estimates.

Previous economic evaluations, discussed in Section 5.2, have excluded a number of state transitions from their analyses, either due to an absence of data or due to an assumed infrequent occurrence of these transitions. HBeAg seroconversion for patients with compensated cirrhosis (either spontaneous or treatment-related) has been excluded in many previous evaluations. Since most evaluations have modelled cohorts of patients who do not initially have cirrhosis, the absence of this transition would not bias the results for evaluations of interferon treatment, as the treatment would be assumed to occur when all patients are non-cirrhotic and would therefore be able to achieve HBeAg seroconversion (though this would apply only to patients with HBeAg positive disease). The exclusion of this transition would be expected to have more impact for continuing therapy, such as lamivudine or adefovir. The table shows that excluding this transition from the model has little effect on the cost-effectiveness of either non-pegylated or pegylated interferon, or of lamivudine. However, the cost-effectiveness ratio for adefovir increases dramatically. The effect of excluding this transition, for all interventions, is to increase total costs and to reduce outcomes. The impact is disproportionately high for adefovir due to its low resistance profile. This means that more patients in the model who progress to compensated cirrhosis would be eligible for treatment than would be the case for lamivudine.

The impact of two other transitions that are commonly excluded from disease progression models was investigated. Excluding transitions from the HBeAg seroconverted state to hepatocellular carcinoma and excluding the HBsAg seroconverted state had little impact on cost-effectiveness estimates.

Changing the discount rates applied from the current guidance (6% for costs and 1.5% for health outcomes) to the rates required for future NICE appraisals has a substantial impact on cost-effectiveness estimates. This, again, primarily impacts on adefovir due to its lower resistance profile compared to lamivudine, which means that patients are eligible for longer periods of treatment. Discounting costs at 3.5% rather than 6% means that the cost of treating those patients in the future has greater weight than in the base case, but raising the discount rate for benefits from 1.5% to 3.5% means that health gains occurring in the future are accorded less weight.

Table 41 - Deterministic sensitivity analysis results (all patients)

		Cost per QALY			
		IFN	**PEG**	**LAM**	**ADV**
Baseline analysis		£5,994	£6,119	£3,685	£16,569
Structural assumptions					
Zero transition probability from compensated cirrhosis to HBeAg seroconverted state		£5,275	£5,696	£3,513	£30,494
Zero transition probability from HBeAg seroconverted state to HCC.		£5,864	£6,047	£3,615	£16,220
Zero transition probability to HBsAg seroconverted state.		£5,927	£6,091	£3,840	£15,934
Discount costs and outcomes at 3.5%		£8,763	£9,016	£5,646	£30,982
Baseline cohort characteristics					
HBeAg positive cohort 50% male		£5,957	£6,100	£3,655	£16,398
HBeAg negative cohort 50% male		£5,915	£5,992	£3,671	£16,448
Baseline cohort is 50% HBeAg positive		£5,181	£4,185	£3,814	£17,264
Increasing age of cohort at start of simulation	- 5 years	£5,472	£5,549	£3,408	£14,966
	+ 5 years	£6,670	£6,875	£4,029	£18,616
	+ 10 years	£7,559	£7,902	£4,459	£21,288
Parameter uncertainty					
Varying the rate of adefovir resistance	+ 0.02				£18,063
	+ 0.04				£19,938
	+ 0.06				£22,349
	+ 0.08				£25,565
Higher cost for compensated cirrhosis state – 2,220 rather than 1,138		£5,740	£5,831	£3,454	£16,452
Utility decrement for compensated cirrhosis set to 0.07 rather than 0.44		£6,819	£7,155	£4,035	£17,594
Utility effect of interferon treatment – 13% reduction while on conventional interferon.		£6,541	£5,919	£3,685	£16,569
Utility effect of interferon treatment – 33% reduction while on conventional interferon.		£7,609	£5,597	£3,685	£16,569
Relapse for HBeAg negative patients treated with pegylated interferon is same as conventional interferon (60%).		£5,994	£15,640	£3,685	£16,569
Relapse for HBeAg negative patients treated with pegylated interferon is 45%		£5,994	£9,457	£3,685	£16,569
Use trial and follow up data directly in model, with extrapolation		£5,994	£6,119	£4,223	£21,363
Use trial and follow up data directly in model, without extrapolation		£5,994	£6,119	£4,728	£50,168
Reduce adefovir and pegylated interferon costs by 20%		£5,994	£5,222	£3,685	£13,006
Reduce adefovir and pegylated interferon costs by 30%		£5,994	£3,105	£3,685	£11,225

Varying the composition of the initial cohort of patients in the model, by reducing the proportion of the cohort assumed to be male and by reducing the proportion assumed to have HBeAg positive disease has little impact on cost-effectiveness. Increasing the age of the cohort at the start of the model has the effect of increasing the cost-effectiveness ratio for all interventions. Where study outcomes are measured using life expectancy, increasing the age of the cohort would be expected to have the effect

of reducing the potential effect of treatment. This occurs in this situation where QALY outcomes for the interventions are reduced by between 20 and 25% over the age range used in this sensitivity analysis. At the same time total costs for the interventions reduce by about 3%, leading to the rise in the cost-effectiveness estimates.

Increasing the rate of resistance to adefovir has the effect of increasing the cost-effectiveness estimate. Over the range of values used in the sensitivity analysis the incremental costs (compared to lamivudine treatment) reduced by 25% while incremental QALYs were reduced by 50%.

Other parameters included in the sensitivity analysis – cost of the compensated cirrhosis state, health state utility for compensated cirrhosis and the impact of interferon treatment on quality of life – had comparatively little impact on cost-effectiveness of interventions. However, varying the assumption over the relapse rate for pegylated interferon responders with HBeAg negative disease had a substantial impact on cost-effectiveness. As stated earlier, there is little evidence on which to base an estimate of the durability of response to treatment for this group of patients. For the base case the relapse probability of 25% used in the manufacturer's submission was adopted. For this sensitivity analysis the relapse rate reported for conventional interferon (60%) has been applied and also a value mid-way between that adopted by the manufacturer and that for conventional interferon (45%).

In the model for the base case analysis the effectiveness of lamivudine and adefovir in promoting HBeAg seroconversion is estimated by applying a relative risk of 2 to the spontaneous seroconversion rate of 9%. This relative risk is based on HBeAg seroconversion rates observed in clinical trials of lamivudine and adefovir compared to placebo, and on reported seroconversion rates in long term follow-up studies compared to the estimated spontaneous seroconversion rate. To test the sensitivity of the cost-effectiveness results to these assumptions the HBeAg seroconversion rates observed in clinical trials and in long term follow-up studies were directly applied in the model. Table 42 shows the HBeAg seroconversion rates used in this analysis.

Table 42 - HBeAg seroconversion rates for lamivudine and adefovir used in sensitivity analysis

Treatment Year	Lamivudine	Adefovir
1	0.19	0.12
2	0.16	0.18
3	0.16	0.18
4	0.16	0.18

We conducted two sensitivity analyses on lamivudine and adefovir HBeAg seroconversion rates:

- Rates observed in the trials and long term follow-up studies were applied directly in the model for treatment years 1 to 4 and the seroconversion rate at year 4 applied to all subsequent years in which a patient was treated;
- Rates observed in the trials and long term follow-up studies were applied directly in the model for treatment years 1 to 4 and the seroconversion rate

reverted to the spontaneous rate for all subsequent years. This was the assumption applied in Crowley and colleagues analysis of lamivudine[84;87].

The result of these analyses is to increase the cost-effectiveness ratio for lamivudine, compared to best supportive care, slightly (from £3,685 per QALY to £4,223 per QALY for the model extrapolating a treatment effect beyond year 4, and £4,728 per QALY for the model in which no extrapolation was applied). The effect on the incremental cost-effectiveness ratio for adefovir is much greater, increasing from £16,569 in the base case to £21,363 for the model that extrapolates beyond four years, and £50,168 for the model with no extrapolation. The two principal causes of this are:

- Low HBeAg seroconversion rate for adefovir in year 1 (12%) compared to the spontaneous rate assumed in the model (9%). In the trial the seroconversion rate with adefovir was double that in the placebo arm (see Section 4.1.2.4);
- The high resistance rate for lamivudine means that comparatively few patients would be treated beyond four years in the base case analysis, whereas the low resistance profile for adefovir means that patients may be maintained on treatment for a longer period. In the analysis using trial seroconversion rates directly beyond year four patients were gaining no therapeutic benefit, in terms of HBeAg seroconversion, but were still generating drug costs for as long as they remained in one of the treatment-eligible health states.

Table 43 reports the sensitivity analysis on the sequential treatment strategies to determine the robustness of the cost-effectiveness results to structural assumptions, baseline cohort characteristics and variation of selected parameters. The incremental cost-effectiveness ratios reported are not referenced to a common base, but are derived from a comparison of each strategy to its closest comparator (see Table 40 for a list of comparators). For example, each strategy which includes pegylated interferon is compared to the equivalent strategy that includes conventional interferon. This means that the cost-effectiveness ratios for sequential strategies including pegylated interferon generally appear to be low as they reflect only the impact of replacing conventional interferon with pegylated interferon in the treatment strategy.

As in the previous sensitivity analysis, excluding transitions from the compensated cirrhosis health state to HBeAg seroconversion produces a substantial increase in the cost-effectiveness ratio for strategies including adefovir, whereas the results appear to be little influenced by variation in transitions from the HBeAg seroconverted state to hepatocellular carcinoma or to HBsAg seroconversion.

Changing the discount rates applied to costs and health outcomes has a similar effect as before, greatly increasing the cost-effectiveness ratio for strategies including adefovir.

Table 43 - Deterministic sensitivity analysis for sequential treatment strategies

		Cost per QALY					
		IFN + LAM	**IFN + ADV**	**IFN + LAM + ADV**	**PEG + LAM**	**PEG + ADV**	**PEG + LAM + ADV**
Baseline analysis		£3,604	£8,987	£11,402	£6,766	£4,649	£4,452
Structural assumptions							
Zero transition probability from compensated cirrhosis to HBeAg seroconverted state		£4,689	£13,045	£18,634	£6,292	£4,081	£3,739
Zero transition probability from HBeAg seroconverted state to HCC.		£3,525	£8,811	£11,220	£6,675	£4,575	£4,374
Zero transition probability to HBsAg seroconverted state.		£3,713	£9,067	£11,410	£6,652	£4,477	£4,130
Discount costs and outcomes at 3.5%		£6,038	£16,671	£23,417	£10,179	£6,347	£5,107
Baseline cohort characteristics							
HBeAg positive cohort 50% male		£3,573	£8,897	£11,282	£6,739	£4,630	£4,432
HBeAg negative cohort 50% male		£3,590	£8,943	£11,326	£6,614	£4,543	£4,346
Baseline cohort is 50% HBeAg positive		£3,753	£9,951	£12,796	£4,538	£1,445	£651
Increasing age of cohort at start of simulation	- 5 years	£3,318	£8,182	£10,302	£6,097	£4,177	£3,981
	+ 5 years	£3,960	£9,995	£12,791	£7,659	£5,288	£5,099
	+ 10 years	£4,407	£11,272	£14,571	£8,885	£4,303	£10,965
Parameter uncertainty							
Varying the rate of adefovir resistance	+ 0.02	£3,604	£9,002	£11,440	£6,766	£4,893	£4,840
	+ 0.04	£3,604	£9,015	£11,483	£6,766	£5,074	£5,127
	+ 0.06	£3,604	£9,026	£11,530	£6,766	£5,211	£5,345
	+ 0.08	£3,604	£9,033	£11,577	£6,766	£5,321	£5,520
Higher cost for compensated cirrhosis state – 2,220 rather than 1,138		£3,454	£8,850	£11,282	£6,492	£4,370	£4,171
Utility decrement for compensated cirrhosis set to 0.07 rather than 0.44		£3,814	£9,551	£12,081	£7,910	£5,462	£5,230
Relapse for HBeAg negative patients treated with pegylated interferon is same as conventional (60%).		£3,604	£8,987	£11,402	£17,472	£19,481	£20,519
Relapse for HBeAg negative patients treated with pegylated interferon is 45%		£3,604	£8,987	£11,402	£10,623	£10,063	£10,485
Reduce pegylated interferon costs by 20%		£3,604	£8,987	£11,402	£3,802	£624	Dominant
Reduce adefovir costs by 20%		£3,604	£7,312	£9,733	£6,766	£5,637	£5,328
Reduce adefovir and pegylated interferon costs by 20%		£3,604	£7,312	£9,733	£3,802	£1,612	£760
Reduce adefovir and peg costs by 30%		£3,604	£6,474	£8,899	£2,320	£94	Dominant

Notes:
IFN + LAM: conventional interferon followed by lamivudine
IFN + ADV: conventional interferon followed by adefovir
IFN + LAM + ADV: conventional interferon followed by lamivudine with adefovir salvage for lamivudine patients who develop resistance
PEG + LAM: pegylated interferon followed by lamivudine
PEG + ADV: pegylated interferon followed by adefovir
PEG + LAM+ ADV: pegylated interferon followed by lamivudine with adefovir salvage for lamivudine patients who develop resistance

The results appear to be robust to changes in the composition of the baseline cohort, except that reducing the proportion of the cohort that is assumed to be HBeAg positive dramatically reduces the incremental cost-effectiveness ratios for strategies that include pegylated interferon and adefovir. One striking observation from this analysis is that variation in the rate of resistance to adefovir over a range of +2% to +8% has very little impact on the incremental cost-effectiveness ratio.

The incremental cost-effectiveness ratios for pegylated interferon appear to be particularly sensitive to variation in the relapse rate for HBeAg negative patients who achieve a response (by normalising ALTs) following treatment.

6.2.1.2 Probabilistic sensitivity analysis

The probabilistic analysis generated cost and QALY estimates for each intervention that were similar to those for the base case analysis (see Table 36 for base case analysis). Table 44 reports the mean costs and outcomes from the probabilistic analysis, including the 2.5 and 97.5 percentiles to give an indication of the range of the simulated values, and the incremental cost-effectiveness ratios based on the values generated in the probabilistic analysis.

Table 44 - Costs and outcomes from probabilistic analysis

	Discounted costs				Discounted QALYs				
	Mean	2.5%		97.5%	Mean	2.5%		97.5%	ICER (£)
Best supportive care	8,604	7,997	-	10,225	17.09	16.56	-	18.50	
Conventional interferon alfa	12,655	12,064	-	14,240	17.77	17.29	-	19.24	5,920
Pegylated interferon alfa	15,782	15,211	-	17,341	18.30	17.80	-	19.73	5,945
Lamivudine	12,336	11,740	-	13,982	18.09	17.61	-	19.53	3,744
Adefovir dipivoxil	30,082	28,849	-	33,676	19.13	18.62	-	20.64	17,078

Figure 5- Cost-effectiveness acceptability curves for best supportive care, lamivudine and adefovir

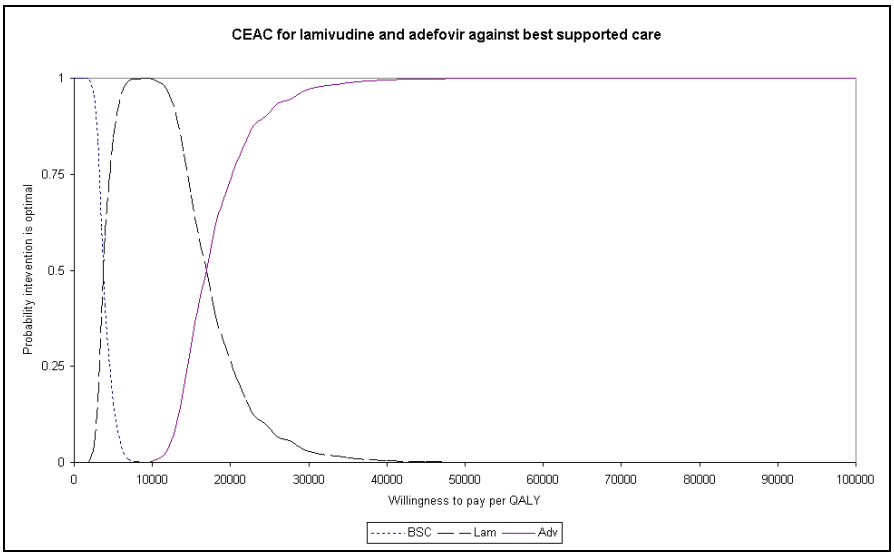


Figure 5 shows the cost-effectiveness acceptability curves for lamivudine, adefovir and best supportive care. The chart indicates the probability that a given intervention is optimal compared to the other illustrated interventions. This suggests that lamivudine is a cost-effective option at lower threshold levels of willingness-to-pay for health outcomes, but as the threshold is increased adefovir is increasingly likely to be the optimal intervention.

Figure 6 - Cost-effectiveness acceptability curves for best supportive care, conventional interferon and pegylated interferon

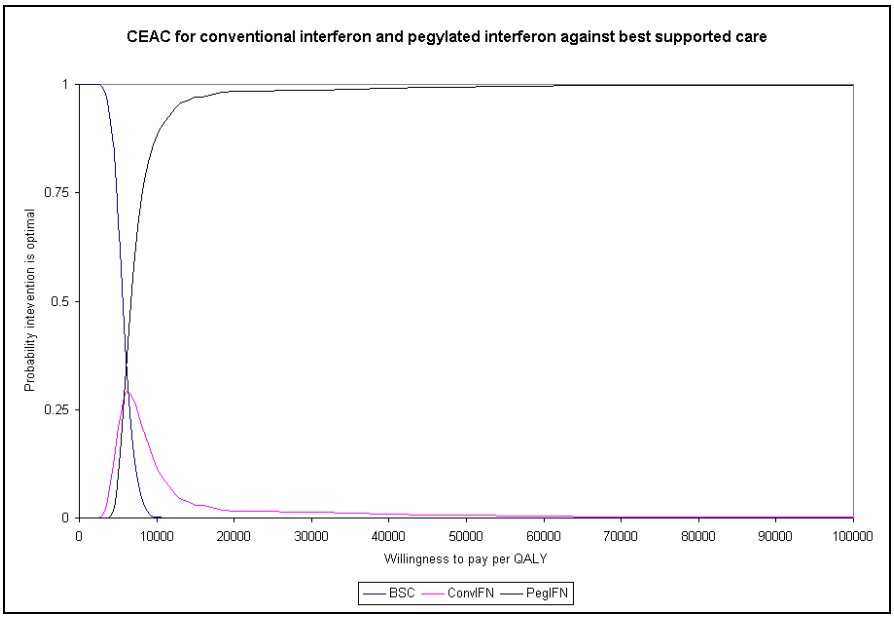


Figure 6 illustrates a similar comparison for conventional interferon and pegylated interferon, which appears to suggest that, from above a threshold willingness to pay of around £10,000 per QALY, pegylated interferon is highly probable to be the optimal intervention. However this analysis was conducted for the cohort including both HBeAg positive and HBeAg negative patients. If similar analyses are conducted for HBeAg positive and negative patients separately then the pattern is somewhat different.

Figure 7 - Cost-effectiveness acceptability curves for best supported care, conventional interferon and pegylated interferon in patients with HBeAg positive disease.

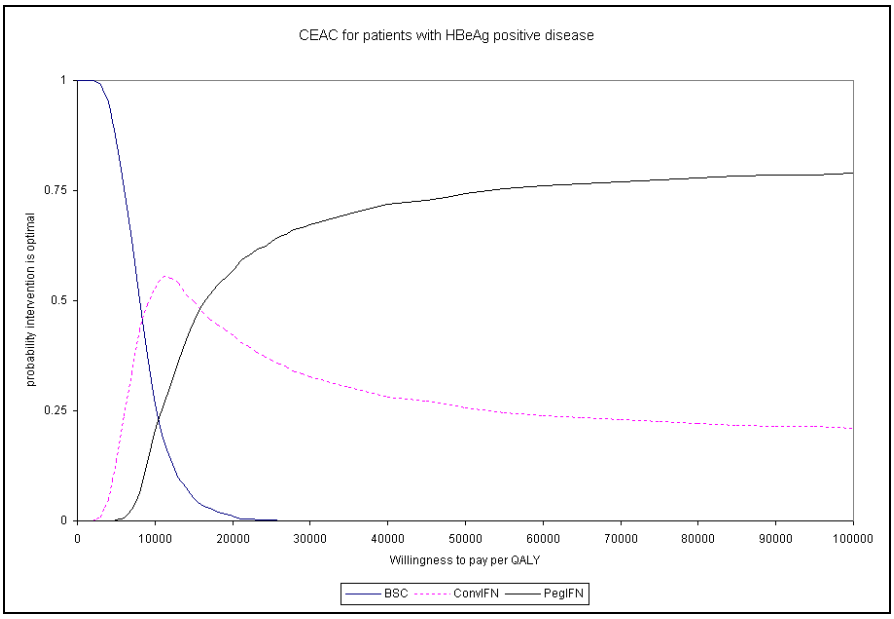


Figure 7 shows the CEACs for best supportive care, conventional interferon and pegylated interferon alfa for patients with HBeAg positive disease. In this case the balance between the probability of conventional interferon and pegylated interferon is less clear than would be suggested by Figure 6.

This partly reflects the assumption that the durability of HBeAg seroconversion following treatment with pegylated interferon alfa is the same as for conventional interferon, as was discussed in Section 6.2.1. This means that for HBeAg positive patients the only benefit from treatment with pegylated interferon alfa is the increased HBeAg seroconversion rate observed in trials of pegylated interferon (see Section 4.1.2.4).

Figure 8 shows the same analysis for patients with HBeAg negative disease which suggests that pegylated interferon is highly likely to be the optimal intervention in comparison to conventional interferon. This is largely due to the assumed substantial benefit of pegylated interferon in maintaining response in biochemical and virological responders. A 60% relapse for conventional interferon has been applied in the model compared to a 25% relapse for pegylated interferon.

Figure 8 - Cost-effectiveness acceptability curves for best supportive care, conventional interferon and pegylated interferon in patients with HBeAg negative disease.

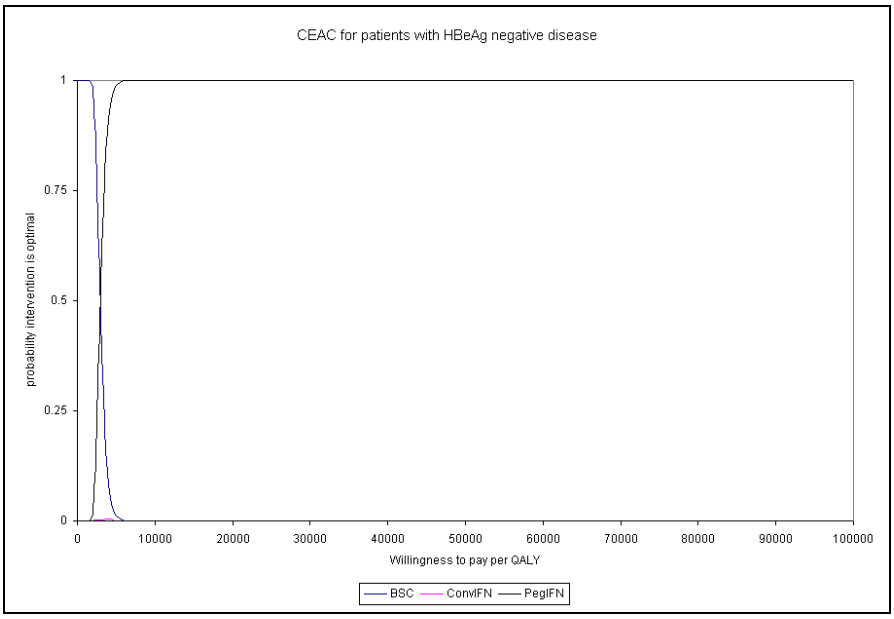


Table 45 reports the mean cost and outcomes and incremental cost-effective ratios for the sequential treatment strategies from the probabilistic analysis. The mean discounted QALYs from this analysis are almost identical to the base case values (see Table 39 for base case analysis). However the mean costs are slightly higher than in the base case analysis.

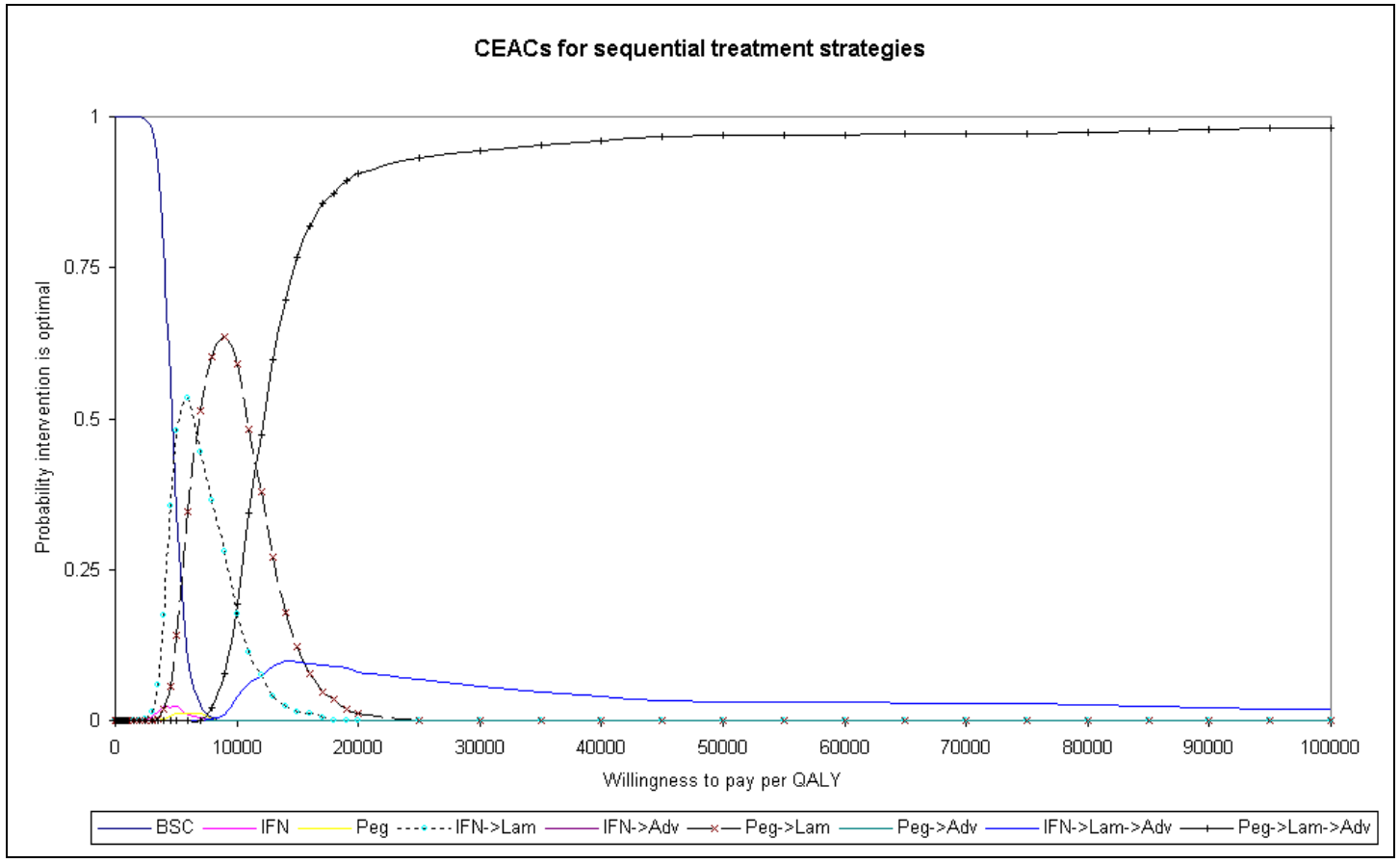
Table 45 – Costs and outcomes from probabilistic analysis of sequential strategies

	Discounted costs			Discounted QALYs			
	Mean	2.5%	97.5%	Mean	2.5%	97.5%	
Best supportive care	8,594	7,601	10,344	17.06	15.62	18.62	ICER (£)
Conventional interferon alfa	12,635	11,679	14,401	17.76	16.44	19.1	5,818
Conventional interferon alfa followed by lamivudine	15,172	14,155	17,170	18.46	17.07	19.89	3,596
Conventional interferon alfa followed by adefovir dipivoxil	27,490	25,492	31,151	19.39	17.88	20.78	9,120
Conventional interferon alfa followed by lamivudine with adefovir salvage	27,826	25,504	32,110	19.55	17.99	20.91	11,677
Pegylated interferon alfa	15,771	14,838	17,581	18.27	16.9	19.81	6,124
Pegylated interferon alfa followed by lamivudine	18,068	17,032	20,150	18.89	17.41	20.37	6,764
Pegylated interferon alfa followed by adefovir dipivoxil	28,954	26,365	33,207	19.7	18.14	21.19	4,623
Pegylated interferon alfa followed by lamivudine with adefovir salvage	29,059	26,335	33,997	19.83	18.26	21.28	4,424

Figure 9 shows the cost-effectiveness acceptability curves for all interventions included in the analysis of sequential treatment strategies. This suggests that interferon (non-pegylated or pegylated) followed by lamivudine would be the optimal strategy at lower threshold values of willingness to pay, but as the threshold increases the sequential treatment strategy including adefovir salvage is increasingly likely to be the optimal intervention.

For a summary of the results of our cont-effectiveness analysis please refer to the Executive Summary.

Figure 9 - Cost-effectiveness acceptability curves for sequential treatment strategies



7 IMPLICATIONS FOR OTHER PARTIES

The availability of safe and effective treatment has positive benefits for people with chronic hepatitis B and their families. The introduction of pegylated interferon alfa and adefovir dipivoxil increases the treatment options available and gives patients greater choice. The fact that pegylated interferon alfa requires only one injection per week instead of three for non-pegylated is more convenient and reduces disruption to lives of patients and their partners and families.

There are implications for the sexual partners of patients undergoing treatment, and for injecting drug users who share needles. Modelling of the costs and consequences of treatment to partners is beyond the scope of this report, although it could be assumed that a potential benefit of successful anti-viral treatment is the reduced likelihood of transmission of HBV to partners. However, expert opinion suggests the possibility of the transmission of drug resistant mutations to partners, although the lower resistance profile of adefovir dipivoxil may reduce the likelihood of mutations occurring. Where transmission is a possibility it is therefore important to minimise risk through vaccination, safer sex practices and, for IDUs, safer injecting practices. Such strategies should also continue to be promoted irrespective of risk of transmission of a mutation, as effective prevention is a desirable outcome in itself. More broadly, it is important for future assessments of clinical and cost-effectiveness to take into account the costs and consequences of anti-viral treatment on sexual partners.

The issuing of NICE guidance and the likely increased availability of anti-viral therapy for hepatitis B may also help to reduce the stigma associated with infectious diseases such as hepatitis. Hopwood and Southgate[134] review the international sociological literature on hepatitis C and report that people living with hepatitis are often subjected to social stigma and discrimination, particularly if acquired through injecting drug use or sexual contact. It is also suggested that there is an over-medicalisation of hepatitis at the expense of a more informed social and cultural understanding of the disease, and that risk groups such as IDUs are often assumed to be a homogenous group, when in reality, they vary in terms of age, background and social and economic status. More research into the social and cultural impact of hepatitis is recommended, to inform effective prevention and management strategies.

The implications for patients (and their families) with advanced liver disease resulting from HBV infection requires further investigation. Some will not be able to work, or work only in a limited capacity. This will have an obvious impact on their socio-economic status and potential knock on effects in terms of their health. They may also require care, particularly following liver transplant. This will place responsibility on family and other carers.

8 FACTORS RELEVANT TO NHS

In terms of implementation issues, there do not appear to be any significant barriers to diffusion of the appraised treatments into routine practice. As mentioned earlier, clinical colleagues consulted during the preparation of this report suggest that both pegylated interferon alfa and adefovir dipivoxil are in current use, to varying extents. Existing NICE guidance on the use of pegylated interferon alfa in the treatment of hepatitis C will have undoubtedly raised its profile within the hepatitis patient community. This may encourage patients with hepatitis B to request this treatment, or even those who think they may be infected to present for assessment (which has consequences for budgets – see below). Specialist hepatology nurses will already be familiar with the administration of pegylated interferon alfa in the treatment of hepatitis C.

Funding arrangements for treatment are of importance. The commissioning of hepatitis B and C services is managed by Primary Care Trusts, often from the same budget. Yet it is argued that funding for hepatitis C often overshadows that for hepatitis B[12]. Although treatment is generally administered by specialist hepatology departments, commissioning and funding arrangements are complicated by the fact that a number of other agencies may be involved in the prevention, investigation, referral and management and rehabilitation of patients. These include primary care, genito-urinary medicine/sexual health services, drug and alcohol services, prison health services, and specialist agencies dealing with the health needs of high risk ethnic groups. An integrated approach to commissioning is therefore desirable. The Foundation for Liver Research suggest the involvement of a nominated lead Primary Care Trust for liver disease, with involvement from Strategic Health Authorities and Regional Specialised Commissioning Groups[12].

Effective implementation of national guidance on anti-viral therapy may be facilitated by the National Plan for Liver Services[20] which recommends that all patients receive treatment and care that is uniformly of high standard, via Managed Clinical Hepatology Networks (MCHN). In particular, it is expected that MCHNs will show commitment in implementing NHS directed research on evidence based treatments. The plan also recommends accurate data collection to monitor clinical-effectiveness to enable planning and adoption of best clinical practice, and to enable comparison of patient outcomes across the country. It is envisaged that there will be 10 to 15 MCHNs in the UK, each responsible for between 1 and 5 million people. It is hoped that patients with liver diseases have equivalent access to specialist treatment as patients with renal or cardiac diseases.

It is also important to ensure equitable access to hepatology services, particularly for those who may be socially and economically disadvantaged. This may include some IDUs, and immigrants to the UK with CHB (e.g. from South East Asia). Many of the latter may be in the immunotolerant stage of HBeAg negative CHB unaware of their infection[12]. Greater effort is needed to identify, assess and diagnose such people (particularly those at highest risk of progression) and to offer anti-viral treatment, where indicated. Outreach services and specialist clinics, as used to target IDUs and men who have sex with men, may be appropriate and all interventions should be subjected to rigorous evaluation.

Attempts to increase identification has implications for Primary Care Trusts in terms of identification/assessment costs, and the cost of treatment and monitoring, particularly if life-long treatment is necessary. It is difficult to assess budget impact as there is no reliable estimate of the proportion of the prevalent pool of people in England and Wales with CHB who may be eligible for treatment. Data from one of the drug manufacturer's submissions[36] to NICE suggests that up to 1.07% (n=1921) of the total prevalent pool of people with CHB in the UK had been treated in 2004, and that each year, on average, around 600 patients receive anti-viral therapy. There is an apparent shortage of hepatologists, gastroenterologists and other specialists in the UK to meet an increased demand (although treatment is increasingly being administered by hepatology specialist nurses). It will therefore be important to identify and treat those at greatest risk of disease progression, based on appropriate clinical markers.

Related to this is the issue of whether or not biopsy is necessary to guide treatment decisions. In hepatitis C there are debates about the need for biopsy, fuelled in part by emerging evidence for the effectiveness of anti-viral treatment in mild disease (NB. NICE are currently appraising treatment in this patient group). If treatment is to be extended to patients regardless of disease severity the role of biopsy in gauging the progression of necro-inflammation and fibrosis is less important. Furthermore, patients often find biopsy painful, and there are obvious risks for haemophiliacs, of whom a proportion are infected with HCV and/or HBV. That said, some specialists still favour the procedure arguing that it provides additional prognostic information. EASL guidelines[3]acknowledge the central role of biopsy in diagnosing and staging infection (although they also call for the development of reliable non-invasive tests as an alternative to biopsy). Furthermore, both pegylated interferon alfa-2a and adefovir dipivoxil are licensed for histologically proven CHB. There does not seem to be the same level of debate about the need for biopsy in HBV infection as there currently is in HCV. Biopsy, therefore, appears to be an accepted tool in the diagnosis of CHB.

9 DISCUSSION

9.1 Clinical effectiveness

The evidence base for the clinical-effectiveness of pegylated interferon alfa-2a comprises three randomised controlled trials (including one yet to be fully published). For adefovir dipivoxil there are four fully published RCTs (of which three are subject to 5 year extension), and one on-going Phase II RCT. Both drugs have been evaluated in relation to existing treatments (but not in relation to each other), both as mono and dual therapies. Patients with both HBeAg negative and positive CHB have been studied, the majority previously untreated (although two studies included patients resistant to lamivudine) with compensated liver disease. The evidence base for patients with co-morbidities is currently limited to unpublished conference abstracts reporting observational studies. Observational studies have also been conducted in patients with advanced liver disease, including pre- and post-transplant patients (RCTs being unlikely in this group).

The pivotal RCTs mainly report results at the end of a year's treatment, and in some cases at an additional 24 weeks later. Data on long-term treatment and follow up are

currently available only in unpublished form, although it is likely that, in time, they will be published in full. The methodological quality of these RCTs as assessed in this systematic review is, with a few exceptions, generally fair. The quality and quantity of the evidence therefore appears to be reasonable for this assessment of clinical-effectiveness, albeit with limitations in respect of patient sub-groups and long term outcomes.

The results of the RCTs show that treatment with both pegylated interferon alfa-2a and adefovir dipivoxil is associated with improvements on a number of outcome measures. Rates of HBeAg seroconversion reached 14% for adefovir dipivoxil and 37% for pegylated interferon alfa. In many patients, seroconversion is associated with a favourable transition to the low or non-replicative phase, and a relatively slower rate of disease progression. The comparably lower seroconversion rate for adefovir dipivoxil suggests that, rather than being 'curative', it is more suited as a maintenance treatment for those who do not respond to interferon, with the aim of suppressing viral replication and limiting disease progression. Its relatively favourable resistance profile supports this.

A small proportion of patients (up to 5%) underwent HBsAg seroconversion, notably associated with pegylated interferon alfa. This outcome, which only a small proportion of patients are expected to achieve, is considered to indicate resolution of HBV infection. The 5% of patients seroconverting in response to anti-viral therapy can be compared to the average spontaneous seroconversion rate of 1-2% in untreated Western patients[3].

Biochemical responses were observed in the form of reductions in alanine aminotransferase, the enzyme that indicates liver inflammation. The proportion of patients whose ALT levels were described as being 'normal' following treatment reached as high as 72% for adefovir dipivoxil, and 60% for pegylated interferon alfa.

In terms of virological response, end of treatment HBV DNA reduced to undetectable levels / levels considered indicative of a response in as many as 85% of adefovir dipivoxil treated patients, and in up to 92% in patients treated with pegylated interferon alfa.

Favourable changes were also observed in liver histology (i.e. necroinflammation and fibrosis) with around two-thirds of patients achieving a histologic response or improvement for both treatments (on Knodell or Ishak biopsy scores).

Some studies also reported the proportion of patients who responded on one or more of the above outcomes, providing a stronger indication of treatment benefit. For example, up to 36% of pegylated interferon alfa treated patients in one study attained both a virological and biochemical response.

Of critical importance in CHB, as in other infectious diseases, is the management of patients who have developed drug resistance. In lamivudine resistant patients it has been shown that switching patients to adefovir dipivoxil is associated with a similar response to the addition of adefvoir dipivoxil to existing lamivudine. Both strategies were significantly more effective than continuation of lamivudine alone. This suggests that it may be more advantageous to switch patients who have developed

lamivudine resistance to adefovir dipivoxil monotherapy. However, expert opinion favours adding adefovir dipivoxil to on-going lamivudine, rather than withdrawing lamivudine altogether. This is on the grounds of a reduced potential for resistance.

In treatment naïve patients, the effectiveness of adefovir dipivoxil / lamivudine combination therapy has been reported only as interim conference abstract data. At 52 weeks of treatment, the results are mixed. Adefovir dipivoxil in combination with lamivudine was of similar effectiveness to lamivudine monotherapy on some outcome measures, but lamivudine was superior on others (e.g. ALT normalisation). Further results are awaited.

The evidence also demonstrates the superiority of pegylated interferon alfa over non-pegylated interferon alfa, a similar scenario observed in the treatment of hepatitis C[123] [29]. In the RCT which made this comparison, there was a statistically significant difference between the two interferons on the combined outcome of HBeAg loss, HBV DNA suppression, and normalisation of ALT. On the basis of these results it is likely that, where an interferon is indicated, pegylated interferon alfa may replace non-pegylated interferon alfa. Expert opinion suggests that in some parts of England and Wales this is current practice.

In terms of the evidence for the effectiveness of combination therapy with pegylated interferon alfa, results from the two RCTs to evaluate this modality suggest that both pegylated interferon alfa monotherapy and pegylated interferon alfa in combination with lamivudine are generally superior to lamivudine monotherapy, in both HBeAg positive and negative patients. There appeared to be little difference in effectiveness between the pegylated interferon alfa mono and combination therapies, suggesting little additional benefit for using combination therapy.

Results of trials evaluating non-pegylated interferon alfa and lamivudine, reviewed by Van Nunen and colleagues, are mixed[135]. One of the included studies (Schlam and colleagues[94]) reported similar HBeAg seroconversion rates after 16 weeks of treatment with interferon alfa and lamivudine (22% and 19%, respectively). The rate for combination therapy was significantly higher (36%, based on the per-protocol analysis). In contrast, another trial[130] reported similar seroconversion rates for combination therapy and placebo (12% and 13% respectively), with highest rates in the lamivudine monotherapy group (18%). The differences between these two studies might be explained by the fact that the latter was conducted in patients who had failed to respond to previous interferon alfa therapy. A further study in HBeAg negative patients, not included in the review, found that the combination therapy was of similar effectiveness to lamivudine monotherapy, although the combination regimen appeared to prevent or delay the emergence of YMDD variants. Based on current evidence there is relatively more support for combination therapy in non-pegylated interferon alfa than in pegylated interferon alfa regimens.

Given the need for long term treatment, particularly for patients with HBeAg negative CHB, it is important to assess the benefit of treatment over a number of years. As mentioned earlier, some of the pivotal RCTs of adefovir dipivoxil are subject to extension studies of up to 5 years. Interim results presented at international conferences suggest that HBV and ALT response rates increase over time with continued adefovir dipivoxil treatment, as do rates of HBeAg seroconversion.

Decisions regarding when to initiate treatment, and with which drug, need to take into account the likelihood of resistance and the inability to continue using the drug in the long term. This is particular importance for adefovir dipivoxil which, on the basis of current evidence, is one of the few options for pre- and post-liver transplant patients. The evidence suggests a much lower rate of resistance in adefovir dipivoxil than lamivudine (7% versus 56% after three years treatment), making it a more attractive option for long term use (although at increased cost). However, its longer term resistance profile remains to be established. Newer drugs may become available in the coming years, potentially extending the range of available treatments (see Section 9.3.3).

In contrast to the adefovir dipivoxil trials, studies of pegylated interferon alfa have evaluated relatively short term treatment (e.g. 24-48 weeks). This reflects clinical practice, which appears to favour the use of interferons in patients with CHB who are relatively healthy (i.e. before liver decompensation) and for a defined period (e.g. up to a year for HBeAg positive patients, or 2 years for HBeAg negative patients)[3].
In terms of durability of response after cessation of treatment, the results for pegylated interferon alfa were mixed. HBeAg seroconversion rates and ALT response rates increased in the 24 weeks between end of treatment and follow-up, but HBV DNA response rates declined. Data on durability of response after 24 weeks follow-up are not currently available, however, an individual patient data meta-analysis of relapse rates (defined as re-appearance of HBeAg in serum) following treatment with non-pegylated interferon alfa, lamivudine, and a combination of the two has been published[97]. Three year cumulative Kaplan-Meier relapse rates were 32%, 54% and 23% respectively. High pre-treatment HBV DNA, low ALT and male sex were independent predictive factors of post-treatment relapse. It could be assumed that relapse rates for pegylated interferon alfa would be similar, if not lower. Longer term data are therefore needed.

9.2 Cost-effectiveness

Our systematic review of cost-effectiveness studies of anti-viral treatments for chronic hepatitis B identified only one economic evaluation of the interventions within the scope of this appraisal. This was a conference abstract for an unpublished economic evaluation of adefovir dipivoxil. No published economic evaluations were found for pegylated interferon alfa. The drug manufacturers have conducted their own cost-effectiveness analyses in their submissions to NICE. They report that the interventions are cost-effective by conventional criteria.

In one of the submissions[36] the incremental cost-effectiveness ratio for pegylated interferon alfa compared to conventional interferon alfa for HBeAg positive patients was estimated as between £2,663 and £13,921 per QALY, depending on the duration of treatment and dosage of conventional interferon alfa. No comparison of pegylated interferon to conventional interferon for HBeAg negative patients was reported. However, compared to best supportive care the ICER was £1,467 and compared to four years of treatment with lamivudine the ICER was £1,886.

The incremental cost-effectiveness of adefovir dipivoxil ranged from £6,651 to £29,359 depending on whether adefovir was used as first or second line therapy[24]. This model did not include estimates of the cost-effectiveness of interferon alfa (either pegylated or non-pegylated) as the cohort of patients being considered were those who had previously failed or were unsuitable for interferon treatment. The lowest cost per QALY ratio was for a comparison of first-line lamivudine followed by second-line adefovir provided in patients with lamivudine resistance, against best supportive care. The ICER comparing this strategy against lamivudine alone was £9,201.

Our analysis estimated a cost per QALY of £5,994 for interferon alfa compared to a best supportive care for a cohort of CHB patients (including both patients with HBeAg positive and those with HBeAg negative disease). For pegylated interferon alfa compared to interferon alfa the ICER was £6,119. For lamivudine therapy the ICER, when compared to best supportive care, was £3,685 and for adefovir compared to lamivudine the ICER was £16,569. These average ratios across HBeAg positive and HBeAg negative patients hide some important differences. Generally, the ICER for interferon (pegylated or non-pegylated) was higher for HBeAg positive patients than for HBeAg negative patients, while the reverse was the case for lamivudine and adefovir. In each of the comparisons the lifetime costs associated with conventional interferon alfa and lamivudine treatment were similar, though they differ in estimated effectiveness and hence cost-effectiveness. In all the comparisons adefovir had the highest lifetime costs – approximately double those for the next most costly option – but consistently provided better outcomes in terms of QALYs.

We also modelled a set of sequential treatment strategies, whereby patients start on one treatment and those who fail to benefit move on to one of the other treatments. In each case, where active anti-viral treatment was provided, interferon alfa (non-pegylated or pegylated) was the first line treatment with either lamivudine or adefovir provided as second line. Incremental cost effectiveness ratios varied from £3,604 to £11,402.

Strategies including pegylated interferon alfa were more effective compared to strategies using non-pegylated interferon, but were also more costly – with ICERs of £4,500 - £6,800 per QALY. Strategies including adefovir were consistently associated with higher total costs, but were also associated with the largest health gains. The strategies were also evaluated separately for patients with HBeAg positive and HBeAg negative disease.

The results of the evaluation were robust to the majority of scenarios tested in the sensitivity analysis. Scenarios that produced large changes in cost-effectiveness estimated were:

- Variation in the probability of patients CHB and cirrhosis achieving HBeAg seroconversion, on treatment;
- Changing the discount rate from 6% for costs and 1.5% for outcomes to 3.5% for both;
- Changing assumptions regarding the durability of treatment response for patients with HBeAg negative disease;
- Changing assumptions regarding the effectiveness of long term adefovir treatment in promoting HBeAg seroconversion.

The results were relatively insensitive to changes in assumptions regarding the composition of the baseline cohort of treated patients, other than in age at start of treatment.

9.3 Assumptions, limitations and uncertainties

There are a number of assumptions, limitations and uncertainties in this assessment which we have endeavoured to account for.

9.3.1 Clinical effectiveness

One uncertainty is about current treatment practice and the likely place of the appraised interventions in routine practice. This has implications for the choice of comparators in the assessment of cost-effectiveness. Clinical experts consulted during the preparation of this report indicated that treatment practice varies between, and sometimes within, centres in England and Wales. For example, whilst interferon alfa (including pegylated interferon alfa) is currently a first line treatment in some areas, in others lamivudine is the first choice (despite EASL guidelines recommending first line interferon alfa). Expert opinion also suggests that adefovir dipivoxil would be used more, possibly as first line treatment, if it were less expensive. Whilst we have attempted to mirror clinical practice in our choice of strategies and comparators it is beyond the scope of the report to assess all possible scenarios. Clearly, existing clinical guidelines need to be updated in the light of this and other emerging evidence for clinical and cost-effectiveness[3].

It also needs to be acknowledged that the RCTs included in this report may not necessarily be generalisable to typical clinical populations in England and Wales. Clinical trials, particularly pivotal trials designed to support drug licence applications, often include highly selected patients and operate stringent inclusion criteria. Therefore, patients with serious illness and co-morbidities that might be seen in routine practice are often excluded. The patients in the clinical trials included here tended to be generally healthy (in spite of chronic infection). For example, patients with cirrhosis and decompensated liver disease tended to be excluded. However, withholding treatment in patients with advanced disease (including before and after liver transplant) would be unethical, making controlled trials problematic. These patients have been included in observational studies, the largest of which demonstrates clinically meaningful benefits associated with adefovir dipivoxil following resistance to lamivudine.

Another possible limitation is the inclusion of only fully published evidence in the assessment of clinical effectiveness. With the exception of a couple of pivotal trials which have yet to be fully published, unpublished literature was not included to support our primary assessment of effectiveness because it is unlikely to have undergone peer review. Its methodological quality cannot, therefore, be guaranteed. Furthermore, only randomised evidence was included as this was considered to be less susceptible to bias than non-randomised designs. Nevertheless, we have endeavoured to take the wider evidence base into consideration through discussing

observational unpublished evidence, where appropriate. Studies currently only reported in conference abstracts have been described, although we have not used their findings to support our primary analysis of effectiveness. Many of these abstracts presented preliminary findings at key international hepatology conferences such as the European Association for the Study of the Liver, and the American Association for the Study of the Liver. These are likely to be fully published in due course. (NB. The 2005 EASL conference took place during the completion of this report and proceedings are not included, other than data on the resistance profile of adefovir dipivoxil submitted in advance to NICE by the manufacturer).

Finally, even though published evidence will have been subjected to peer review it is still necessary to assess its methodological quality and to take into account its strengths and weaknesses. The published studies included in this review were of reasonable quality. However, reporting of procedures for randomisation and concealment of allocation were poor, making it hard to judge whether selection bias may be present. Further, the heterogeneous nature of the study comparisons, and patient groups prohibited quantitative synthesis through meta-analysis.

9.3.2 Cost effectiveness

Much of the supporting evidence incorporated into our economic model was derived from countries other than the UK. This issue is common to all the published economic evaluations of anti-viral interventions in chronic hepatitis B. Evidence on the composition of cohorts of patients with CHB presenting for treatment and on the natural history of the disease is relatively limited. Where possible, we have used published evidence that is relevant to a European setting. However, even within Europe it is possible that population differences may limit the generalisability of evidence to the UK. In general, the evidence that was applied for modelling disease progression and treatment effects in patients with HBeAg negative disease was more uncertain than that used for HBeAg positive disease since the latter group has been more extensively studied.

The treatment effects applied in the economic model were derived from multi-national, multi-centre trials which, generally, recruited the majority of patients from outside Europe. It is not clear whether differences in the response of different patient populations would have a substantial impact on the effectiveness of these interventions. There is some evidence of the effectiveness and durability of interventions for up to four years, but very little evidence to support extrapolations beyond this. Economic evaluations with a lifetime horizon need to make such projections and in this evaluation we have considered the impact of assumptions over long term effectiveness and durability of treatment during the sensitivity analysis. The evaluation has not explicitly addressed the issue of technological change, with new approaches to treatment (including combination therapies intended to address the risk of individuals developing drug resistance). There was insufficient long term evidence of efficacy to include these in the economic model. However, any analysis projecting outcomes over patients' lifetimes needs to consider how the development of new interventions and management strategies will impact the study findings.

The cost estimates used in the economic model are a combination of protocol-based costings developed for this study, for the chronic hepatitis B and HBeAg seroconverted health states, and patient-based costings reported in the literature. The latter costings were estimated for patients with progressive liver disease associated with chronic hepatitis C infection. We discussed with clinical advisors to the project the applicability of costs for hepatitis C. They indicated that management of patients with compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma was primarily driven by the clinical manifestations of these disease states and not the underlying cause of the liver disease. These data provide the advantage for this analysis that they are patient-based costings, providing estimates both of average and variation, but require the assumption that costs derived for one group of UK patients can be applied to CHB patients.

There is very little published evidence on which to base the utility values included in the analysis. Our review of the literature suggested that CHB had a lower impact on quality of life than chronic hepatitis C, without cirrhosis. For these states utilities based on valuations used in previous economic evaluations were adopted. However, for the more progressive stages of liver disease patient-derived valuations, from patients with chronic hepatitis C were used. The validity of applying these values to patients with chronic hepatitis B may be questioned. The utility value adopted for compensated cirrhosis was similar to that adopted for other recent economic evaluations of anti-viral treatment for chronic hepatitis B. However, the values used for decompensated cirrhosis and hepatocellular carcinoma were higher than those used in other most previous evaluations.

9.3.3 Research needs

Pegylated interferon alfa and adefovir dipivoxil are relatively new interventions in the treatment of hepatitis B and there are gaps in the evidence where further research would be helpful:

- There are limited data on the effectiveness of treating patient sub-groups, including those with different genotypes, patients with cirrhosis, and different ethnic groups. These patients are routinely encountered in clinical practice.
- Many patients with HBV are co-infected with HIV, HCV or other viral infections. The RCTs reported here exclude these patients, so randomised studies in these specific groups would be beneficial.
- Patients with co-morbidities such as renal problems were excluded from the RCTs discussed in this review. Further research in therefore needed.
- Further research is needed on treatment in children and adolescents, as they form a large patient group in some areas of the world. Previous trials have not included children, and the long-term safety of these treatments should be assessed in this patient group.
- The impact of anti-viral treatment on health related quality of life (HRQOL) requires evaluation. We did not identify any fully published studies of HRQOL of patients taking adefovir dipivoxil, and only limited, unpublished data on patients taking pegylated interferon alfa.
- There is a lack of published evidence on the effectiveness of pegylated interferon alfa in lamivudine non-responders, and in interferon alfa non-responders. The manufacturer reports that relevant studies are underway.

- More evidence of the effectiveness of adefovir dipivoxil in combination with lamivudine in patients not previously treated (as opposed to patients resistant to lamivudine) is required. A phase II RCT is in progress and fully published results are awaited.
- We did not identify any direct comparisons of between adefovir dipivoxil and pegylated interferon alfa. Clinical opinion solicited during the production of this report suggested that such a comparison is not necessarily clinically meaningful. However, such a study (where relevant to practice) would be beneficial for informing the assessment of the relative cost-effectiveness of these two drugs.
- There is emerging evidence for the effectiveness of pegylated interferon alfa 2b ('PegIntron', 'Viraferon Peg', Schering-Plough) as a treatment for chronic hepatitis B[136] (currently not licensed in the UK for hepatitis B). A recently published RCT reported that benefit, with HBV genotype an important predictor of treatment response.
- Newer drug treatments, such as entecavir and tenofovir, are not within the scope of this appraisal. Small, non-randomised studies have found that tenofovir disoproxil fumarate may be effective for the treatment of lamivudine-resistant HBV infection in HIV-co-infected patients[137;138]. Entecavir has been shown to be well tolerated, and has a similar safety profile to lamivudine. Ongoing studies of efficacy are in progress. Neither of these drugs are currently licensed for the treatment of hepatitis B in the UK, although a licence application has been lodged with the US Food and Drug Administration for entecavir.

Research in progress:
The following titles have been registered for future Cochrane reviews, although they are not yet available as protocols:

- Lamivudine and hepatitis B immune globulin for preventing hepatitis B recurrence after liver transplantation
- Adefovir dipivoxil for chronic hepatitis B
- Acupuncture for chronic hepatitis B virus infection

10 CONCLUSIONS

The conclusion of this systematic review and economic evaluation is that adefovir dipivoxil and pegylated interferon alfa are both clinically-effective and cost-effective in the treatment of chronic hepatitis B, in relation to current standard treatments and supportive care. The results of randomised controlled trials show that both drugs are associated with improvements on a number of short term biochemical, virological and histological outcomes in both HBeAg positive and negative patients. Despite the potential for relapse and drug resistance in a proportion of patients, it is generally thought that these short-term gains are associated with long-term health benefits through reduced rates of progression to cirrhosis, decompensated liver disease, and hepatocellular carcinoma. Furthermore, the severity and frequency of serious adverse events associated with treatment appeared to be relatively low.

There were no fully published cost-effectiveness evaluations of adefovir dipivoxil or pegylated interferon alfa. We therefore designed a state transition Markov model to inform our own cost-effectiveness assessment. The results of our base case analysis demonstrate that incremental costs per QALY for a range of comparisons were between £5,994 to £16,569, and within the range considered by NHS decision-makers to represent good value for money. Estimates generally remained below £30,000 when assumptions and input parameters were subjected to variation. The analysis of all scenarios suggests that interferon alfa (non-pegylated or pegylated) followed by lamivudine would be the optimal strategy at lower threshold values of willingness to pay. As the threshold increases the sequential treatment strategy of pegylated interferon alfa, followed by lamivudine with adefovir added as salvage therapy is increasingly likely to be the optimal intervention.

Policy makers need to view the evidence for clinical and cost-effectiveness within the wider context of hepatitis B, taking into consideration primary prevention, vaccination, screening and investigation, and the changing epidemiology of infection in England and Wales. A cohesive strategy for hepatitis B would appear to be necessary, which takes into account the evidence and policy issues relating to wider management.

The evidence base is generally robust, although there are deficiencies in methodological reporting. Further evidence on the clinical effectiveness of long-term treatment and follow-up is awaiting publication, and new drugs are currently undergoing evaluation in clinical trials. More evidence is required in patients with presenting with more advanced disease (e.g. cirrhosis, decompensation, and pre and post liver transplant) as well as sub-groups of patients, particularly those with co-infections and co-morbidities.

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Appendix 1 Glossary

Acute hepatitis B	defined by abrupt manifestations of hepatic injury that occur within 6 months of exposure to HBV and that resolve within 6 months after onset.
Alanine aminotransferase (ALT)	Alanine aminotransferase. An enzyme that indicates liver inflammation.
Antigen	Any substance that the body regards as foreign or potentially dangerous and against which it produces an antibody.
Anti-HBe	Anti-bodies to the HBeAg antigen
Anti-HBs	Anti-bodies to the HBsAg (surface) antigen
Ascites	Large accumulation of fluid in the cavity which surrounds the bowel
Biochemical Response	a fall in serum aminotransferase levels to the normal range
Chronic hepatitis B	Characterised by persistent hepatic inflammatory injury. HBsAg is present in serum and there is histological evidence of necro-inflammation or elevated serum aminotransferase levels that cannot be explained by another cause of liver injury.
Cirrhosis	A condition in which the liver responds to injury or death of some of its cells by producing interlacing stands of fibrous tissue between which are nodules or regenerating cells.
Compensated liver disease	Compensation is the act of making up for a functional or structural deficiency. For example, compensation for the loss of a diseased kidney is brought about by an increase in size of the remaining kidney, so restoring the urine producing capacity.
Complete response	Defined as the loss of HBsAg with the development of anti-HBs
Decompensated cirrhosis	A state where the liver can no longer compensate for the damaged (scarred) tissue.
Decompensated liver disease	Ascites, variceal haemorrhage and hepatic encephalopathy are complications that can follow decompensated liver disease
fibrosis	Thickening and scarring of connective tissue, most often a consequence of inflammation or injury
Flares	Characterised by a short-lived rise in levels of alanine aminotransferase liver enzyme, which is caused by the destruction of infected hepatocytes by the immune system. Flares often indicate that the body is attempting to clear the infection.
Fulminant hepatitis B	A severe form of acute hepatitis B that is complicated by encephalopathy in an individual with no pre-existing HBV infection.
HBeAg	The non-structural viral protein exported from infected cells in non-viral proteins while hepatitis B is actively replicating.
HBeAg-positive chronic hepatitis B	HBeAg and HBV DNA are present in serum, and anti-HBe is undetectable. Characterised by inflammation and fibrosis of the liver
HBeAg-negative chronic hepatitis B	Infection by an HBV variant that prevents or down regulates secretion of HBeAg in serum where it becomes undetectable; anti-HBe is detectable; HBV DNA is present in serum. Characterised by inflammation and fibrosis of the liver
HBeAg seroconversion	Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative.
HBeAg seroreversion	Re-acquisition of HBeAg and loss of anti-HBe in a person who had previously undergone HBeAg seroconversion.
HBIG	Hepatitis B immunoglobin
HBV related active liver disease	Defined by raised serum aminotransferase and/or histological evidence of liver inflammation that cannot be explained by another cause.
HBV mutant	a variant that develops under specific selection pressure and that has been shown to confer a specific phenotype
HBV variant	characterized by any naturally occurring variation from published wild-type

	sequences
High HBV endemicity	prevalence of chronic infection > 8%
Histological Response	a pre-determined decrease in histological activity score with no worsening in fibrosis
Icteric hepatitis	Icteric pertaining to jaundice
Inactive HBsAg carrier-state	HBsAg and anti-HBe are present in serum, but serum aminotransferase levels are persistently normal and there is little or no necro-inflammatory activity on liver biopsy; HBV DNA levels in serum are either low or undetectable.
Inactive liver disease	defined by normal serum aminotransferase levels and/or no histological evidence of inflammation
Interferon alfa	Naturally occurring protein in the body. There are several forms of interferon alfa. Unless otherwise stated it is used in this report to refer to interferon alfa.
Low HBV endemicity	prevalence of chronic infection < 1%
Occult HBV infection	characterized by undetectable serum HBsAg but detectable HBV DNA in serum or liver
Pre-core mutant HBV	a mutant strain of HBV that does not express HBeAg and which is particularly found in patients who have been infected since early childhood and who have been immmunotolerant for most of that time
Relapse	Patients who have shown evidence of having cleared the hepatitis B virus during treatment, but who did not maintain a sustained virological response, i.e., the virus became detectable again within the follow-up period.
Serum	the fluid that separates from clotted blood or blood plasma that is allowed to stand
Viraemia	the presence in the blood of virus
Virological response	HBV DNA levels falling below 10^5 copies/ml and undetectable HBeAg
Wild type HBV	'Wild type' refers to the typical form of an organism, strain, gene, or characteristic as it occurs in nature, as distinguished from mutant forms that may result from selective breeding. Wild type HBV is distinguished from pre-core mutant HBV.

Appendix 2 Clinical effectiveness search strategy

Search strategy for clinical effectiveness – Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B

Database: Ovid MEDLINE(R)

1 exp Hepatitis B/ or Hepatitis B, Chronic/
2 exp Hepatitis B Virus/ or exp Hepatitis B Antibodies/
3 (hbv or hepatitis-B or hepatitis B or HBeAg negative or HBeAg positive or HBsAG).mp.
4 1 or 2 or 3
5 ((pegylat$ adj3 interferon$) or peg-ifn or peginterferon$ or peg-interferon$ or pegasys or pegintron or viraferonpeg).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6 (interferon alpha 2a or interferon alfa 2a or interferon alpha 2b or interferon alfa 2b or alpha interferon or intron$ or viraferon or roferon).mp.
7 exp interferon-alpha/
8 6 or 7
9 exp Polyethylene Glycols/
10 polyethylene glycol$.mp. or peg$.tw. [mp=title, original title, abstract, name of substance, mesh subject heading]
11 9 or 10
12 8 and 11
13 5 or 12
14 13 and 4
15 limit 14 to english language
16 (adefovir dipivoxil or adefovir$ or hepsera).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
17 16 and 4
18 17
19 limit 18 to english language

Appendix 3 Cost effectiveness and Quality of Life search strategies

Cost effectiveness

Database: Ovid MEDLINE(R)

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1 exp Hepatitis B/ or Hepatitis B, Chronic/
2 exp Hepatitis B Virus/ or exp Hepatitis B Antibodies/
3 (hbv or hepatitis-B or hepatitis B or HBeAg negative or HBeAg positive or HBsAG).mp.
4 1 or 2 or 3
5 ((pegylat$ adj3 interferon$) or peg-ifn or peginterferon$ or peg-interferon$ or pegasys or pegintron or viraferonpeg).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6 (interferon alpha 2a or interferon alfa 2a or interferon alpha 2b or interferon alfa 2b or alpha interferon or intron$ or viraferon or roferon).mp.
7 exp interferon-alpha/
8 6 or 7
9 exp Polyethylene Glycols/
10 polyethylene glycol$.mp. or peg$.tw. [mp=title, original title, abstract, name of substance, mesh subject heading]
11 9 or 10
12 8 and 11
13 5 or 12
14 13 and 4
15 limit 14 to english language
16 (adefovir dipivoxil or adefovir$ or hepsera).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
17 16 and 4
18 17
19 limit 18 to english language
20 exp ECONOMICS/
21 exp ECONOMICS, HOSPITAL/
22 exp ECONOMICS, PHARMACEUTICAL/
23 exp ECONOMICS, NURSING/
24 exp ECONOMICS, DENTAL/
25 exp ECONOMICS, MEDICAL/
26 exp "Costs and Cost Analysis"/
27 Cost-Benefit Analysis/
28 VALUE OF LIFE/
29 exp MODELS, ECONOMIC/
30 exp FEES/ and CHARGES/
31 exp BUDGETS/
32 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw.
33 (cost$ or costly or costing$ or costed).tw.
34 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw.
35 (expenditure$ not energy).tw.
36 (value adj2 (money or monetary)).tw.
37 budget$.tw.
38 (economic adj2 burden).tw.
39 "resource use".ti,ab.
40 or/20-38
41 news.pt.
42 letter.pt.
43 editorial.pt.
44 comment.pt.
45 or/41-44
46 40 not 45
47 46 and 4
48 46 and 15
49 46 and 19

50 47
51 limit 50 to english language
52 limit 51 to yr=1980 - 2004

Quality of Life

Database: Ovid MEDLINE(R)

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1 value of life/
2 quality adjusted life year/
3 quality adjusted life.ti,ab.
4 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
5 disability adjusted life.ti,ab.
6 daly$.ti,ab.
7 health status indicators/
8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.
13 (euroqol or euro qol or eq5d or eq 5d).ti,ab.
14 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
15 (hye or hyes).ti,ab.
16 health$ year$ equivalent$.ti,ab.
17 health utilit$.ab.
18 (hui or hui1 or hui2 or hui3).ti,ab.
19 disutil$.ti,ab.
20 rosser.ti,ab.
21 quality of well being.ti,ab.
22 quality of wellbeing.ti,ab.
23 qwb.ti,ab.
24 willingness to pay.ti,ab.
25 standard gamble$.ti,ab.
26 time trade off.ti,ab.
27 time tradeoff.ti,ab.
28 tto.ti,ab.
29 (index adj2 well being).mp.
30 (quality adj2 well being).mp.
31 (health adj3 utilit$ ind$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
32 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
33 quality adjusted life year$.mp.
34 (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
35 (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
36 rating scale$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
37 linear scal$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
38 linear analog$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
39 visual analog$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
40 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]

41 or/1-40
42 (letter or editorial or comment).pt.
43 41 not 42
44 exp Hepatitis B/ or Hepatitis B, Chronic/
45 exp Hepatitis B Virus/ or exp Hepatitis B Antibodies/
46 (hbv or hepatitis-B or hepatitis B or HBeAg negative or HBeAg positive or HBsAG).mp.
47 44 or 45 or 46
48 43 and 47
49 limit 48 to english language

Appendix 4 Epidemiology search strategy

Epidemiology
Database: Ovid MEDLINE(R)
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1 *EPIDEMIOLOGY/
2 *INCIDENCE/
3 *PREVALENCE/
4 incidence.ti.
5 prevalence.ti.
6 epidemiol$.ti.
7 (etiolog$ or aetiolog$).ti.
8 or/1-7
9 exp *Hepatitis B/ (21933)
10 8 and 9
11 limit 10 to (human and english language)
12 limit 11 to yr=1995 - 2004

Appendix 5 Inclusion worksheet

Trial Name or Number:				
Patients with **chronic Hepatitis B**? (treatment naïve, relapsed, or not responded to previous treatment regardless of source of infection or severity) Patients may be co-infected	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	Type:
Pegylated interferon alfa treatment or **adefovir dipivoxil** treatment programme?	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Design: fully published RCT or systematic review (any conference abstracts identified will have a note made of their content, but they will not be included in the review).	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Report one or more of **primary outcomes**: **short term outcomes:** biochemical, histological and virological response to treatment; long term outcomes: survival, progression to advanced disease states (e.g. cirrhosis), quality of life	Yes ↓ next question	Unclear ↓ next question	No → EXCLUDE	
Final Decision	**INCLUDE**	**UNCLEAR (Discuss)**	**EXCLUDE**	**Results of Discussion:**

Appendix 6 Data extraction – Cooksley et al.

Extracted by: JS		Date: 22/1/05	
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Cooksley *et al.* (2003) Multi-centre trial (n=18) Phase II RCT Open label Australia; New Zealand; Taiwan; Thailand; China Funding: Not stated	<u>Group A:</u> n = 51 IFN ά 2a 4.5 MIU 3 x wk 24 weeks <u>Group B:</u> n = 49 PEG ά 2a 90 µg: once weekly 24 weeks <u>Group C:</u> n = 46 PEG ά 2a 180 µg: once weekly 24 weeks <u>Group D:</u> n = 48 PEG ά 2a 270 µg: once weekly 24 weeks	HBeAg status: positive Total randomised: 194 Inclusion criteria: • HBsAg + ve > 6 months • HBeAg + ve • HBV DNA > 500, 000 copies • ALT 2-10 times ULN • Biopsy demonstrating CHB liver disease Exclusion criteria: • Not previously treated with interferon alfa • nucleoside or nucleotide analogue (e.g. lamivudine, lobucavir and adefovir dipivoxil) use for longer than 6 months and/or within 6 months of study entry; • other systemic antiviral therapy; • positive test at screening for anti-HAV IgM, HCV RNA or anti-HCV, anti-HDV or anti-HIV; • an increased risk of metabolic liver disease; • decompensated liver disease (Child-Pugh grades B–C); • a medical condition associated with chronic liver disease other than viral hepatitis; • pregnancy or breast-feeding; neutrophil count <1500 cells/mL or platelet count <90 000 cells/mL; • serum creatinine level >1.5 ULN; • serum a-fetoprotein levels >100 ng/mL, unless stability over time had been documented; • alcohol and/or drug abuse within 1 year of entry; • history of severe psychiatric disease or immunologically mediated disease; bleeding from oesophageal varices or other conditions consistent with decompensated liver disease; • severe cardiac or chronic pulmonary disease; • severe seizure disorder or current anticonvulsant use; active or suspected cancer or a history of malignancy where the risk • of recurrence is ‡20% within 2 years; • history of anti-neoplastic or immunomodulatory treatment including systemic corticosteroids; • major organ transplantation; • thyroid disease; • severe retinopathy and a history of other severe • illnesses or conditions. Sex: 74% male Age (mean & range): mean age across groups 29-32 (range 18-69)	• loss of HBeAg • suppression of HBV DNA levels to <500 000 • copies/mL • normalization of ALT, seroconversion to anti-HBe, • loss of HBsAg, • combined response of HBeAg loss, HBV DNA suppression, and ALT normalisation. Length of follow up: 24 weeks

		Ethnic groups: 97% Asian Compliance: 95% of patients completed 24 weeks treatment Baseline measurements: Log10 HBeAg (PEIU/mL); mean (SE) • Group A = 2.57 (0.19) • Group B = 2.64 (0.18) • Group C = 2.67 (0.19) • Group D = 2.80 (0.17) ALT (U/L); mean (SE) • Group A = 114.5 (9.8) • Group B = 157.9 (18.7) • Group C = 134.8 (16.7) • Group D = 125.3 (15.5) Log10 HBV DNA (copies/mL); mean (SE) • Group A = 9.29 (0.19) • Group B = 9.23 (0.25) • Group C = 9.25 (0.19) • Group D = 9.44 (0.16) Cirrhosis or transition to cirrhosis: 9% Genotype B = 33% Genotype C = 67% Previous anti-viral treatment: not reported	

Outcomes	**Group A**	**Group B**	**Group C**	**Group D**	**All Peg doses**	**Equality of 4 doses p value**	**All Peg vs IFN p value**
HBV DNA suppression (<500,000 copies) at follow-up n (%) [95% CI (%, %)]	13 (25) [14, 40]	21 (43) [29, 58]	18 (39) [25, 55]	13 (27) [15, 42]	52 (36)	0.096	0.085
HBeAg loss n (%) [95% CI (%, %)]	13 (25) [14, 40]	18 (37) [23, 52]	16 (35) [21, 50]	14 (29) [17, 44]	48 (34)	0.295	0.127
Seroconversion n (%) [95% CI (%, %)]	13 (25) [14, 40]	18 (37) [23, 52]	15 (33) [20, 48]	13 (27) [15, 42]	46 (32)	0.428	0.185
ALT normalisation n (%) [95% CI (%, %)]	13 (25) [14, 40]	21 (43) [29, 58]	16 (35) [21, 50]	15 (31) [19, 46]	52 (36)	0.290	0.153
Combined response n (%) [95% CI (%, %)]	6 (12) [5, 24]	13 (27) [15, 41]	13 (28) [16, 44]	9 (19) [9, 33]	35 (24)	0.088	0.036

Adverse Events	**Group A (n=50)**	**Group B (n=48)**	**Group C (n=45)**	**Group D (n=48)**

Pyrexia	72	52	58	71
Myalgia	42	38	36	46
Fatigue	28	29	22	27
Headache	26	46	38	46
Alopecia	24	17	33	44
Anorexia	20	8	18	19
Insomnia	16	17	20	10
Dizziness	10	19	16	15
Diarrhoea	8	8	18	17
Nausea	8	10	18	15
Upper respiratory infection	8	23	13	8
Cough	6	15	7	8

- The proportion of patients who prematurely discontinued study medication for safety reasons was comparable in the PEG and IFN groups (2% and 4% respectively).
- More patients in the PEG groups required dose modification for laboratory abnormalities than those in the IFN group (22-30% vs 10%). Neutropaenia and elevated ALT values were the most common reasons for dose modification.
- Thirteen serious adverse events were reported in 12 patients (2 in the IFN group, and 1, 4 and 5 in the 90-, 180- and 270 µg PEG groups respectively).
- Three serious adverse events (thyroid nodule, sepsis, anaphylactic shock) were considered to be related to study medication.
- Treatment discontinued prematurely because of a serious adverse event in two patients (1 each of 180 and 270ug PEG)
- The most common serious adverse events were gastrointestinal disorders and infections.

Additional Results

- Hepatitis B virus DNA levels dropped rapidly in all PEG groups, approximately 1.5 $\log_{10}$ copies/mL during weeks 1 through 4, compared with 0.76 $\log_{10}$ copies/mL in the IFN group.
- The greatest drop in mean $\log_{10}$ HBV DNA from baseline to end of treatment was 3.5 $\log_{10}$ copies/mL with PEG 180 µg compared with 2.2 $\log_{10}$ copies/mL with IFN. Reductions for the other two PEG groups (as read-off from the graph) were approximately 2.83 for PEG 90 µg/wk and 3.14 for PEG 270 µg/wk.
- A rapid reduction in HBeAg was observed with all dosages of PEG with median HBeAg approaching zero within the first 4 weeks. These reductions remained stable throughout the 24 week treatment period.
- Two patients on PEG cleared HBsAg during the course of the study. Both cleared HBsAg at week 24 and remained negative at the end of follow-up.
- For 13 patients with cirrhosis or transition to cirrhosis treated with Peg: 7 (54%) lost HBeAg and seroconverted; 6 (46%) had an undetectable HBV DNA; 5 (38%) normalised ALT. Of 4 patients treated with IFN, none had a response in any of the outcome measures at the end of follow-up.
- Among patients with baseline ALT levels < twice ULN a combined response was observed in 6 of 22 patients (27%) treated with PEG. Only 1 of the 9 patients (11%) treated with IFN responded.
- HBeAg loss was higher with PEG than with IFN regardless of baseline HBV DNA: in the group with HBV DNA 5.0-8.49 $\log_{10}$ copies/mL, 56 and 38% respectively. In the group with baseline HBV DNA of 8.50-10.99 $\log_{10}$ copies/mL, 36% and 24% respectively; and in the group of patients with HBV DNA titers >11.0 $\log_{10}$ copies/mL, 20 and 0% respectively (significance values not reported).
- Of note is the greater than twofold difference in combined response rates seen with the 90 µg and180 µg PEG doses (27% and 28% respectively) compared with that of IFN (12%).
- Response rates were significantly higher in patients with genotype B than C. Combined response rates were 31% in patients with genotype B, compared with 17.5% in those with genotype C ($p<0.05$).
- For both genotypes, combined response rates were higher in patients treated with PEG (33% for genotype B and 21% for genotype C) compared with IFN (25% and 6% for Genotype B and C, respectively).

Methodological comments

- *Allocation to treatment groups:* Random, no further information given.
- *Blinding:* Open label.
- *Comparability of treatment groups:* Authors report that all four treatment groups were comparable with respect to baseline demographics and disease characteristics. Table 1 on page 300 provides these data, although no significance values are provided.
- *Method of data analysis:* An intention-to-treat analysis was undertaken on the 194 individuals randomised. For the safety analysis the number analysed was 191 (Three patients [one each randomized to IFN and 90 µg and 180 µg doses of PEG did not receive study drug because of pregnancy, jaundice, and treatment with lamivudine within 6 months of study entry, respectively). Response rates and corresponding 95% confidence intervals for the efficacy end points were computed and multiple logistic regression was used to test differences between treatment arms.
- *Sample size/power calculation: "*The sample size provided sufficient power only to detect considerable differences in response rates, such as an increase in response between doses of ≥ 15% for the dose-response relationship. The power of the study was improved by combining treatment arms".
- *Attrition/drop-out:* 95% of patients completed the 24 weeks of treatment and 97% of all patients completed the 24 weeks follow-up. Twenty two patients on PEG and 9 patients on IFN with screening ALT >2 x ULN but whose baseline ALT levels had fallen below 2 x ULN remained in the study.

General comments

- *Generalisability:* inclusion/exclusion criteria adequately defined.
- *Outcome measures:* appear to be clinically relevant.
- *Inter-centre variability:* not reported.
- *Conflict of interests:* none reported.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unclear – no details provided on randomisation method
2. Was the treatment allocation concealed?	Unclear
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	N/A
6. Was the care provider blinded?	N/A
7. Was the patient blinded?	N/A
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Adequate
10. Were losses to follow-up completely described?	Partial

N/A = Not applicable, since the trial was reported to be open label

Appendix 7 Data extraction – Hadziyannis et al. (study 438)

Extracted by: AT Date: 10/11/04 Checked by JS Updated 7/01/05

Reference and Design	Intervention	Participants	Outcome measures
Hadziyannis, 2003, ref id 144: Trial design: multicentre RCT Number of centres: 32 Country: Greece (also Canada, Israel, France, Italy, Austria, Taiwan and Singapore) Funding: Gilead Sciences	<u>Group A:</u> n = 123 Drug 1: adefovir dipivoxil (ADV) Dose: 10mg/day Duration: 48 weeks *Ongoing phase:* *Drug 2: ADV or placebo (random reassignment)* *Dose:* *Duration:* <u>Group B:</u> n = 62 Drug 1: placebo Dose: Duration: 48 weeks *Ongoing phase:* *Drug 2: ADV* *Dose:* *Duration:*	HBeAg status: negative Total randomised: 185 N in each group: (2:1 ratio): A: n=123, B:n=62* * one patient never received treatment and was excluded from all analyses. Inclusion/exclusion criteria: Inclusion: • aged 16-65 with HBeAg-negative chronic hepatitis B and compensated liver disease (CHB defined by the presence of detectable HBsAg for at least 6 months, undetectable HBeAg, detectable anti-HBe, a serum HBV DNA level of at least 10^5 copies per mm, and an ALT level between 1.5 and 15 times the upper limit of the normal range. • Patients had to have a total bilirubin level of no more than 2.5mg/dl, a prothrombin time that was no more than 1s above the normal range, a serum albumin level that was at least 3g/dl, a serum creatinine level of no more than 1.5mg/d, and an adequate blood count. Exclusion: • a coexisting serious medical or psychiatric illness; • immune globulin, interferon alfa or other immune- or cytokine-based therapies with possible activity against HBV disease within 6 months before screening; • recent treatment with systemic corticosteroids, immunosuppressants or chemotherapeutic agents; • a serum alpha-fetoprotein level of at least 50ng/ml; • evidence of a hepatic mass; • liver disease that was not due to hep B; • prior therapy for more than 12 weeks with a nucleoside or nucleotide analogue with activity against HBV; • seropositivity for HIV, HCV or HDV. Baseline measurements: characteristic / A (n=123) / B (n=61) Age (yr) mean ± SD (range) / 46±9.8 (18-65) / 45±10.4 (22-65) no (%) male / 102(83) / 50(82) race no (%) white / 82(67) / 40(66) black / 5(4) / 1(2) Asian / 36(29) / 20(33) weight (kg) mean± SD (range) / 75±11.5 (50-111) / 73±15.4 (46-135) ALT mean±SD - U/Litre / 143.5±125.3 / 149.9±195.2 median - U/Litre / 93 / 100 Range - U/Litre / 24-742 / 29-1459 ≤ ULN - no.(%) / 7(6) / 2(3) > ULN - no.(%) / 116(94) / 59(97) Multiples of ULN mean ±SD / 3.5±3.0 / 3.6±4.5	Primary outcomes: histologic improvement, defined as a reduction of at least 2 points in the Knodell necroinflammatory score, with no concurrent worsening of the Knodell fibrosis score; ranked assessments of necroinflammatory activity and fibrosis (improved, no change or worse). Secondary outcomes: change from baseline in serum HBV DNA levels, ALT levels and proportion of patients with HBsAg seroconversion; adverse events Length of follow up: Results are reported at week 48, but the study is ongoing and will continue for up to 5 years.

		median	2.3	2.4	
		range	0.7-17.3	0.7-33.9	
		HBV DNA - log copies/ml*			
		Mean±SD	6.9±3.3	6.0±1.0	
		Median	7.1	7.1	
		Range	3.67-9.46	4.42-8.45	
		Knodell score			
		Total			
		Mean±SD	9.6±3.3	8.9±3.4	
		median	10	9	
		range	2-17	2-16	
		Necroinflammatory activity			
		Mean±SD	7.7±2.7	7.1±2.7	
		median	8	7	
		range	1-14	1-12	
		Fibrosis			
		Mean±SD	1.9±1.2	1.8±1.1	
		median	1	1	
		range	0-4	1-4	
		cirrhosis - no.(%)	14(11)	6(10)	
		Prior HBV medications - no. (%)†			
		Interferon alfa	48(39)	28(46)	
		Lamivudine	10(8)	4(7)	
		Famciclovir	7(6)	7(11)	
		* values were log-transformed with use of a base 10 scale. † some pts had received more than one type of medication. ULN = upper limit of the normal range. Losses to follow up: 1 placebo pt dropped out before receiving any drug and was excluded from analysis. Another is said to have dropped out after HIV infection was diagnosed. No other drop outs are mentioned. Compliance: not reported Patient characteristics, e.g. carriers, those with liver disease, genotype etc. No further details given			

Outcome	Group A (ADV) (n=117)	Group B (placebo) (n=55)	Difference
HBV DNA mean change from baseline at week 48 (log copies per ml)	3.91	1.35	p<0.001
n (%) with undetectable HBV DNA levels	63/123 (51)	0/61(0)	p<0.001
Comments: Graphs in Fig 2 show changes through time at 4-weekly intervals, but not data extracted at this stage as treatment end points already taken from tables.			
ALT at 48 weeks	n=116	n=59	
n(%) with normalized ALT levels	84(72)	17(29)	p<0.001
median decrease from baseline (U per litre)	55	38	p=0.01
Comments:			
Other Viral Response outcomes			

Histology (proportion with improvement, defined by a reduction of at least 2 points in Knodell necroinflammatory score, with no worsening of fibrosis)	(n=121) 77 (64%)	(n=57) 19 (33%)	p<0.001; absolute difference (95% CI) 30.0% (15.4 to 45.2).
Change in total Knodell score Mean±SD Median Range	(n=112) -3.7±3.1 -4 -11 to 2	(n=55) 0.4±3.7 1 -9 to 8	p<0.001
Change in Knodell necroinflammatory score Mean±SD Median Range	(n=112) -3.4±2.9 -3 -9 to 2	(n=55) 0.3±3.2 0 -7 to 8	p<0.001
Change in Knodell fibrosis score at week 48 Mean±SD Median Range	(n=112) -0.3±0.7 0 -3 to 1	(n=55) 0.1±0.9 0 -2 to 2	p=0.005
Ranked assessment (%) Necroinflammatory activity Worse No Change Improved Fibrosis Worse No Change Improved	 3 17 80 4 47 48	 51 7 42 38 36 25	not reported
Comments: Primary analysis based on 178 pts (97%) with assessable base-line liver-biopsy specimens. 167 (91%) had assessable pre-treatment and post-treatment liver-biopsy specimens. P values were calculated with the Wilcoxon rank-sum test.			
Adverse Events (AE) dose discontinuation for any AE dose reduction for any AE Severe (grade 3 or 4) AE n(%) Serious AE AE n(%): any AE headache pharyngitis abdominal pain asthemia influenza-like syndrome back pain pain increased cough insomnia dyspepsia rhinitis	n=123 0 0 7(6) 4* (7) 94(76) 29(24) 23(19) 18(15) 16(13) 13(11) 12(10) 10(8) 10(8) 6(5) 6(5) 6(5)	n=61 0 0 6(10) 4* * (3) 45(74) 10(16) 14(23) 3(5) 10(16) 13(21) 4(7) 6(10) 4(7) 4(7) 2(3) 1(2)	
Comments: * hip abscess, transient ischemic attack, acute hepatitis, sialadenitis. ** perianal abscess, pain after liver biopsy, dengue fever, renal colic None of the serious AE were considered to be related to treatment.			
Additional outcomes Resistance: The polymerase–reverse-transcriptase domain of the HBV polymerase gene was sequenced from serum samples obtained at base line and week 48 from 117 patients with detectable serum HBV DNA levels. 4 different novel substitutions occurred at conserved sites in the HBV polymerase in 3 patients, all of whom were in Group B (placebo). In vitro phenotypic analyses showed that viruses with the mutations remained fully susceptible to adefovir dipivoxil.			

Methodological comments

- *Allocation to treatment groups:* Patients assigned to ADV or placebo in a 2:1 ratio. Central randomisation was stratified according to 5 geographic regions. Permuted blocks (with a block size of 6) were used in each stratum. At week 48, treatment patients were randomly assigned to receive either continuing treatment or placebo for the remainder of the study, and placebo participants were reassigned to treatment. This part of the study is ongoing and remains blinded.
- *Blinding: (for patients, health workers and study personnel, and method)* Clinical data were collected, monitored and entered into a database by a contract research organisation. Lab tests were conducted by Covance, and the sponsor held the data and conducted the statistical analyses. Knodell scores were assessed by an independent histopathologist who was unaware of the patients' treatment assignments and the timing of liver biopsy'.
- *Comparability of treatment groups: (any differences in baseline characteristics of patients and controls?)* no significant differences are reported between groups' baseline values.
- *Method of data analysis: (ITT, point estimates given? confidence intervals given?)* 'Statistical analyses included all patients who received at least one dose of study drug'. The analysis of histologic end points included a subgroup of this population that had an assessable base-line biopsy specimen. Total n varies for each outcome measure, so true ITT not performed. An unstratified Cochran-Mantel-Haenszel test was used for the primary efficacy end point, conducted as a nominal two-sided α level of 0.05. All confidence intervals, significance tests and resulting P values were 2-sided, with an α level of 0.05. Standard deviations are given for all mean values.
- *Sample size/power calculation:* The study was designed to enrol 180 patients and to have at least 90% power to detect an absolute difference of 30% between groups (60% vs. 30%) with respect to the primary end point, assuming that 25% of patients would have missing biopsy specimens at week 48 or base-line Knodell scores of less than 2 and would therefore be counted as having no response and that 8% would have missing biopsy specimens at base-line and would thus be excluded from the primary efficacy analysis.
- *Attrition/drop-out:* 1 placebo pt dropped out before receiving any drug and was excluded from analysis. Another is said to have dropped out after HIV infection was diagnosed. No other drop outs are mentioned.

General comments

- *Generalisability:* Male and female patients 16-65 years of age who had HBeAg-negative chronic hepatitis B and compensated liver disease were eligible.
- inclusion/exclusion criteria are clearly defined above
- *Outcome measures:* appropriate outcome measures are used
- *Inter-centre variability:* Not assessed
- *Conflict of interests:* Supported by Gilead Sciences
- No data provided for patient sub-groups e.g. genotype, ethnicity, gender.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown§
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Adequate
7. Was the patient blinded?	Partial*
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Inadequate**
10. Were losses to follow-up completely described?	Partial

§ paper doesn't report actual method of randomisation
* just 'double blind' in text and no further description of procedures or nature of the placebo
** as not all outcomes were reported for all patients

Appendix 8 Data extraction – Marcellin et al. (study 437)

Extracted by: ST checked by AT Date: 24 Jan 2005

Reference and Design	Intervention	Participants	Outcome measures
Marcellin, 2003, ref id 143 Trial design: Double blind RCT Number of centres: 78 Country: North America, Europe, Australia, Southeast Asia Funding: Supported by Gilead Sciences	<u>Group A:</u> n = 172 ADV Dose: 10mg/d Duration: 48 weeks <u>Group B:</u> n = 173 ADV Dose: 30mg/d Duration: 48 weeks <u>Group C:</u> n = 170 Placebo Duration: 48 weeks (n=numbers randomised. Numbers analysed vary – see results)	HBeAg status: positive Total randomised: 515 N in each group: Group A (10mg ADV) Randomised: n=172; 1 took no study medication leaving n=171; Baseline biopsy available for: n-168 Group B (30mg ADV) Randomised: n=173 Baseline biopsy available for n=165 Group C (placebo) Randomised n=170; 3 took no study medication leaving n=167; Baseline biopsy available for n=161 Inclusion Criteria: • Male & Female patients 16 to 65yrs; (Note baseline characteristics list age range as 16 to 68yrs) • Hepatitis Be antigen-positive chronic hepatitis B and compensated liver disease (parameters defined); • Women eligible if negative pregnancy test and using effective contraception. Exclusion criteria: • Co-existing serious medical or psychiatric illness; • Immune globulin, interferon alfa or other immune or cytokine based therapies with possible activity against HBV disease within 6 mths before screening; • Organ or bone marrow transplantation; • Recent treatment with systemiccorticosteroids, immunosuppressants, or chemotherapeutic agents; • Serum alpha—fetoprotein level of ≥50ng/millilitre; • Evidence of hepatic mass; • Liver disease not due to Hep B; • Prior therapy >12 weeks with nucleoside or nucleotide analogue with activity against HBV; • Seropositivity for HIV or Hep C or D virus Baseline measurements: Formatted Table	Primary outcomes used:Histologic improvement, defined as: Reduction of ≥ 2 points in Knodell necroinflammatory sore with no concurrent worsening of Knodell fibrosis score 48 wks from baseline. Secondary outcomes used: • Change from baseline in serum HBV DNA levels; • Proportion of patients with undetectable levels of HBV DNA; • Effect of treatment on alanine aminotransferase level; • Proportion of patients with loss or seroconversion of HBeAg. Length of follow up: 48 weeks

	Placebo (n=167)	10mg ADV (n=171)	30mg ADB (n=173)
Age – yr Median (range)	35 (16 to 66)	32 (16 to 65)	32 (17 to 68)
Male sex n(%)	119 (71)	130 (76)	129 (75)
Race n(%)			

			White Black Asian Other	60 (36) 3 (2) 101 (60) 3 (2)	60 (35) 8 (3) 102 (60) 1 (1)	64 (37) 5 (3) 101 (58) 3 (2)
			Alanine aminotransferase Mean ±SD u/litre Median U/litre ≤ULN n(%) >ULN n(%) Multiples of ULN Mean ±SD Median	 139±131 94 3 (2) 164 (98) 3.4±3.1 2.4	 139±154 95 3 (2) 168 (98) 3.4±4.0 2.3	 124±9.6 92 4 (2) 169 (98) 3.0±2.3 2.3
			HBV DNA – log copies/ml* Mean±SD Median	 8.12±0.8 8.33	 8.25±0.9 8.40	 8.22±0.84 8.34
			Total Knodell score Mean±SD Median (Range)	 9.65±3.45 10 (1-17)	 9.01±3.33 9.5 (0-17)	 9.55±3.33 10 (0-16)
			Knodell Necroinflammatory score Mean ±SD Median (Range)	 7.83±2.89 8 (1-14)	 7.37±2.75 7 (0-14)	 7.84±2.82 8 (0-12)
			Knodell Fibrosis score Mean±SD Median (range)	 1.83±1.12 1 (0-4)	 1.64±1.09 1 (0-4)	 1.71±1.06 1 (0-4)
			*Values were log-transformed with use of a base 10 scale. Compliance: Not reported Treatment history subjects were excluded if on interferon alfa or other drugs with possible activity against HBV disease <6mths before screening, but study states 123 (24%) had received treatment with interferon alfa. Patient characteristics: All with compensated liver disease			

Outcome				
HBV DNA change from baseline -log copies/ml Results at 48 wks	Placebo (n=167)	10mg ADV (n=171)	30mg ADV (n=173)	
Mean±SD	-0.98±1.32	-3.57±1.64	-4.45±1.62	
Median	-0.55	-3.52	-4.76	
95% CI	-1.20 to –0.77	-3.84 to –3.31	-4.72 to -4.19	
P value		<0.001	<0.001	
Comments: (Figure 1 shows mean change from Baseline in Serum levels of HBV DNA per week. Data not extracted).				
Serum HBV DNA<400 copies/ml Results at 48wks	Placebo (n=167)	10mg ADV (n=171)	30mg ADV (n=173)	
N (%)	0	36 (21)	67 (39)	
P Value		<0.001	<0.001	
Comments:				

HBeAg seroconversion Results at 48 wks	Placebo (n=167)	10mg ADV (n=171)	30mg ADV n=173	
N/Total N (%)	9/161 (6)	20/171 (12)	23/165 (14)	
P Value		<0.049	<0.011	
Comments: Note: seroconversion defined as loss of HBeAg and concurrent gain of antibody against HBeAg at 48 weeks.				
HBeAg Loss Results at 48 wks	Placebo (n=167)	10mg ADV (n=171)	30mg ADV (n=173)	
N/Total N (%)	17/161 (11)	41/171 (24)	44/165 (27)	
P Value		<0.001	<0.001	
Comments: Note: Patients positive for HBeAg at baseline were included in the analysis.				
Change in ALT - IU/Litre (at 48wks)	Placebo (n=167)	10mg ADV (n=171)	30mg ADV (n=173)	
Mean ±SD	-23±140.7	-92.1±167.2	-74.4±128.4	
Median	-17	-51	-54	
95% CI	-45.9 to –0.2	-118.8 to –65.3	-95.6 to –53.3	
P Value		<0.001	<0.001	
Comments:				
Normalisation of ALT At 48 wks	Placebo (n=167)	10mg ADV (n=171)	30mg ADV (n=173)	
N/total n (%)	26/164 (16)	81/168 (48)	93/169 (55)	
P Value		<0.001	<0.001	
Comments: Patients with base-line ALT levels that exceeded the upper limit of the normal range were included in the analysis.				
Other Viral Response outcomes Number of patients*	Placebo (N=161)	10mg ADB (n=168)	30mg ADV (n=165)	

(All figures are at 48 wks)			
Histologic improvement n(%)	41 (25)	89 (53)	98 (59)
No improvement n(%)	105 (65)	61 (36)	47 (28)
Unstratified relative risk		2.1	2.3
95% CI		1.5 to 2.8	1.7 to 3.1
P Value		<0.001	<0.001
Stratum-adjusted relative risk		2.1	2.3
95% CI		1.6 to 2.8	1.7 to 3.1
P Value		<0.001	<0.001
Necroinflammatory activity			
Knodell Score (n of patients)**	146	150	145
Mean ±SD change in score	-0.16±3.06	-2.58±3.22	-3.17±3.30
Median change in score	0	-2	-3
Range of scores	-10 to 7	-9 to 6	-9 to 5
P Value[a]		<0.001	<0.001
Ranked Assessment (n of patients)**	145	150	145
Improved n(%)	59 (41)	107 (71)	112 (77)
No change n (%)	37 (26)	23 (15)	18 (12)
Worse n(%)	49 (34)	20 (13)	15 (10)
P Value[a]		<0.001	<0.001
Fibrosis			
Knodell Score (n of patients)**	146	150	145
Mean±SD change in score	-0.01±0.86	-0.18±0.84	-0.32±0.80
Median change in score	0	0	0
Range of scores	-3 to 2	-2 to 2	-2 to 2
P value[a]		0.061	0.001
Ranked assessment (n of patients)**	145	150	145
Improved – n (%)	35 (24)	62 (41)	78 (54)
No change n(%)	72 (50)	67 (45)	53 (37)
Worse n(%)	38 (26)	21 (14)	14 (10)
P Value[a]		<0.001	<0.001

Comments:
Relative risks & P values for comparison with placebo group;

Histologic improvement defined as decrease of at least 2 points in Knodell necroinflammatory score from baseline to week 48 with no concurrent worsening of Knodell fibrosis score. Patients who didn't satisfy definition considered not to have histologic improvements. Patients with missing or unassessable data at week 48 considered not to have histologic improvement in comparison between each ADV group and placebo.

*number of patients with assessable liver biopsy specimens at baseline.
** Number of patients with assessable liver-biopsy specimens at baseline and week 48.
[a] P values for comparisons of 10mg group or 30mg group with placebo.

Adverse Events	Placebo (N=167)	10mg ADV (n=171)	30mg ADV (n=173)
Discontinued study prematurely	8%	7%	8%
Incidence of severe (grade 3 or 4) clinical adverse events:	8%	10%	9%
dose discontinuation for any adverse event[a]	<1%	2%	3%
Adverse events experienced by at least 10% of ADV 30mg group: N (%)			
Headache	37 (22)	43 (25)	45 (26)
Asthenia	32 (19)	42 (25)	45 (26)
Abdominal pain	32 (19)	31 (18)	38 (22)
Flu-like syndrome	31 (19)	28 (16)	32 (18)
Pain	21 (13)	19 (11)	13 (8)
Back Pain	11 (7)	11 (6)	17 (10)
Digestive Tract			
Nausea	23 (14)	17 (10)	31 (18)
Diarrhoea	13 (8)	23 (13)	25 (14)
Dyspepsia	14 (8)	15 (9)	19 (11)
Flatulence	10 (6)	13 (8)	18 10)
Anorexia	9 (5)	6 (4)	18 (10)
Nervous System			
Dizziness	13 (8)	9 (5)	18 (10)
Respiratory Tract			
Pharyngitis	54 (32)	44 (26)	70 (40)
Increased Cough	21 (13)	11 (6)	19 (11)
Adverse events leading to discontinuation of study drug	Nausea	Increased alanine aminotransferase or asparate aminotransferase levels; weight loss; rash	Nausea, abdominal pain, headache, fanconi-like syndrome, amblyopia, myocardial infarction
Alanine aminotransferase levels to >10 times upper limit of Normal range	19%	10%	8%
	1 patient had concurrent changes in total bilirubin level to >2.5mg per decilitre and to at least 1mg per decilitre (17.1 umol/ltr) above baseline value, and 1 patient had concurrent decrease in serum albumin level (to <3g per ltre		

Comments:

[A] Events included (10mg ADV):increased ALT or Asparate aminotransferase levels; weight loss, rash; (30mg ADV): nausea, abdominal pain, headache, fanconi-like syndrome, amblyopia, myocardial infarction; (Placebo): Nausea.
Note: Adverse Events reported by at least 10% of 30mg ADV group

Resistance profile: (n=381) No mutations occurred at higher than background frequencies (<1.6%).

7 different novel substitutions found at conserved sites in HBV polymerase in 7 patients (4 in ADV group; 3 placebo). All four ADV patients had significant reductions in serum HBV DNA levels at week 48. In vitro phenotypic analyses demonstrated viruses containing any of 7 substitutions remained fully susceptible to ADV (results from page 813).

Additional Results (e.g., early response factors): After week 48 all patients reassigned to new treatment groups for second 48 weeks of study (results not fully reported in this paper). All patients in placebo group received 10mg ADV/day; Patients in 10mg group randomly assigned to receive either continued treatment with 10mg/day or placebo. All patients in 30mg group received placebo. Brief interim results reported.

Methodological comments

- *Allocation to treatment groups: (method of randomisation and concealment of allocation)* Randomly assigned in a 1:1:1 ratio; Central randomisation scheme stratified according to 7 geographic regions. Permuted blocks (with a block size of six) used in each stratum. No other info on randomisation reported
- *Blinding: (for patients, health workers and study personnel, and method).* *****Study states placebo and ADV tables formulated to be indistinguishable from one another in appearance and taste. No other info on blinding reported. The sponsor held the data and conducted statistical analyses, which were predefined; the academic investigators had full access to the data and contributed substantially to the design of the study, the collection of the data, and the analysis and interpretation of the data. Liver-biopsy specimens for primary end-point were evaluated by an independent histopathologist who was unaware of the patients' treatment assignments or of the timing of liver biopsy.
- *Comparability of treatment groups: (any differences in baseline characteristics of patients and controls?)* No significant differences in demographic or HBV disease characteristics or previous anti-HBV treatments among groups.
- *Method of data analysis: (ITT, point estimates given? confidence intervals given?)* Patients who received at least one dose of study medication were included in the analyses. Patients with missing or unassessable base-line liver-biopsy specimens were prospectively excluded from primary efficacy analysis; Patients with missing or unassessable data at 48 wks were considered not to have had responses. The unstratified Cochran-Mantel-Haenszel test was used to compare each of the ADV groups with placebo, and all P values were 2-sided at a significance level of 0.05, with no adjustments for multiple comparisons.
- *Sample size/power calculation: (given?)* Yes Designed to enrol 166 patients per group with 90% power to detect absolute difference of 20% (50% vs 30%) between group given 10mg ADV and placebo (further info given); Study had 79% power to detect absolute difference of 10% (16% vs 6%) in rate of seroconversion between 10mg ADV group and placebo, assuming that 10% or patients would have missing values (which were counted as treatment failures);
- *Attrition/drop-out: (percentages given?).* Patients with missing or unassessable base-line liver-biopsy specimens were prospectively excluded from primary efficacy analysis; Patients with missing or unassessable data at 48 wks were considered not to have had responses.

General comments

- *Generalisability: (inclusion/exclusion criteria defined?) Patients were male & female, aged 16 to 65yrs with chronic Hep B (HBeAg positive)*
- *Outcome measures: (appropriate outcome measures used?)* Appropriate outcome measures used.
- *Inter-centre variability: (assessed?)* Not reported
- *Conflict of interests:* Supported by Gilead Sciences
- No subgroup analysis by genotype or ethnic group reported.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Reported
5. Were outcome assessors blinded to the treatment allocation?	Adequate*
6. Was the care provider blinded?	Adequate
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Inadequate
10. Were losses to follow-up completely described?	Partial**

Appendix 9 Data extraction – Marcellin et al.

Extracted by: AT Date:11/11/04 Checked by JS Updated 7/01/05

Reference and Design	Intervention	Participants	Outcome measures
Marcellin, 2004, ref id: 256 Trial design: multicentre RCT, partially double-blind. Number of centres: 54 Country: 13 countries, mainly in Asia and Europe. Funding: Roche	<u>Group A:</u> n = 177 pegylated interferon alfa-2a Dose:180µg once weekly Duration: 48 weeks placebo Dose: n/a Duration: 48 weeks <u>Group B:</u> n = 179 pegylated interferon alfa-2a Dose:180µg once weekly Duration: 48 weeks lamivudine Dose: 100mg daily Duration: <u>Group C:</u> n = 181 lamivudine Dose: 100mg daily Duration: 48 weeks	HBE Ag status: HBeAg negative Total randomised: 552, of whom 537 were included in analyses. 5 group A, 7 group B and 3 group C were excluded from analyses – 6 did not receive study medication and all 9 pts from a single centre were excluded due to irregularities in study conduct. Inclusion: • Adult patients negative for HBeAg and positive for anti-HBe antibody and hepatitis B surface antigen (HBsAg) for at least six months, with an HBV DNA level of more than 100,000 copies per ml, a serum alanine aminotransferase level > 1 but ≤10 times the upper limit of the normal range; • findings on a liver biopsy within the previous 24 months consistent with the presence of CHB, with evidence of prominent necroinflammatory activity. Exclusion: • decompensated liver disease; • a coexisting serious medical or psychiatric illness; • a neutrophil count of < 1500 per cubic mm, a platelet count of < 90,000 per cubic mm, a serum creatinine level > 1.5 times the upper limit of the normal range; • a history of alcohol or drug abuse within one year before entry; • treatment for CHB within the previous six months; • coinfection with HCV, HDV or HIV. Baseline measurements: A (n=177) / B (n=179) / C (n=181) Male n(%): 151(85) / 147(82) / 156(86) Race n(%) White: 66(37) / 65(36) / 69(38) Asian: 107(60) / 111(62) / 111(61) Black: 3(2) / 2(1) / 0 Other: 1(1) / 1(1) / 1(1) Age mean ±SD: 40±11.7 / 41±10.8 / 40±11.1 Range: 18-71 / 18-70 / 18-66 Weight kg mean±SD: 71±12.5 / 70±13.0 / 71±12.1 range: 47-119 / 41-114 / 48-109 ALT IU/litre* mean±SD: 94.4±85.9 / 90.8±76.2 / 105.7±128.2 range: 10.2-507.8 / 11.3-513.8 / 9.8-1050.9 HBV DNA log copies/ml mean±SD: 7.14±1.84 / 7.35±2.00 / 7.24±1.78 range: 2.3-13.1 / 2.7-16.9 / 2.8-13.0	Primary outcomes used: Normalization of ALT levels; suppression of HBV DNA to below 20000 copies per ml. ALT measured at local labs following standard procedures, HBV DNA measured at one of 3 central labs. Secondary outcomes used: Proportion of pts with HBsAg loss; HBsAg seroconversion (defined by loss of HBsAg and presence of anti-HBs antibody); histologic response (reduction of at least 2 points in the modified histologic activity index); suppression of HBV DNA to below 400 copies per ml; ranked assessments of necroinflammatory activity and fibrosis. Also safety analysis and resistance analysis. Length of follow up: 48 weeks treatment plus 24 week follow up.

		Bridging fibrosis or cirrhosis n(%)	54(31)	40(22)	53(29)	
		Prior use of lamivudine n(%)	7(4)	15(8)	9(5)	
		Prior use of intereron alfa n(%)	11(6)	18(10)	14(8)	
		* The upper limit of the normal range is 30 IU per litre. Compliance: Not reported Patient characteristics, e.g. carriers, those with compensated/decompensated liver disease, genotype etc.: Not reported				
Outcome		Group A (n=177)		Group B (n=179)		Group C (n=181)
HBV DNA <20000 copies/ml§ end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with Group C* odds ratio 95% CI‡ HBV DNA <400 copies/ml end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with Group C Change in HBV DNA end of treatment (week 48) Total number of patients Mean log copies/ml 95% CI log copies/ml end of follow-up (week 72) Total number of patients Mean log copies/ml 95% CI log copies/ml		144(81) 74.8 to 86.8 76(43) 35.5 to 50.6 0.007 1.8 (1.2 to 2.9) 112(63) 55.7 to 70.4 34(19) 13.7 to 25.8 <0.001 166 -4.1 -3.8 to -4.5 165 -2.3 -1.9 to -2.7		164(92) 86.6 to 95.2 79(44) 36.7 to 51.7 0.003 1.9 (1.2 to 3.0) 156(87) 81.3 to 91.7 35(20) 14.0 to 26.1 <0.001 165 -5.0 -4.7 to -5.3 170 -2.4 -1.9 to -2.8		154(85) 79.0 to 89.9 53(29) 22.8 to 36.5 133(73) 66.4 to 79.8 12(7) 3.5 to 11.3 174 -4.2 -3.9 to -4.5 154 -1.6 -1.2 to -2.0
Comments: *Virologic response Group A compared with Group B is P=0.849 Graphs in Fig 2 show changes through time at weekly intervals, but not data extracted at this stage as treatment end point and follow-up end points already taken from tables.						
ALT normalization† end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with GroupC* odds ratio 95% CI‡		67(38) 30.7 to 45.4 105(59) 51.7 to 66.6 0.004 1.9 (7.2 to 2.8)		87(49) 41.1 to 56.2 107(60) 52.2 to 67.0 0.003 1.9 (1.2 to 2.9)		132(73) 65.8 to 79.3 80 (44) 36.8 to 51.8

Comments: During therapy, marked elevations in ALT (>10 times the upper limit of the normal range, or more than 300 IU per litre) were observed in a significantly higher % of Group A pts (12%) than Group B pts (4%) or Group C pts (6%) (p=0.007 and P=0.038, respectively). % of pts with marked elevations in ALT levels after therapy was significantly higher in Group C (14%) or Group B (15%) than in group A (7%; P=0.03 and P=0.02, respectively). There was a significant association between a marked elevation in ALT during therapy and normalization of ALT levels at week 72 (P=0.01). *Biochemical response Group A compared with Group B is P=0.0915 Graphs in Fig 2 show changes through time at weekly intervals, but not data extracted at this stage as treatment end point and follow-up end points already taken from tables.			
Combined response ALT normalization and HBV DNA <20000 copies/ml end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value compared with GroupC ALT normalization and HBV DNA <400 copies/ml end of treatment (week 48) n(%) of pts 95% CI % end of follow-up (week 72) n(%) of pts 95% CI % p value	 63(36) 28.6 to 43.1 63(36) 28.6 to 43.1 0.011 47(27) 20.2 to 33.7 26(15) 9.8 to 20.8 0.007	 87 (49) 41.1 to 56.2 68(38) 30.9 to 45.5 0.0002 82(46) 38.4 to 53.4 29(16) 11.1 to 22.4 0.003	 125(69) 61.8 to 75.7 42(23) 17.3 to 30.0 109(60) 52.7 to 67.4 11(6) 3.1 to 10.6
Histologic response¶ at end of follow up (week 72) Total n. pts* Improved n(%) 95% CI % No. pts with paired biopsy samples ** - n. patients improved (%) - 95% CI % Ranked assessments of histologic response†† Necroinflammatory activity Total n. pts Improved n(%) Worse n(%) Fibrosis Total n. pts Improved n(%) Worse n(%)	 177 85(48) 40.5 to 55.6 143 85(69) 50.9 to 67.6 143 79(55) 16(11) 143 21(15) 11(8)	 179 68(38) 30.9 to 45.5 143 68(48) 39.1 to 56.1 143 66(46) 23(16) 143 18(13) 15(10)	 181 72(40) 32.6 to 47.3 125 72(58) 48.4 to 66.4 125 57(46) 21(17) 125 22(18) 6(5)

Comments:
All p values are from the CMH test for the pairwise comparison of each peg group with the lam monotherapy group at week 72.
† p=0.003 for the overall test of treatment effect
‡ odds ratios are given with 95% CI for the two primary outcomes only
§ p=0.005 for the overall test of treatment effect.
¶Histologic response defined as a reduction from baseline of at least 2 points in the modified histologic activity index (HAI). Scores for this index range from 0 to 24, with inflammation graded from 0 (none) to 6 (cirrhosis).
*patients without paired biopsy samples were classified as having no response. P=0.144 for the overall test of treatment effect.
** patients without paired biopsy samples were excluded. P=0.101 for overall test of treatment effect.
†† ranked assessments included patients with assessable liver-biopsy specimens at baseline and at week 72. 'Improved' and 'worse' were defined as a reduction of at least 2 points and an increase of at least 2 points in the modified HAI score, respectively.

There was a significant association between histologic activity and either a biochemical or virologic response at week 72, regardless of treatment group (p<0.001). A histologic response occurred in 151 of 292 patients with a biochemical response (52%) compared with 70 of 245 pts without a biochemical response (29%). A histological response was seen in 116 of 208 pts with a virologic response (56%) as compare with 105 of 329 pts without a virologic response (32%).

	Group A (n=177)	Group B (n=179)	Group C (n=181)
Adverse Events [all figs n(%)]			
Discontinuation			
For safety reasons†	13(7)	7(4)	0
For other reasons‡	2(1)	3(2)	4(2)
Dose modification§			
Total	83(47)	86(48)	-
for AE	13(7)	23(13)	-
for Laboratory abnormality	65(37)	64(36)	-
ALT elevation	15(8)	6(3)	-
Neutropenia	30(17)	44(25)	-
Thrombocytopenia	34(19)	22(12)	-
Adverse events			
≥1 reported serious AE¶	9(5)	12(7)	5(3)
Death	1(1)*	0	0
≥1 reported AE†	155(88)	155(87)	86(48)
Most common AE**			
Pyrexia	105(59)	98(55)	8(4)
Fatigue	74(42)	75(42)	33(18)
Myalgia	47(27)	49(27)	11(6)
Headache	42(24)	34(19)	14(8)
Decreased appetite	31(18)	26(15)	6(3)
Arthralgia	27(15)	27(15)	6(3)
Alopecia	24(14)	20(11)	1(1)
Diarrhoea	20(11)	10(6)	5(3)
Dizziness	15(8)	12(7)	8(4)
Insomnia	15(8)	15(8)	5(3)
Nausea	14(8)	13(7)	9(5)
Irritability	12(7)	8(4)	4(2)
Sore throat	11(6)	5(3)	8(4)
Rigors	10(6)	5(3)	0
Injection-site reaction	10(6)	21(12)	0
Cough	10(6)	5(3)	2(1)
Upper respiratory tract infection	9(5)	4(2)	7(4)
Pruritus	9(5)	11(6)	4(2)
Upper abdominal pain	9(5)	12(7)	14(8)
Back pain	4(2)	11(6)	6(3)

Comments:
† P<0.001 for overall test of treatment effect
‡P=0.913 for overall test of treatment effect
§ Some patients who required a dose modification had both an adverse event and a lab abnormality.
¶A serious AE was one that presented a clinically significant hazard or resulted in a contraindication or side effect
* Thrombotic thrombocytopenic purpura developed in this patient
**Patients may have had more than 1 AE. The AE listed are those reported by at least 5% of pts in Group A or B up to 8 weeks after therapy.

Depression was infrequent during the study and was reported by 6 group A patients (3%), 8 (4%) group B and 2(1%) group C patients.
9 patients had serious infections, with a similar incidence in each group (1-2%). There were 2 cases of thyroid disorders in Group A. All other serious adverse events were single cases in a variety of body systems.
Hepatic decompensation was not reported in any patient during the study period, even though 37% had bridging fibrosis or cirrhosis on pre-treatment liver biopsy.

Additional Results:
HBsAg loss (at week 72) occurred in 7 pts in Group A (5 Asian and 2 white pts) and in five Group B pts (4 Asian and 1 white). HBsAg seroconversion, defined by the loss of HBsAg and the presence of anti-HBs antibody) occurred in 5 Group A pts and 3 Group B pts. No group C pts had seroconverted at week 72. Differences in HBsAg loss and seroconversion between groups A and C were significant (P=0.007 and P=0.029, respectively). The HBsAg response elicited by conventional interferon alfa tends to occur later than that observed with pegylated interferon alfa-2a in this study.

At week 48, YMDD mutations were detected in 32 of 179 Group C pts (18%), and 1 of 173 Group B pts (1%, p<0.001).

Methodological comments

- *Allocation to treatment groups: (method of randomisation and concealment of allocation):* Randomization was centralised and stratified according to geographic region and alanine aminotransferase levels. No detail given on actual procedure.
- *Blinding: (for patients, health workers and study personnel, and method).* Clinical data were collected by the Study Group, the sponsor held the data and conducted the statistical analyses, and the principal authors had full access to the data and were involved in its analysis and interpretation. Biopsy samples were scored on the HAI by an independent histopathologist who was unaware of the timing of the biopsy or the patient's treatment assignment.
- *Comparability of treatment groups: (any differences in baseline characteristics of patients and controls?):* No significant differences between groups were reported.
- *Method of data analysis: (ITT, point estimates given? confidence intervals given?):* Efficacy analyses included all randomized patients who received at least one does of study medication. Cochran-Mantel-Haenszel test, stratified according to geographic region and pre-treatment ALT level was used to compare differences in response rates between the treatment groups. Fischer's exact test was used to perform pairwise comparisons in cases where there was a significant difference between groups. Response rates were calculated for all patients who received at least 1 dose of study drug, and 95% CI were computed for each treatment group's response rate. Patients with values missing at week 72 were classified as having no response.
- *Sample size/power calculation:* A sample size of 160 patients per treatment group gave statistical power of 80% at the 0.025 level of significance to detect a difference in response rates of 15%. The sample size was increased to 175 to allow for withdrawals. The goals of the study were considered to have been reached in the event of a significant result for either primary outcome, so a significance level of 0.025 was chosen to maintain the overall significance level of 0.05. Significance was set at 0.05 for secondary measures.
- *Attrition/drop-out:* A total of 55 patients withdrew: pegylated interferon alfa-2a monotherapy group: 12 , lamivudine + pegylated interferon alfa-2a group:17, lamivudine group: 26 .
-

General comments

- *Generalisability:* Adult patients negative for HBeAg and positive for anti-HBe antibody and hepatitis B surface antigen (HBsAg) for at least six months
- *Outcome measures:* Appropriate outcome measures were used.
- *Inter-centre variability:* Not reported
- *Conflict of interests:* Supported by Roche
- No data provided for patient sub-groups e.g. genotype, ethnicity, gender.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown*
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Adequate
7. Was the patient blinded?	Partial
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Partial
10. Were losses to follow-up completely described?	Adequate ?

* actual method of randomisation not reported

Appendix 10 Data extraction – Perrillo et al.

Extracted by: AT checked by ST Date: 24-01-05

Reference and Design	Intervention	Participants	Outcome measures
Perrillo ,2004, ref citation: 104 Trial design: RCT with concurrent non-randomised study Number of centres: not stated Country: Not stated Funding: GlaxoSmith-Kilne; Adefovir dipivoxil provided by Gilead Sciences	<u>Group A1</u> n = 49* ongoing lamivudine Dose: 100mg/d plus placebo *ITT excluded 1 patient due to screening ALT level <1.3 times ULN and the absence of documented past HBsAg positivity. <u>Group A2</u> n = 46 ongoing lamivudine Dose: 100mg/d plus ADV Dose: 10mg/day Duration: 52 weeks <u>Group B:</u> n = 40 ADV (open label) Dose: 10mg/d Duration: 52 weeks plus ongoing lamivudine Dose: 100mg/d	HBeAg status: Group A positive, Group B mixed Total randomised: Group A n=95, Group B n= 40 Inclusion criteria: • HBsAg+ adults receiving ongoing lamivudine therapy for > 6months for CHB. • HBV DNA concentration ≥ 10^6 copies/mL • ALT > 1.3 times ULN on at least 2 occasions in previous 6 months. • Group A pts had HBeAg+ CHB with compensated liver disease • Group B pts had signs of decompensated disease or recurrent hep B after liver transplantation. Group B pts could be either HBeAg+ or HBeAg- Exclusion criteria: • Coinfection with HCV, HDV or HIV. • Documented or suspected HCC • anaemia, leukopenia and granulocytopenia or thrombocytopenia • a screening calculated creatine clearance <50 mL/min or a serum creatine value > 1.5mg/dL • evidence of pancreatitis • Prs who had previously received treatment with ADV or other drugs with activity against HBV within the prior 3 months Baseline measurements:	Primary outcomes: • Reduction in HBV DNA level Secondary outcomes: • ALT normalisation • HBeAg loss and seroconversion • Proportion of pts with undetectable serum HBV DNA • Proportion of pts with YMDD mutant HBV DNA Length of follow up: 52 weeks

	A1 (N=48)	A2 (N=46)	B with LT (N=14)	B w/o LT (N=26)	All B (N=40)
Median age, yr (range)	42 (25-68)	43 (24-67)	54.5 (22-72)	52 (33-73)	53 (22-73)
Median duration prior LAM, mo (range)	34 (4-61)	34 (10-64)	32 (9-55)	33 (1-62)	33 (1-62)
No. male (%)	45 (94)	45 (98)	13 (93)	22 (85)	35 (88)
No. HBeAg+ (%)[a]	42 (88)	40 (87)	9 (64)	18 (69)	27 (68)
No. HBe antibody positive[a] (%)	0	0	3 (21)	4 (15)	7 (18)
No. HBsAG+ (%)[a]	48 (100)	44 (96)	13 (93)	26 (100)	39 (98)
Median	8.61	8.95	9.01	8.14	8.61

		HBV DNA level*	(4.2-10.1)	(6.6-10.1)	(7.2 - 10.1)	(5.4-9.4)	(5.4-10.1)
		ALT (IU/L), mean (SD)	185 (258)	135 (148)	120 (126)	130 (155)	127 (144)
		ALT level times ULN, median	2.71	2.20	1.67	1.97	1.86
		[a] Baseline sera were not available for testing in all patients. All patients were HBsAg and HBeAg positive at screening. LT=liver transplant, w/o=without *log_{10} copies/mL (range) Ethnic groups: Not reported Compliance: not reported Treatment history: not reported Genotype data: not reported 26 Group B patients met eligibility criteria for decompensated liver disease and 14 were treated because of recurrent hepatitis B after liver transplantation. Of these 14, 6 had a history of ascites, variceal haemorrhage or hepatic encephalopathy after liver transplantation and 3 (21%) had a CPT > 8 on entry.					
Outcome		Lam plus placebo (n=48)			Lam plus ADV (n=46)		Difference
No. with HBV DNA level >10^5 copies/mL at baseline (%)		46/48 (96)			46/46 (100)		
No. with HBV DNA response at weeks 48 and 52%		5/46 (11)[a]			39/46 (85) [a]		P<0.001
No. HBV DNA – by polymerase chain reaction at week 52 (%)		0/48 [a]			9/46 (20) [a]		P=0.001
Median change from baseline in HBV DNA level at week 52 (range)		+0.3 (-6.0 to 5.4) [a]			-4.6 (-7.3 to 1.5) [a]		P<0.001
Comments: [a] P≤ 0.01 HBV DNA time series presented in paper but not data extracted							
Outcome		Lam plus placebo (n=48)			Lam plus ADV (n=46)		Difference
HBeAg loss		1/42 (2)			6/40 (15)		
Comments: Among those patients who were HBeAg+ before treatment, 8% (3 of 40) receiving ADV and lamivudine underwent HBeAg seroconversion compared with 2% (1of 42) receiving lamivudine and placebo at week 52. Loss of HBeAg occurred in 6 of 40 (15%) of patients receiving lamivudine and ADV and 1 of 42 (2%) of those receiving lamivudine and placebo. No patient lost HBsAg during the treatment period.							
Outcome		Lam plus placebo (n=48)			Lam plus ADV (n=46)		Difference
ALT change from baseline (IU/L) at 52 weeks Mean (SD) (Range)		-44 (312) (-1643 to 758)			-90 (160) (-793 to 43)		
Change from baseline in ALT times the ULN at 52 weeks Median (Range)		-0.2 (-38.2 to 17.6) [a]			-1.1 (-18.4 to 1.0) [a]		
ALT normalisation at 52 weeks*		9%			37%		A1:A2 p=0.003

Comments: Percentiles also given in paper for changes from baseline
[a] P≤ 0.01
* Figures represent only those individuals who achieved the secondary end point of having a normal ALT at both weeks 48 and 52. This seems to be contradicted by the text, which suggests: 'At the end of treatment, ALT response (normalisation at both weeks 48 and 52) was significantly more frequent in the combined therapy group, occurring in 31% of patients (14 of 45) compared with only 6% (3 of 48) receiving lamivudine and placebo (P=0.002).

Outcome	Lam plus placebo (n=48*)	Lam plus ADV (n=44)	Difference
No (%) with detectable YMDD mutant at baseline	47/47 (100)	44/44 (100)	
No (%) with detectable YMDD mutant at week 52	44/46 (96)	26/42 (62)	P<0.001
No (%) with YMDD mutant not detectable at week 52	2/46 (4)	16/42 (38)	
HBV DNA negative(%)	2/46 (4)	14/42 (33)	
Wild type (%)	0 (0)	2/42 (5)	

Comments
* one patient received rescue medication and is not presented in this analysis.

	Lam plus placebo (n=48*)	Lam plus ADV (n=44)	
Adverse Events (AE) No.(%) with at least one AE	40 (83%)	36 (82%)	

Comments: No further details of particular AEs are reported.
No serious adverse events were considered attributable to either study drug by the investigators. There were no deaths in group A (and 1 death in group B).

GROUP B ANALYSES BELOW – NB THIS IS A DIFFERENT PATIENT GROUP AND IS NOT COMPARABLE WITH GROUP A

Outcome	Group B (LT before entry) (n=14)		Group B (no LT) (n=26)		Overall (n=40)	
	Baseline	Wk 52	Baseline	Wk 52	Baseline	Wk 52
No. with HBV DNA response at weeks 48 and 52	-	13/14 (93)	-	23/25 (92)	-	36/39 (92)
Median HBV DNA (log_{10} copies/mL)	9.0	4.6	8.1	2.5	8.6	3.2
HBeAg loss (%)	-	1/9 (11)	-	7/18 (39)	-	8/27 (30)
Median ALT times ULN	1.7	0.9	2.0	0.8	1.9	0.9
% with Alt normalization (from fig 2b)						61%

Comments:
LT = liver transplant
There was a significant decrease in serum HBV DNA levels from baseline to week 52, with a median change of -4.6 log_{10} copies/mL (p<0.001). 95% of patients (38/40) had ALT levels greater than the ULN at baseline; of these, 53% (20/38) achieved normalization of ALT levels at weeks 48 and 52.
1 patient HBeAg seroconverted.

Outcome	Group B (LT before entry) (n=14)	Group B (no LT) (n=26)	Overall (n=40)
No (%) with detectable YMDD mutant at baseline	13/13 (100)	24/25 (96)	37/38 (97)*
No (%) with detectable YMDD mutant at week 52	8/13 (62)	13/24 (54)	21/37 (57)
No (%) with YMDD mutant not detectable at week 52	5/13 (38)	11/24 (46)	16/37 (43)
HBV DNA negative(%)	5/13 (38)	11/24 (46)	16/37 (43)
Wild type (%)	0 (0)	0 (0)	0 (0)

Comments:
* one patient had YMDD mutant detected at screening but not at baseline.

Methodological comments

- *Allocation to treatment groups: (method of randomisation and concealment of allocation):* patients in group A were randomly assigned to receive either ADV or placebo, patients in group B received open-label ADV. Clinical and laboratory criteria were predefined in the study to allow the use of open-label combination therapy if disease progression was observed. Centralized reference laboratories evaluated blood counts and routine serum chemistries.
- *Blinding: (for patients, health workers and study personnel, and method):* Matching placebo used
- *Comparability of treatment groups: (any differences in baseline characteristics of patients and controls?):* No significant differences were reported
- *Method of data analysis: (ITT, point estimates given? confidence intervals given?):* Primary efficacy analyses used ITT population, defined as all patients with confirmed CHB who were randomized regardless of whether or not the study drug was taken or whether the patient completed the planned duration of the study. Safety analyses used as-treated population, defined as all patients for whom no clear evidence was available of failure to take study medicine.
- *Sample size/power calculation: (given?):* The study was powered to detect a difference in virologic response (reduction in HBV DNA levels), assessed as the proportion of patients with either HBV DNA level $\leq 10^5$ copies/mL or a > 2 $\log_{10}$ copies/mL reduction from baseline HBV DNA level at weeks 48 and 52 for the patients in group A. The sample size calculations were based on hypothesized HBV DNA response rates of 14% in the lamivudine plus placebo group and 44% in the lamivudine plus ADV group. The planned sample size of 90 patients provided > 80% power to detect such a difference (2-sided) between the 2 treatments. No sample size calculations were performed for group B.
- *Attrition/drop-out: (percentages given?)* 96% (46 of 48) patients who received lamivudine plus placebo completed the 52 weeks. One patient withdrew due to adverse events and one was lost to follow-up. One of the 46 patients who completed received open-label combination therapy because predefined criteria for disease progression were met. 91% (42 of 46) patients who received lamivudine and ADV completed treatment. One patient was withdrawn due to a protocol violation, one withdrew consent, and 2 were lost to follow-up. 95% (38 of 40) group B patients completed treatment; 1 withdrew due to adverse events and 1 withdrew due to a decrease in estimated creatinine clearance that was considered unrelated to the study drug.

General comments

- *Generalisability: (inclusion/exclusion criteria defined?):* The randomised element of this trial was HBeAg positive with compensated live disease. Further inclusion/exclusion criteria are detailed in an earlier section.
- *Outcome measures:* appropriate outcome measures were used.
- *Conflict of interests:* Supported by GlaxoSmithKline R&D. Adefovir dipivoxil provided by Gilead Sciences

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	unknown
2. Was the treatment allocation concealed?	unknown
3. Were the groups similar at baseline in terms of prognostic factors?	reported
4. Were the eligibility criteria specified?	adequate
5. Were outcome assessors blinded to the treatment allocation?	unknown
6. Was the care provider blinded?	unknown
7. Was the patient blinded?	adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	adequate
9. Did the analyses include an intention to treat analysis?	Inadequate*
10. Were losses to follow-up completely described?	adequate

*ITT excluded 1 patient due to screening ALT level <1.3 times ULN and the absence of documented past HBsAg positivity.

Appendix 11 Data extraction – Peters et al.

Extracted by: AT Checked by : ST Date: 22-01-05

Reference and Design	Intervention	Participants	Outcome measures
Peters, 2004, ref citation:103 Trial design: double blind RCT Number of centres: 20 Country:Australia, Canada, France, Germany, UK and USA Funding: Not stated	<u>Group A:</u> n = 19 lamivudine Dose: 100mg/d Duration: 48 weeks Plus placebo <u>Group B:</u> n = 19 ADV Dose: 10mg/d Duration: 48 weeks Plus placebo <u>Group C:</u> n = 20 ADV Dose: 10mg/d Duration: 48 weeks lamivudine Dose: 100mg/d Duration: 48 weeks	HBeAg status: positive Total randomised: 59 Inclusion criteria: • 16-65 years old • HBsAg present for at least 6 months • HBeAg + • An elevated serum ALT level 1.2-10 times ULN on at least 2 occasions at least 1 month apart within the preceding 6 months. • Ongoing lamivudine therapy for at least 6 months • Well preserved liver function and no history of variceal bleeding, ascites or encephalopathy. Exclusion criteria: • Serum phosphorous level, serum creatinine level, creatinine clearance, absolute neutrophil count, haemoglobin and serum α-fetoprotein level less than specified limits • Prior use of ADV or treatment with interferon alfa or other immunomodulatory therapies within the 6 months proceeding study screening. • Treatment with nephrotic drugs, competitors of renal excretion and/or hepatotoxic drugs within 2 months before study screening or during the study period • Prior organ transplantation • Serious concurrent medical conditions, including other concurrent liver diseases • Coinfection with HIV • Current alcohol or substance abuse • Pregnancy/lactation Baseline measurements:	Primary outcome: time-weighted average change from baseline in serum HBV DNA level up to 16 weeks Secondary outcomes: • time-weighted average change from baseline in serum HBV DNA level at 48 weeks • serum HBV DNA change form baseline • % of patients with ALT normalization • HBeAg loss • Seroconversion to anti-HBe • Loss of HBsAg. Length of follow up: 48 weeks

	Lam (n=19)	Adv (n=19)	Adv+Lam (n=20)
Age (yr) median (range)	44.0 (33-69)	45.0 (26-64)	46.5 (28-66)
Male %	14 (74)	17 (89)	15 (75)
Race White Asian Black Other	 14 (74) 5(26) 0 0	 12(63) 7(37) 0 0	 9 (45) 9(45) 1(5) 1(5)
Prior LAM therapy (mo) median (range)	24.0 (9-58)	37.0 (16-75)	29.5 (12-86)
HBV DNA* median (range)	8.2 (6.08 - 8.82)	8.42 (7.30-9.21)	7.94 (5.89-8.88)
HBeAg (%) positive negative	 19(100) 0	 19(100) 0	 18(90) 2(10)
Serum ALT			

		Median (IU/L)	70	101	74
		Multiples ULN Median (range)	1.91(1.05-5.74)	2.35 (1.09-14.79)	1.92 (0.98-8.56)
		*log_{10} copies/ml Compliance: not reported Treatment history: all patients had received treatment with lamivudine for at least 6 months and had no prior use of ADV genotype: genotypic analyses of HBV polymerase performed on all 58 patients had lamivudine resistance mutations by sequencing at baseline. All 4 major patterns of lamivudine resistance mutations were observed in these patients.			
Outcome		LAM + placebo (n=19)	ADV + placebo (n=19)	ADV+Lam (n=20)	Difference
$DAVG_{16}$ Mean ± SD		-0.0±0.34	-2.66* ± 0.80	-2.50* ± 0.54	*P<0.001
$DAVG_{48}$ Mean ± SD		-0.10±0.39	-3.88* ± 1.05	-3.09* ± 0.67	*P<0.001
Change in serum HBV DNA mean ± SD (95% CI) Week 16 Week 48		 0.0 ± 0.28 (-0.14, 0.13) -0.31± 0.93 (-0.74, 0.12)	 -3.11* ± 0.94 (-3.54, -2.69) -4.00*± 1.41 (-4.65, -3.35)	 -2.95* ± 0.64 (-3.23, -2.66) -3.46*±1.10 (-3.94, -2.97)	 *P<0.001 *P<0.001
Comments: $DAVG_{16}$ ($DAVG_{48}$) is calculated as the difference between baseline and the area under the curve up to week 16 (week 48) in serum HBV DNA level (log_{10} copies/mL) divided by the number of days from baseline up to the last included value.					
Outcome		LAM + placebo (n=19)	ADV + placebo (n=19)	ADV+Lam (n=18)	Difference
HBeAg status Neg at week 48 n/total (%) Rate of seroconversion		 0 (0) 0 (0)	 3* (16) 2* (11)	 3**(17) 1**(6)	 *p=0.075, **p=0.067 *p=0.152, **p=0.304
Comments: total includes only patients with positive HBeAg at baseline Nb text states that 11% of ADV+Lam patients were HBeAg negative at week 48, but table 2 states that 17% were (as shown here).					
Outcome		LAM + placebo (n=19)	ADV + placebo (n=19)	ADV+Lam (n=20)	Difference
Change in serum ALT level (IU/L) mean ± SD (95% CI) Normalization of serum ALT, n/total (%)		0.0 ± 30.8 (-4.2, 14.2) 1/19 (5)	-87.7 ± 121.7 (-143.9, -31.5) 9*/19 (47)	-48.6 ± 82.0 (-84.5, -12.6) 10**/19 (53)	 *p=0.004, **p=0.001
Comments: For normalization of ALT analysis, 'total' includes only patients with an ALT level > ULN at baseline					
Outcome		LAM + placebo (n=19)	ADV + placebo (n=19)	ADV+Lam (n=20)	Difference
Adverse Events dose discontinuation for any adverse event dose reduction for any adverse event No. (%) pts experiencing any adverse event:		 0(0) 19 (100)	 0(0) 18(95)	 0(0) 18(90)	

Adverse events experienced:				
Asthenia	6(32)	9(47)	10(50)	
Headache	5(26)	5(26)	6(30)	
Pharyngitis	6(32)	5(26)	1(5)	
Abdominal pain	5(26)	4(21)	6(30)	
Insomnia	2(11)	4(21)	0(0)	
Rash	4(21)	4(21)	0(0)	
Fever	1(5)	3(16)	0(0)	
Sinusistis	5(26)	3(16)	1(5)	
Arthralgia	3(16)	2(11)	1(5)	
Back pain	3(16)	2(11)	3(15)	
Increased cough	3(16)	2(11)	0(0)	
Nausea	1(5)	2(11)	4(20)	
Pain	4(21)	2(11)	4(20)	
Diarrhoea	6(32)	1(5)	2(10)	
Gastroenteritis	3(16)	1(5)	0(0)	
Infection	1(5)	1(5)	3(15)	
Rhinitis	5(26)	1(5)	2(10)	
Bacterial infection	0(0)	0(0)	3(15)	
Comments: Adverse events reported at any time during the study in more than 2 pts in any treatment group. There were 5 serious adverse events (1 in LAM group, 3 in ADV group, 1 patient receiving open label ADV post-48 weeks). None of these adverse events were thought to be related to study medication.				

Methodological comments

- *Allocation to treatment groups: (method of randomisation and concealment of allocation):* 'randomly assigned' but no further details given. Eligible patients were randomized centrally (Interactive Clinical Technologies Inc, Yardley PA).
- *Blinding: (for patients, health workers and study personnel, and method)* Haematology and biochemistry were analyzed at central laboratories in the USA, Switzerland or Australia. HBeAg, HBsAg and HBV DNA assessment results were not provided to investigators before study unblinding.
- *Comparability of treatment groups: (any differences in baseline characteristics of patients and controls?)* No significant differences at baseline reported (Exceptions: slightly higher serum ALT levels in ADV monotherapy group and somewhat higher % of Asian patients in ADV/LAM group. Patients randomised to ADV monotherapy received prior LAM therapy for a median of 6-12mth longer than other 2 groups.
- *Method of data analysis: (ITT, point estimates given? confidence intervals given?):* 'Analysis included all randomized patients who received at least one dose of study medication' and one patient form the ADV monotherapy group discontinued the study before receiving any treatment so was not included in the analysis; i.e. not true ITT. For categorical end points at week 48, relative risk (relative to lamivudine) and 95% CI for each of the ADV treatment groups were calculated and presented along with P values from the Cochran-Mantel Haenszel test. Patients whose postbaseline categorical response was missing at a given time were considered nonresponders at the corresponding time point. For continuous timepoints at weeks 16 and 48, Wilcoxon-Mann-Whitney tests were used to compare each secondary efficacy end point. The Kaplan-Meier method was used to estimate the time to the onset of the response for HBeAg loss, confirmed HBeAg seroconversion, serum HBV DNA levels below the lower level of quantification and confirmed normalization of serum ALT levels.
- *Sample size/power calculation: (given?)* Assumptions made for sample size were that 17 patients per treatment group would provide 93% power to detect a 1.0 $\log_{10}$ difference in $DAVG_{16}$ between the lamivudine monotherapy group and each of the other groups. Sample size calculation was based on $\alpha = 0.025$ and a standard deviation of 0.76. A dropout rate of approximately 15% was assumed and 14 evaluable patients per treatment group were required.
- *Attrition/drop-out:* One ADV patient discontinued at week 32 due to non-compliance, and one LAM patient discontinued at week 44 due to progression of disease.

General comments

- *Generalisability:* The study population was HBeAg positive CHB patients with well preserved liver function. Inclusion/exclusion criteria defined in earlier section.
- *Outcome measures:* Appropriate outcome measures were used
- *Inter-centre variability: (assessed?)* Not reported
- *Conflict of interests:* Funding not reported, but listed authors include staff from GlaxoSmithKline and Gilead Sciences
- No data on primary outcome provided for patient sub-groups e.g. genotype, ethnicity, gender.

Patients who showed HBeAg seroconversion or durable HBeAg loss in conjunction with a serum HBV DNA level <1000 copies/mL at week 48 were eligible to enrol in a long term follow-up protocol designed to evaluate the durability of HBeAg seroconversion. After the planned 16 week interim analysis, the protocol was amended to allow access to open-label ADV 10mg for patients experiencing a severe exacerbation of CHB either during or after the 48 week treatment period.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Adequate*
7. Was the patient blinded?	Adequate*
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an intention to treat analysis?	Inadequate
10. Were losses to follow-up completely described?	Adequate

* Text states that 'lamivudine placebo' and 'adefovir dipivoxil placebo' were used, and it is assumed that these are 'official' placebos indistinguishable from the treatments.

Appendix 12 Data extraction – Plosker and Dando systematic review

Data Extraction Table

reviewers: AT Date: 21-01-05

Reference and Design	**Methods**
Author: Dando and Plosker *Year*: 2003 *Ref ID*: 101 *Study design*: Systematic review	*Aim (Question):* Not stated clearly *Search strategy*: databases searched: Medical literature published in any language since 1980, identified using Medline, Embase and AdisBase. Medline and Embase search terms were 'adefovir dipivoxil' or 'adefovir dipivoxil' or 'PMEA'. AdisBase search terms in addition to these were 'GS 840' or 'BIS-POM' or 'PIV2PMEA'. Searches were last updated 12 September 2003. *Inclusion criteria used*. Criteria are not clearly stated. Inclusion was based on trial methodology. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data were also included. The review focuses on trials using the approved dosage of 10mg/day, and only trials with at least 20 patients were included. *Interventions:* Adefovir dipivoxil *Participants:* Patients with chronic hepatitis B who received adefovir dipivoxil *Outcome measures:* Outcome measures are not pre-specified by the reviewers. The two included studies used proportion of histological improvement as a primary endpoint, and change from baseline in serum HBV DNA levels, the proportion of patients with undetectable levels of serum HBV DNA, ALT levels and HBeAg loss or seroconversion as secondary measures. *Study design:* Not prespecified by reviewers. The two included studies are RCTs *Quality assessment:* The reviewers do not report the use of any quality scales or present criteria used for judging quality. *Application of methods:* Not stated

Results (including):

- *Quantity and quality of included studies.* The reviewers do not state clearly how many studies were retrieved or excluded from the review, and they do not present any assessment of quality. The text suggests that 5 trials have been carried out, but only 2 have been published in full. These 2 RCTs were included in the review (and are in the SHTAC review). The unpublished trials were: 2 conference papers and one abstract. The review also identified several noncomparative trials assessing the effects of ADV in specific patient populations, e.g. patients co-infected with HIV, patients with hepatic decompensation, and pre- and post-liver transplant patients. The review briefly covers these patients.
- *What was the combined treatment effect? (Should include point estimates and confidence intervals/standard deviations, P values etc for each outcome assessed):*48-week data from the two trials were used in a pooled analysis of tolerability.
- *Assessment of heterogeneity:* Not stated

Comments:

- e.g. funding, any other methodological elements that may affect the rigour of the systematic review
- The review is not presented as a classic systematic review. The reviewers included detail on pharmacokinetics etc. in addition to a summary of efficacy.
- The 2 reviewers are employed by Adis International, New Zealand.

Pooled analysis – % of patients experiencing adverse events (treatment-related events occurring in ≥ 3% of all ADV treated patients) *Numbers estimated from graph*

Adverse event	ADV 10mg/day (n=294)	Placebo (n=228)
Dyspepsia	3%	2.5%
Diarrhoea	3%	4%
Flatulence	4%	4%

Nausea	5%	8%
Abdominal pain	9%	11%
Headache	9%	10%
Asthenia	13%	14%
Pooled analysis – % of patients with laboratory abnormalities *Numbers estimated from graph*		
Abnormality	ADV 10mg/day (n=294)	Placebo (n=228)
Glycosuria ≥ 3+	1%	3%
Amylase > 2 x ULN	4%	4%
Creatine kinase >4 x ULN	7%	7%
AST >5 x ULN	8%	23%
Haematuria ≥ 3+	11%	10%
ALT >5 x ULN	20%	41%

Quality assessment for reviews using the DARE criteria

Quality Item	Yes/No/Uncertain	Methodological Comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Uncertain	
2. Is there evidence of a substantial effort to search for all relevant research?	Yes	No language restrictions were used, and 2 key databases were searched.
3. Is the validity of included studies adequately assessed?	No	
4. Is sufficient detail of the individual studies presented?	Yes	
5. Are the primary studies summarised appropriately?	Yes	

Appendix 13 CRD quality criteria

Quality assessment for RCTs (Quality Criteria - CRD Report 4)[139]

Quality criteria for assessment of experimental studies

Criterion	*Judgement**
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

* e.g. adequate; inadequate; not reported; unclear

b. Quality assessment for Systematic Reviews

Quality assessment for systematic reviews using the DARE criteria

Quality Item	**Yes/No/Uncertain**	**Methodological Comments**
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?		
2. Is there evidence of a substantial effort to search for all relevant research?		
3. Is the validity of included studies adequately assessed?		
4. Is sufficient detail of the individual studies presented?		
5. Are the primary studies summarised appropriately?		

Appendix 14 Costs of new patient and pre-treatment evaluations

Evaluation of a new patient with HBV		
ITEM		**COSTS**
Outpatient appointment:		
Time with nurse - 30 mins (Grade H)		£10.55
Time with doctor - 20 mins (Consultant)		£15.22
Overheads for clinic administration (pulling notes etc)		£4.51
STAFF cost for outpatient appointment		**£30.27**
Tests and investigations		
Hepatitis c screen (HCV RNA) 3% of patients only	Virology	£2.81
Hcv antibody test (Hep C IGM)		£12.80
Hbv	Virology	£11.80
Hbv viral load	Virology	£77.30
Liver function tests (LFT)	Chem Path	£4.12
Alpha – fetoprotein (all patients irrespective of whether cirrhotic) (AFP)	Chem Path	£9.85
Alpha - antitrypsin (A1AT)	Chem Path	£6.28
Thyroid stimulating hormone (only for patients to be treated with interferon alfa?) (TSH)	Chem Path	£4.12
Full blood count	Haematology	£2.49
Autoantibodies (AAS)	Immunology?	£3.57
Immunoglobulins IGA	Immunochemistry	£4.76
Immunoglobulins IGG		£4.76
Immunoglobulins IGM		£4.76
Ferritin	Haematology	£11.70
Caeruloplasmin	Chem Path	£7.47
Iron	Chem Path	£4.87
U & E's (including renal profile and urea)	Chem Path	£4.12
INR	Haematology	£2.70
Glucose	Chem Path	£2.82
Ultrasound scan of liver	Radiology	£119.57
Cryoglobulin	Immunochemistry	£12.89
TOTAL		**£345.84**

Further Investigations Of A Patient With HBV Considered For Treatment

ITEM		**COSTS**
Outpatient visit:		
To review results from above tests and brief on treatment options		
Time with nurse - 30 mins (Grade H)		£10.55
Time with doctor - 20 mins (Consultant assumed)		£15.22
Overheads for clinic administration (pulling notes etc)		£4.51
STAFF cost for outpatient appointment		**£30.27**
Daycase for liver biopsy:		
Additional tests undertaken prior to biopsy:		
FBC	Haematology	£2.49
INR	Haematology	£2.70
LFT		£4.12
Blood group	Haematology	£3.79
Ultrasound guided biopsy (by Radiologists)	Radiology	£141.31
Liver biopsy costs in Pathology	Histopathology	£176.60
Clerking in patient – 30 mins Grade D nurse assumed		£6.49
Ward time for recovery post-biopsy - 6 hours		£20.28
TOTAL		**£388.05**

Decision making about further Treatment of Follow Up		
Outpatient Visit		
decision has been made to treat and further tests are carried out.		
Time with nurse - 30 mins (Grade H)		£10.55
Time with doctor - 20 mins (Consultant assumed)		£15.22
Overheads for clinic administration (pulling notes etc)		£4.51
STAFF cost for outpatient appointment		**£30.27**

Final Tests Prior to Treatment		
Time with nurse - 30 mins (Grade H)		£10.55
Overheads for clinic administration (pulling notes etc)		£4.51
STAFF cost for outpatient appointment		**£15.05**
Tests		
ECG		20.00
Full Thyroid FT4		4.12
FBC		£2.49
LFT		£4.12
HBeAg	virology	£11.70
HBsAg	virology	£11.70
HBV DNA	virology	£77.30
Chest Xray		32.61
TOTAL		**£179.09**

Appendix 15 Costing protocols for monitoring patients during and post treatment

Monitoring during treatment - Conventional Interferon. 24 week course

Standard Examination (during treatment with Interferon) (weeks 1, 2, 3, 6, 8, 16,20)		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for Standard Appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
Total for Standard Assessment		**£29.58**

Week 4 Examination

Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
Total for Week 4 Examination		**£32.28**

Week 12 Examination

Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
HBeAg		£11.70
HBsAg		£11.70
HBV DNA		£77.30
Thyroid Function Test		£4.12
Total for detailed examination on treatment		**£137.10**

End of Treatment Examination

Time with nurse 30 minutes (Grade H)		£10.55
Time with Consultant		£15.22
Overheads for clinic administration		£4.51
Staff cost for appointment		**£30.27**
FBC	Haematology	£2.49

LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
HBeAg		£11.70
HBsAg		£11.70
HBV DNA		£77.30
Thyroid Function Test		£4.12
Total for detailed examination on treatment		**£152.32**

Detailed examination (at approximately 6 months)		
ITEM		**COSTS (£)**
Time with nurse 1 hour (Grade H)		£21.09
Overheads for clinic administration (pulling notes etc)		£4.51
STAFF cost for Standard Treatment at Week 16		**£25.60**
FBC	Haematology	£2.49
LFT (liver function test)	Chem Path	£4.12
U & E		£4.12
Blood clotting (for decompensation) (CS)	Haematology	£3.80
Alpha Fetoprotein		£9.85
Abdominal Ultrasound		£119.57
Total for Detailed Examination		**£169.55**

Detailed annual examination - as for untreated patients

Monitoring during treatment - Pegylated Interferon. 48 week course

Standard examination (during treatment with Interferon) (weeks 1, 2, 3, 6, 8, 16, 20, 28, 32, 36, 44)		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
Total for each basic assessment		**£29.58**

Week 4 Examination

Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
Total for each basic assessment		**£32.28**

Week 12, 24 and 36 Examination

Time with nurse 30 minutes (Grade H)		£10.55

Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
HBeAg		£11.70
HBsAg		£11.70
HBV DNA		£77.30
Thyroid Function Test		£4.12
Total for detailed examination on treatment		**£137.10**

End of Treatment Examination

Time with nurse 30 minutes (Grade H)		£10.55
Time with Consultant		£15.22
Overheads for clinic administration		£4.51
Staff cost for appointment		**£30.27**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
HBeAg		£11.70
HBsAg		£11.70
HBV DNA		£77.30
Thyroid Function Test		£4.12
Total for detailed examination on treatment		**£152.32**

Detailed examination (at approximately 6 months)		
ITEM		**COSTS (£)**
Time with nurse 1 hour (Grade H)		£21.09
Overheads for clinic administration (pulling notes etc)		£4.51
STAFF cost for Standard Treatment at 24 weeks		**£25.60**
FBC	Haematology	£2.49
LFT (liver function test)	Chem Path	£4.12
U & E		£4.12
Blood clotting (for decompensation) (CS)	Haematology	£3.80
Alpha Fetoprotein		£9.85
Abdominal Ultrasound		£119.57
Total for detailed examination on treatment		**£169.55**

Detailed annual examination - as for untreated patients

Monitoring during treatment - Lamivudine/ Adefovir. Per year of treatment.

Standard examination plus week 4		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
INR		£2.70
Total for Standard Plus Examination		**£32.28**

Standard examination weeks 8, 18, 22, 30, 34 and 44		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
U & E		£4.12
Blood Clotting		£3.80
Total for Standard Examination		**£29.58**

Detailed examination Week 13 and 39		
ITEM		**COSTS (£)**
Time with nurse 30mins hr (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
HBeAg		£11.70
HBsAg		£11.70
HBV DNA		£77.30
U&Es	Chem Path	£4.12
INR	Haematology	£2.70
Blood clotting (for decompensation)	Chem Path	£3.80
alpha fetoprotein		£9.85
Total for detailed examination on treatment		**£142.83**

Standard examination plus week 26 and 52		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
FBC	Haematology	£2.49
LFT	Chem Path	£4.12
HBeAg		£11.70
HBsAg		£11.70

HBV DNA		£77.30
U&Es	Chem Path	£4.12
INR	Haematology	£2.70
Blood clotting (for decompensation)	Chem Path	£3.80
alpha fetoprotein AFP		£9.85
abdominal ultrasound		£119.57
Total for Standard Plus Examination		**£262.40**

Surveillance of patients following treatment or for those refusing / unsuitable for treatment – per year

Standard Examination months 3 and 9		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H)		£10.55
Overheads for clinic administration		£4.51
Staff cost for appointment		**£15.05**
LFT	Chem Path	£4.12
INR		£2.70
FBC		£2.49
Total for detailed examination on treatment		**£24.36**

Detailed examination 6 months		
ITEM		**COSTS (£)**
Time with nurse 30 minutes (Grade H) or 30mins with Consultant		£16.70
Overheads for clinic administration		£4.51
Staff cost for appointment		**£21.21**
LFT	Chem Path	£4.12
INR		£2.70
FBC		£2.49
HBeAg		£11.70
HBsAg		£11.70
HBV DNA - 50% of patients		£38.65
alpha fetoprotein		£9.85
abdominal ultrasound		£119.57
Total for detailed examination on treatment		**£221.99**

Detailed examination Annually		
ITEM		**COSTS (£)**
Time 30mins with Consultant		£22.84
Overheads for clinic administration		£4.51
Staff cost for appointment		**£27.34**
LFT	Chem Path	£4.12
INR		£2.70
FBC		£2.49
HBeAg		£11.70
HBsAg		£11.70
HBV DNA		£77.30
alpha fetoprotein		£9.85
abdominal ultrasound		£119.57
Total for detailed examination on treatment		**£266.77**

Appendix 16 Costs and outcomes of sequential treatment strategies

Table 46 - costs and outcomes of sequential treatment strategies for patients with HBeAg positive disease

Strategy	Costs	Life expectancy (discounted at 1.5%)	Discounted QALYs	Incremental cost-effectiveness ratio
Best supportive care	7402	34.29 (25.27)	20.08	
Conventional interferon alfa	11359	35.06 (25.78)	20.58	7,936
Conventional interferon alfa followed by lamivudine	13672	36.19 (26.52)	21.26	3,369
Conventional interferon alfa followed by adefovir dipivoxil	23620	37.84 (27.54)	22.21	7,514
Conventional interferon alfa followed by lamivudine with adefovir salvage	22905	38.00 (27.64)	22.29	9,034
Pegylated interferon alfa	14704	35.37 (25.99)	20.78	16,166
Pegylated interferon alfa followed by lamivudine	16911	36.48 (26.71)	21.45	17,162
Pegylated interferon alfa followed by adefovir dipivoxil	26361	38.22 (27.78)	22.36	18,167
Pegylated interferon alfa followed by lamivudine with adefovir salvage	25637	38.07 (27.70)	22.43	18,762

Table 47 - costs and outcomes of sequential treatment strategies for patients with HBeAg negative disease

Strategy	Costs	Life expectancy (discounted at 1.5%)	Discounted QALYs	Incremental cost-effectiveness ratio
Best supportive care	11,247	18.35 (15.32)	10.05	
Conventional interferon alfa	15,524	19.99 (16.45)	11.14	3,922
Conventional interferon alfa followed by lamivudine	18,628	21.17 (17.32)	11.89	4,101
Conventional interferon alfa followed by adefovir dipivoxil	36,361	22.79 (18.44)	12.83	12,298
Conventional interferon alfa followed by lamivudine with adefovir salvage	39,022	23.39 (18.85)	13.19	15,770
Pegylated interferon alfa	18,172	21.85 (17.72)	12.36	2,162
Pegylated interferon alfa followed by lamivudine	20,719	22.69 (18.34)	12.88	2,122
Pegylated interferon alfa followed by adefovir dipivoxil	34,846	23.86 (19.16)	13.53	-2,172
Pegylated interferon alfa followed by lamivudine with adefovir salvage	36,766	24.29 (19.45)	13.77	-3,856

Appendix 17 Additional tables used in economic analysis

Table 48 - Effectiveness of treatment (HBeAg positive patients) in probabilistic analysis

Parameter	Intervention	Mean	Min	Max	Distribution	Parameters
CHB to HBeAg seroconverted	IFN	25%			Beta	n =51; r = 13
	PEG	32%			Beta	n = 271; r = 87
Natural log of relative risk of HBeAg seroconvertion	LAM/ADV	0.6931			Normal	μ = 0.6931; stdev = 0.1447
HBeAg seroconverted patients reactivating disease	IFN/ PEG	9%	5%	15%	Beta	α = 44.6291; β = 481.2494
	LAM	25%	20%	30%	Beta	α = 283.8144; β = 851.4432
	ADV	9%			Beta	n = 66; r = 6
CHB to CC	LAM	2%	0%	7%	Beta	α = 3.7085; β = 181.7161

Notes: exponent of natural log of RR of HBeAg seroconvertion is multiplied by the spontaneous HBeAg seroconversion rate (which is also sampled probabilistically) to get treatment response

Table 49 - Effectiveness of treatment (HBeAg negative patients) in probabilistic analysis

Parameter	Intervention	Mean	Min	Max	Distribution	Parameters
CHB to response	IFN	50%	40%	60%	Beta	α = 189.2096; β = 189.2096
	PEG	59%	49%	69%	Beta	α = 216.0335; β = 150.1250
	LAM	73%			Beta	n = 181; r =132
	ADV	72%			Beta	n = 116; r = 84
Relapse to CHB from treatment response	IFN	60%	50%	80%	Beta	α = 116.4115; β = 77.6077
	PEG	25%	15%	35%	Beta	α = 70.9533; β = 212.8599
	LAM/ADV	80%	70%	90%	Beta	α = 193.7498; β = 48.4378
CHB to CC	LAM	2%	0%	7%	Beta	α = 3.7085; β = 181.7161

Table 50 - Transition probabilities for HBeAg positive patients used in probabilistic analysis

From	To	Mean	Min	Max	Distribution	Alpha	Beta
HBsAg	HCC	0.005%	0.00041%	0.04100%	Beta	0.9187	18372.989
HBeAg	HBsAg	2.000%	0.500%	3.000%	Beta	37.9750	1860.7733
	CHB	3.000%	0.000%	14.000%	Beta	2.6968	87.1967
	CC	1.000%	0.100%	2.000%	Beta	16.6043	1643.8210

	HCC	0.500%	0.020%	2.000%	Beta	3.8417	764.4994
CHB	HBsAg	1.750%	0.000%	2.500%	Beta	29.1488	1636.4943
	HBeAg	9.000%	5.000%	20.000%	Beta	19.8351	200.5553
	CC	5.000%	2.000%	9.000%	Beta	29.3467	557.5868
	HCC	0.500%	0.020%	2.000%	Beta	3.8417	764.4994
	Die	0.350%	0.000%	1.000%	Beta	7.3910	2104.3307
CC	HBeAg	9.000%	5.000%	20.000%	Beta	19.8351	200.5553
	DC	5.000%	3.800%	9.500%	Beta	44.2594	840.9281
	HCC	2.500%	0.200%	8.000%	Beta	6.0644	236.5110
	Die	5.100%	3.100%	6.400%	Beta	137.2366	2553.6776
DC	HCC	2.500%	0.200%	8.000%	Beta	6.0644	236.5110
	LT	3.000%	1.000%	10.000%	Beta	6.5256	210.9945
	Die	39.000%	30.000%	50.000%	Beta	140.4399	219.6624
HCC	Die	56.000%	45.000%	90.000%	Beta	41.2568	32.4160
LT	Die	21.000%	6.000%	42.000%	Beta	16.2762	61.2294
Post-LT	Die	5.700%	2.000%	11.000%	Beta	22.9017	378.8825

Table 51 - Transition probabilities for HBeAg negative patients

From	To	Mean	Min	Max	Distribution	Alpha	Beta
HBsAg	HCC	0.00500%	0.00041%	0.04100%	Beta	0.9187	18372.9890
Respond	HBsAg	1.750%	0.000%	2.500%	Beta	29.1488	1636.4943
	CHB	3.000%	0.000%	14.000%	Beta	2.6968	87.1967
	CC	1.000%	0.100%	2.000%	Beta	16.6043	1643.8210
	HCC	0.500%	0.020%	2.000%	Beta	3.8417	764.4994
	Die	0.350%	0.000%	1.000%	Beta	7.3910	2104.3307
CHB	HBsAg	0.50%	0.00%	0.75%	Beta	26.7751	5328.2548
	ALT norm	14.000%	7.660%	25.960%	Beta	30.4750	187.2036
	CC	9.000%	6.000%	13.000%	Beta	91.0797	920.9171
	HCC	0.500%	0.020%	2.000%	Beta	3.8417	764.4994
	Die	0.350%	0.000%	1.000%	Beta	7.3910	2104.3307
CC	ALT norm	14.000%	7.660%	25.960%	Beta	30.4750	187.2036
	DC	5.000%	3.800%	9.500%	Beta	44.2594	840.9281
	HCC	2.500%	0.200%	8.000%	Beta	6.0644	236.5110
	Die	5.100%	3.100%	6.400%	Beta	137.2366	2553.6776
DC	HCC	2.500%	0.200%	8.000%	Beta	6.0644	236.5110
	LT	3.000%	1.000%	10.000%	Beta	6.5256	210.9945
	Die	39.000%	30.000%	50.000%	Beta	140.4399	219.6624
HCC	Die	56.000%	45.000%	90.000%	Beta	41.2568	32.4160
LT	Die	21.000%	6.000%	42.000%	Beta	16.2762	61.2294
Post-LT	Die	5.700%	2.000%	11.000%	Beta	22.9017	378.8825

Table 52 - Utility decrements to age-specific health state utilities. Values used in probabilistic analysis

	Mean	Min	Max	Distribution	Alpha	Beta
CHB	0.04	0.02	0.06	Beta	14.7512	354.0288
Compensated cirrhosis	0.44	0.25	0.70	Beta	37.5142	47.7453
Decompensated cirrhosis	0.54	0.40	0.70	Beta	46.4138	39.5377
Hepatocellular carcinoma	0.54	0.40	0.70	Beta	46.4138	39.5377
Liver transplantation	0.54	0.40	0.70	Beta	46.4138	39.5377
Post-liver transplantation	0.32	0.05	0.50	Beta	24.0941	51.2000

Table 53 - Health State Cost Distributions

	Mean	Std Err	Distribution	Alpha	Beta
HBsAg seroconverted	0.00	-		-	-
HBeAg seroconverted	266.77	53.354	Gamma	25.0000	10.6708
CHB	537.48	107.496	Gamma	25.0000	21.4992
Compensated cirrhosis	1,138.00	21.56	Gamma	2786.9370	0.4083
Decompensated cirrhosis	9,120.00	240.25	Gamma	1440.9964	6.3290
Hepatocellular carcinoma	8,127.00	427.05	Gamma	362.1622	22.4402
Liver transplantation	27,330.00	352.43	Gamma	6013.4892	4.5448
	9,458.00	311.28	Gamma	923.1796	10.2450
Post-liver transplantation	1,385.00	43.37	Gamma	1019.6660	1.3583

Notes:
Standard error for HBeAg SC and CHB costs assumed to be 20% of mean value
Costs of transplant and first year care are estimated separately. Liver transplant cost is the sum of the two values