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

J Shepherd, J Jones, A Takeda, P Davidson and A Price

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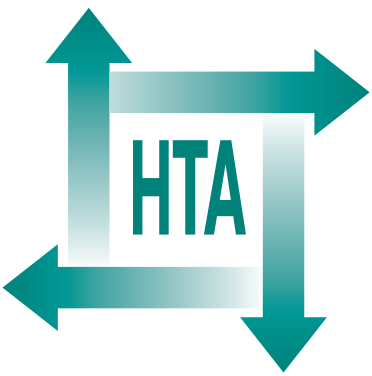

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Abstract

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

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Objectives: To assess the clinical effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alfa-2a (PEG) for the treatment of adults with chronic hepatitis B infection (CHB).
Data sources: Electronic databases for the period from 1995–6 to April 2005. Websites of the relevant organisations.
Review methods: Searches were made for studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history. Randomised controlled trials (RCTs) were included that compared PEG and ADV with currently licensed treatments for CHB, including non-pegylated ('standard') interferon alfa (IFN), lamivudine (LAM), and best supportive care. The trials were reviewed in a narrative synthesis but meta-analysis was not undertaken owing to heterogeneity in the interventions and comparators evaluated. A model was developed to estimate the cost-effectiveness (cost–utility) of PEG and of ADV compared with IFN, LAM and best supportive care in a UK cohort of adults with CHB. 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 CHB. Interventions were evaluated against their closest comparator (for PEG this is IFN, and for ADV this is LAM). In addition, the cost-effectiveness of sequential treatment scenarios was modelled.
Results: A total of 1086 references to clinical effectiveness studies were identified, of which seven fully published RCTs and one systematic review met the inclusion criteria. Four of the RCTs evaluated the effectiveness of ADV and three reported results for PEG. In addition, a conference abstract was included reporting interim results from an on-going Phase II RCT of ADV in combination with LAM. The published trials were of good quality, although details of randomisation and allocation of concealment were poorly reported. ADV was significantly more effective than placebo. Response rates were in the range 21–51% compared with 0%, respectively. For patients resistant to LAM, response rates were significantly higher for those treated with ADV in addition to on-going LAM (35–85%) than those who continued on LAM with placebo (0–11%). Significant alanine aminotransferase (ALT) reductions to normal levels were observed in all studies. For treatment-naïve patients, seroconversion rates were 12–14% for ADV compared with 6% for placebo (statistically significant), rates were higher for LAM-resistant patients who received ADV in addition to on-going LAM (8%) than those who continued on LAM with placebo (2%) (no significance value was reported), and rates were higher for LAM-resistant patients who switched to ADV than those who continued on LAM with placebo (11 versus 0%, respectively; not statistically significant). HBsAg loss or seroconversion was observed in less than 5% of patients taking ADV. Two ADV studies reported changes in liver histology. In general, histological improvement and necroinflammatory activity/fibrosis scores were significantly better in ADV groups than in placebo groups. Dose discontinuations for safety reasons were low for patients receiving ADV. With the exception of headache, the most commonly reported adverse events were often seen in the placebo groups in similar proportions to the ADV groups, with different trials reporting conflicting results. PEG/LAM dual therapy and PEG monotherapy were similar in effect on HBV DNA and ALT levels, and both were significantly superior to LAM monotherapy. Response rates were higher for HBeAg-negative patients than for HBeAg-positive patients. HBeAg seroconversion rates at follow-up were significantly higher for PEG monotherapy patients than for those receiving either a combination of PEG and LAM or LAM monotherapy

(32, 27 and 19%, respectively). For the comparison between PEG and IFN-2a, there was a significant difference in the combined outcome of ALT normalisation, HBV DNA response and HBeAg seroconversion at follow-up (24 versus 12%, respectively). Changes in liver histology were reported by two studies. There was no statistically significant difference in histological improvement between the PEG monotherapy groups, the LAM monotherapy groups and the dual therapy groups. Two PEG trials reported small percentages (up to 5%) of HBsAg loss or seroconversion among patients receiving PEG either as monotherapy or in combination with LAM, but no HBsAg loss or seroconversion was reported in those receiving LAM monotherapy. Health-related quality of life (HRQoL) scores, as measured by the Short Form with 36 Items, 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 treatment groups. Dose discontinuations for safety reasons were significantly higher for patients receiving PEG than for patients receiving LAM monotherapy. The most commonly reported adverse events in the PEG studies were headache, pyrexia, fatigue, myalgia and alopecia. Only one fully published economic evaluation was identified, reporting a US cost-effectiveness study of ADV as salvage therapy for chronic hepatitis B with LAM resistance. A Markov model was used to estimate cost-effectiveness of interferon alfa (6–12 months), LAM and LAM followed by ADV when resistance occurs. ADV generated the most (undiscounted) life-years, but at highest costs, with an incremental cost-effectiveness ratio (ICER) of US$14,204 per life-year gained. Using our model, incremental cost per QALY estimates (baseline cohort of all patients) were: £5994 for IFN compared with best supportive care, £6119 for PEG compared with IFN, £3685 for LAM compared with best supportive care, and £16,569 for ADV compared with LAM. Incremental cost per QALY estimates (HBeAg-positive patients only) were: £7936 for IFN (24 weeks) compared with best supportive care, £16,166 for PEG (48 weeks) compared with IFN (24 weeks), £3489 for LAM compared with best supportive care, and £15,289 for ADV compared with LAM. Incremental cost per QALY estimates (HBeAg-negative patients only) were: £3922 for IFN (48 weeks) compared with best supportive care, £2162 for PEG (48 weeks) compared with IFN (24 weeks), £4131 for LAM compared with best supportive care, and £18,620 for ADV compared with LAM. For the sequential treatment strategies, incremental cost per QALY estimates ranged from £3604 (IFN followed by LAM versus IFN alone) to £11,402 (IFN followed by LAM with adefovir salvage versus IFN followed by LAM). In all of these cases, the ICERs are well within the range that would conventionally be regarded as being cost-effective. The probabilistic sensitivity analysis found that LAM is a cost-effective option at lower willingness-to-pay thresholds 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, PEG is highly likely to be the optimal intervention compared with IFN (based on a cohort of HBeAg-positive and -negative patients). Interferon alfa (non-pegylated or pegylated) followed by LAM would be the optimal strategy at lower willingness-to-pay thresholds. As the threshold increases, the sequential treatment strategy of PEG followed by LAM with adefovir added as salvage therapy is increasingly likely to be the optimal intervention.

Conclusions: ADV and PEG are associated with significant improvements in 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, retreatment with another agent is necessary. The results of our cost-effectiveness analysis demonstrate that incremental costs per QALY for a range of comparisons were between £5994 and £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. Further RCT evidence of the effectiveness of anti-viral treatment is required, particularly for subgroups 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.

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

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) 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 Antibodies to the HBeAg antigen.

Anti-HBs Antibodies 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 necroinflammation 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 strands 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.

continued

Glossary *continued*

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.

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 Characterised 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 necroinflammatory 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.

Low HBV endemicity Prevalence of chronic infection <1%.

Occult HBV infection Characterised 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 immunotolerant 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.

List of abbreviations

AASL	American Association for the Study of the Liver
AASLD	American Association for the Study of Liver Diseases
ADV	adefovir dipivoxil
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
anti-HBc	antibodies to the HBcAg (core) antigen
BASL	British Association for the Study of the Liver
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CI	confidence interval
CRD	Centre for Reviews and Dissemination
DARE	Database or Abstracts and Reviews of Effects
DNA	deoxyribonucleic acid
EASL	European Association for the Study of the Liver
FDA	Food and Drug Administration
HAART	highly active antiretroviral therapy
HAI	histological activity index
HAV	hepatitis A virus
HAV IgM	IgM antibody to hepatitis A antigen
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B s (surface) antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IDU	intravenous drug user
IFN	non-pegylated interferon alfa (either α-2a or α-2b)
ITT	intention-to-treat
LAM	lamivudine
MCHN	Managed Clinical Hepatology Network
MCS	mental health component score
MIU	million international units
MU	million units
NICE	National Institute for Health and Clinical Excellence
PCR	polymerase chain reaction
PCS	physical health component score
PEG	pegylated interferon alfa-2a
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RNA	ribonucleic acid
SD	standard deviation
SF-36	Short Form with 36 Items
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
ULN	upper limit of normal range
YMDD	tyrosine–methionine–aspartate-aspartate

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive 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-2a (PEG) for the treatment of adults with chronic hepatitis B (CHB) infection. This independent assessment was 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).

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 may be HBeAg positive or HBeAg negative, depending on the presence or absence of the e antigen.

There are approximately 156,000 people in England and Wales infected with CHB [180,000 (0.3%) in the UK], with around 7000 new cases every year (mostly from immigration of established HBV carriers). 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.

Methods

Electronic databases were searched from 1995–6 to April 2005 for studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history. For the clinical effectiveness review, randomised controlled trials (RCTs) were included that compared PEG and ADV with currently licensed treatments for CHB, including non-pegylated ('standard') interferon alfa (IFN), lamivudine (LAM), and best supportive care. Short-term outcomes were biochemical, histological and virological response to treatment, drug resistance and adverse effects. The trials were reviewed in a narrative synthesis but meta-analysis was not undertaken owing to heterogeneity in the interventions and comparators evaluated.

A model was developed to estimate the cost-effectiveness (cost–utility) of PEG and of ADV compared with IFN, LAM and best supportive care in a UK cohort of adults with CHB. 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 CHB. In the state transition model, 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:

- CHB
- HBeAg seroconversion/remission
- HBsAg seroconversion
- compensated cirrhosis
- decompensated cirrhosis
- hepatocellular carcinoma
- liver transplant
- death.

The model has a lifetime horizon and a cycle length of 1 year, with a half-cycle correction applied. For treated patients, clinical effectiveness results [HBeAg seroconversion rates and alanine aminotransferase (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). About 70% of HBeAg-positive and 90% of HBeAg-negative patients are male. All have CHB, but have not progressed to cirrhosis.

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

Interventions were evaluated against their closest comparator (for PEG this is IFN, and for ADV this is LAM). In addition, the cost-effectiveness of sequential treatment scenarios was modelled. The results of these comparisons were reported in terms of the incremental gain in quality-adjusted-life years (QALYs) and the incremental costs determined in the cohort analysis.

Results

Clinical effectiveness

A total of 1086 references to clinical effectiveness studies were identified. After screening, seven fully published RCTs and one systematic review met the inclusion criteria. Four of the RCTs evaluated the effectiveness of ADV and three reported results for PEG. In addition, a conference abstract was reviewed which reported interim results from an on-going Phase II RCT of ADV in combination with LAM. The published trials were of good quality, although details of randomisation and allocation of concealment were poorly reported.

ADV

1. In terms of reductions in HBV DNA:
   (a) ADV was significantly more effective than placebo. Response rates were in the range 21–51% compared with 0%, respectively.
   (b) For patients resistant to LAM, response rates were significantly higher for those treated with ADV in addition to on-going LAM (35–85%) than for those who continued on LAM with placebo (0–11%).
2. Significant ALT reductions to normal levels were observed in all studies:
   (a) Response rates for ADV monotherapy after 1 year's treatment were in the range 48–72%, compared with 16–29% for placebo.
   (b) In LAM-resistant patients, significantly higher response rates were observed for those given ADV in addition to LAM, compared with those who continued on LAM with placebo (37 versus 9%).
3. In terms of HBeAg loss and seroconversion:
   (a) For treatment-naïve patients, seroconversion rates were 12–14% for ADV compared with 6% for placebo (statistically significant).
   (b) Rates were higher for LAM-resistant patients who received ADV in addition to on-going LAM (8%) than for those who continued on LAM with placebo (2%). No significance value was reported.
   (c) Rates were higher for LAM-resistant patients who switched to ADV than for those who continued on LAM with placebo (11 versus 0%, respectively; not statistically significant).
4. HBsAg loss or seroconversion was observed in a minority of patients (<5%) taking ADV.
5. Two ADV studies reported changes in liver histology. In general, histological improvement and necroinflammatory activity/fibrosis scores were significantly better in ADV groups than in placebo groups.
6. Dose discontinuations for safety reasons were low for patients receiving ADV. With the exception of headache, the most commonly reported adverse events were often seen in the placebo groups in similar proportions to the ADV groups, with different trials reporting conflicting results.

PEG

1. PEG/LAM dual therapy and PEG monotherapy were similar in effect on HBV DNA and ALT levels, and both were significantly superior to LAM monotherapy. Response rates were higher for HBeAg-negative patients than for HBeAg-positive patients.
   (a) For HBeAg-positive patients, end of follow-up HBV DNA response rates were 32, 34 and 22%, respectively.
   (b) For HBeAg-negative patients, end of follow-up HBV DNA response rates were 43, 44 and 29%, respectively.
   (c) For HBeAg-positive patients, end of follow-up ALT response rates were 41, 39 and 28%, respectively.
   (d) For HBeAg-negative patients, end of follow-up ALT response rates were 59, 60 and 44%, respectively.

2. HBeAg seroconversion rates at follow-up were significantly higher for PEG monotherapy patients than for those receiving either a combination of PEG and LAM or LAM monotherapy (32, 27 and 19%, respectively).
3. For the comparison between PEG and IFN-2a, there was a significant difference in the combined outcome of ALT normalisation, HBV DNA response and HBeAg seroconversion at follow-up (24 versus 12%, respectively).
4. Changes in liver histology were reported by two studies. There was no statistically significant difference in histological improvement between the PEG monotherapy groups, the LAM monotherapy groups and the dual therapy groups.
5. Two PEG trials reported small percentages (up to 5%) of HBsAg loss or seroconversion among patients receiving PEG either as monotherapy or in combination with LAM, but no HBsAg loss or seroconversion was reported in those receiving LAM monotherapy.
6. HRQoL scores, as measured by the Short Form with 36 Items, 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 treatment groups.
7. Dose discontinuations for safety reasons were significantly higher for patients receiving PEG than for patients receiving LAM monotherapy. The most commonly reported adverse events in the PEG studies were headache, pyrexia, fatigue, myalgia and alopecia.

Cost-effectiveness

Systematic review of cost-effectiveness studies

Only one fully published economic evaluation was identified, reporting a US cost-effectiveness study of ADV as salvage therapy for CHB with LAM resistance. A Markov model was used to estimate cost-effectiveness of interferon alfa (6–12 months), LAM and LAM followed by ADV when resistance occurs. ADV generated the most (undiscounted) life-years, but at highest costs, with an incremental cost-effectiveness ratio (ICER) of US$14,204 per life-year gained.

In addition to this study, six cost-effectiveness studies of existing treatments for CHB were identified, published between 1995 and 2002. There was little published literature on HRQoL in CHB.

Modelled cost-effectiveness analysis

From a model developed for this study by the authors, the incremental cost per QALY estimates (baseline cohort of all patients) were:

- £5994 – IFN compared with best supportive care
- £6119 – PEG compared with IFN
- £3685 – LAM compared with best supportive care
- £16,569 – ADV compared with LAM.

Incremental cost per QALY estimates (HBeAg-positive patients only) were:

- £7936 – IFN (24 weeks) compared with best supportive care
- £16,166 – PEG (48 weeks) compared with IFN (24 weeks)
- £3489 – LAM compared with best supportive care
- £15,289 – ADV compared with LAM.

Incremental cost per QALY estimates (HBeAg-negative patients only) were:

- £3922 – IFN (48 weeks) compared with best supportive care
- £2162 – PEG (48 weeks) compared with IFN (24 weeks)
- £4131 – LAM compared with best supportive care
- £18,620 – ADV compared with LAM.

For the sequential treatment strategies, incremental cost per QALY estimates ranged from £3604 (IFN followed by LAM versus IFN alone) to £11,402 (IFN followed by LAM with adefovir salvage versus IFN followed by LAM). 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 ICERs are well within the range that would conventionally be regarded as being cost-effective.

Deterministic sensitivity analysis showed that:

- Excluding transitions from the compensated cirrhosis health state to HBeAg seroconversion produces a substantial increase in the ICER 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.
- 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 ICERs for strategies that include PEG and ADV.
- 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 ICER for strategies including ADV.

- 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, had a dramatic effect on the ICER for ADV, which increased from £16,569 in the base case to £21,363 for the model that extrapolates beyond 4 years and to £50,168 for the model with no extrapolation (i.e. the spontaneous rate).
- The ICERs for PEG appear to be particularly sensitive to variations in the relapse rate for HBeAg-negative patients who achieve a response (by normalising ALTs) following treatment.

The probabilistic sensitivity analysis found that:

- LAM is a cost-effective option at lower willingness-to-pay thresholds for health outcomes, but as the threshold is increased ADV is increasingly likely to be the optimal intervention.
- Where a willingness-to-pay threshold of above £10,000 per QALY is employed, PEG is highly likely to be the optimal intervention compared with IFN (based on a cohort of HBeAg-positive and -negative patients).
- Interferon alfa (non-pegylated or pegylated) followed by LAM would be the optimal strategy at lower willingness-to-pay thresholds. As the threshold increases, the sequential treatment strategy of PEG followed by LAM with ADV added as salvage therapy is increasingly likely to be the optimal intervention.

Conclusions

ADV and PEG are associated with significant improvements in 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, retreatment with another agent is necessary.

The results of our cost-effectiveness analysis demonstrate that incremental costs per QALY for a range of comparisons were between £5994 and £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 RCT evidence of the effectiveness of anti-viral treatment is required, particularly for subgroups 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 ADV in combination with LAM in treatment-naïve patients
- the long-term effectiveness of ADV
- the effectiveness of PEG in LAM non-responders and in interferon alfa non-responders
- long-term follow-up of PEG treatment
- HRQoL.

Chapter 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 (ADV) and pegylated interferon alfa-2a (PEG) for the treatment of chronic hepatitis B (CHB) infection.

Comparators include currently licensed treatments for CHB, including non-pegylated interferon alfa-2a (IFN) and lamivudine (LAM) and also best supportive care. Long-term outcomes include survival, progression to advanced disease states (e.g. cirrhosis) and health-related quality of life (HRQoL). 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 Health and Clinical Excellence (NICE) to issue guidance to the health service in England and Wales on treatment for patients with CHB.

Chapter 2
Background

Description of underlying health problem

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 healthcare 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 [in addition to being infected with hepatitis C virus (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 transplantation.

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

Initial stages of chronic infection

Figure 1 illustrates the natural history and stages of infection of hepatitis B (see also the Glossary for definitions of terms). Chronic disease status is defined by the presence of hepatitis B surface 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 CHB. For children who acquired the infection between ages 1 and 5 years 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, intravenous drug use, acupuncture and transfusion, which are the main forms of transmission in the UK.[1]

Hepatitis B e antigen (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. 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 (ALT) levels (ALT is 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.

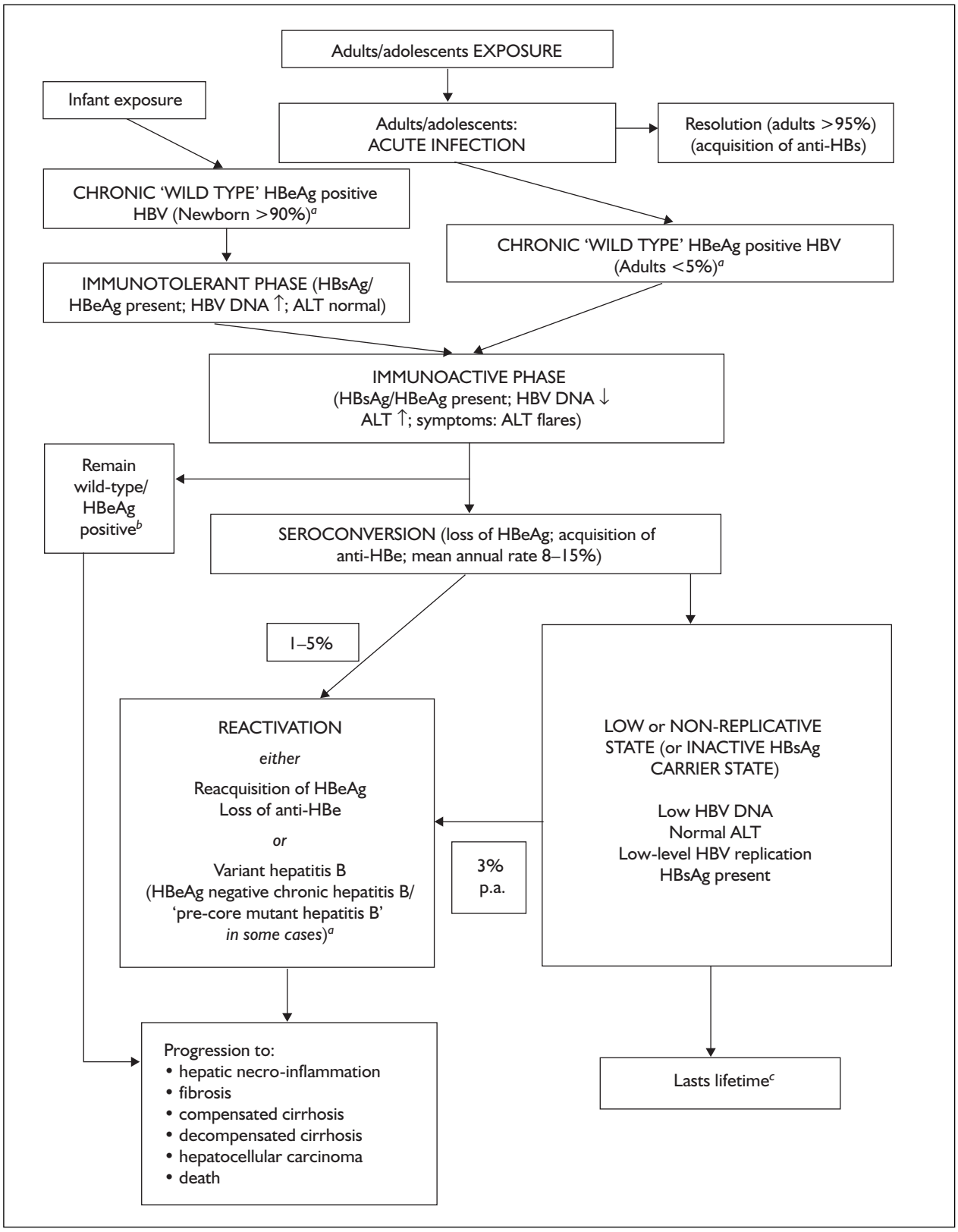

FIGURE 1 *Hepatitis B natural history and stages of infection*

[a] *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.*

[b] *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.*

[c] *Between 1 and 2% of people in Western countries will experience infection resolution each year, characterised by loss of HBsAg and acquisition of anti-HBs.*

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[a]	Detectable[a]	High

[a] Liable to fluctuations.

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]

The low- or 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 South East 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 normalisation in between; recurrent flares with persistently abnormal serum aminotransferase levels in between; and persistently abnormal ALT without flares[3] (*Table 1*).

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 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]

Long-term complications

As with hepatitis C, patients with CHB are at increased risk of progressing to long-term complications including cirrhosis (scarring) of the liver, decompensated liver disease and/or 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 5-year mortality rate for CHB 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 CHB. It is estimated that there are over 1200 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.

Co-infection

Owing 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] Lessells 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.

LAM 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] LAM resistance is reported to be higher in HBV patients who are co-infected with HIV and HIV viral resistance to LAM may also develop. Combination therapy with LAM 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 have shown that HBV replication is suppressed in co-infected patients whereas 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.

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 (IDUs) 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 7000 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 therefore 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]

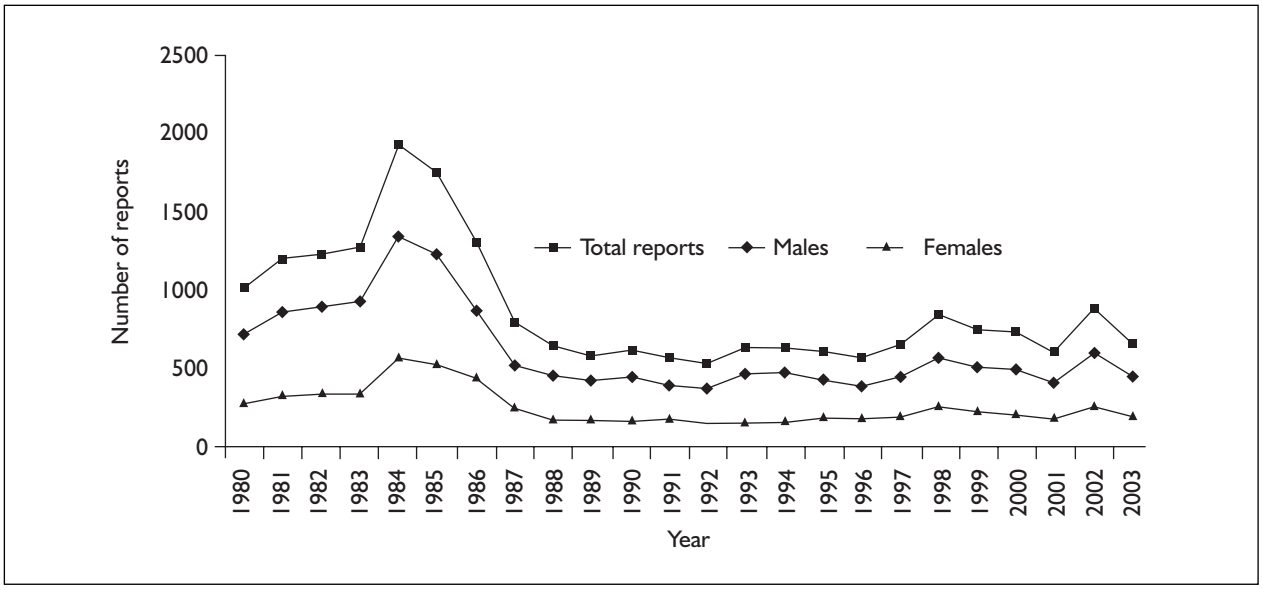

FIGURE 2 *Acute hepatitis B infections 1980–2003 (2003 provisional). Source: Laboratory reports to Communicable Disease Surveillance Centre. Obtained via Health Protection Agency (URL: www.hpa.org.uk; accessed 21 October 2004).*

TABLE 2 *Acute hepatitis B laboratory reports: England and Wales, by sex, 1990–2003*[a]

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003[b]
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

[a] 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.
[b] Provisional.
Source: Laboratory reports to Communicable Disease Surveillance Centre. Obtained via Health Protection Agency (URL: www.hpa.org.uk; accessed 20 May 2005).

The incidence of acute hepatitis in England and Wales fell markedly in the late 1980s owing to education campaigns and schemes to reduce needle sharing among IDUs 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 years (80%) and male (70%). Mode of transmission was unknown in 46% of cases, 21% acquired the virus through intravenous drug use, 13% 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 4400 new cases per 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 owing to targeted vaccination campaigns), with a concurrent increase in transmission among 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.

The unlinked anonymous prevalence monitoring programme found that in 2001 21% of IDUs had

evidence of previous or current infection (anti-HBc – the antibody against the core antigen HBcAg). Intravenous drug use remains the single greatest risk factor for HBV infection. Vaccination coverage in this group was from 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 eight of the 135 prisons in England and Wales found that 8% were positive for anti-HBc (the core antigen).[13] About 24% 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 and 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 years were positive for anti-HBc, 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 antenatal 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 five 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 antenatal 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 are not known.

In summary, it is estimated that there are around 156,000 people in England and Wales infected with CHB[9] and around 7000 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.

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 CHB infection.[1] A diagnosis of HBeAg-positive CHB 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.

Morbidity and quality of life

The impact of CHB on quality of life (QoL) 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 with 36 Items (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, QoL 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 QoL. There is evidence to suggest that QoL impairment in CHB is not as great as it is with chronic hepatitis C.[15,17]

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 WHO, the UK has not introduced such a policy, instead offering selective vaccination to key risk groups (e.g. men who have

sex with men, IDUs, healthcare workers). However, uptake by risk groups has been reported to be low. Hahne and colleagues[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 and 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 and an urgent review of commissioning of specialised liver disease services
- 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 Association for Sexual Health and HIV (BASHH) have published guidelines on the management of viral hepatitides A, B and C.[22] The British HIV Association (BHIVA) have published guidelines on 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.

Current service provision

Management of people with hepatitis B is the responsibility of a variety of people. In the healthcare 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 (Primary Care Trusts), 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 antiviral 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 whereas 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]

Antiviral treatment for hepatitis B is dependent on a number of factors, notably the stage of disease the patient is in (e.g. acute HBV, immunotolerant infection, immunoactive CHB, compensated cirrhosis), 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 antiviral 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 contraindicated. This would usually involve LAM, a nucleotide analogue. This mode of treatment may be particularly suitable for those HBeAg-negative patients with high levels of HBV DNA and ALT. 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' will likely limit disease progression.

There is considerable debate regarding the place of monotherapy versus 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 reinfection rates tend to be high, necessitating continuing antiviral therapy. Recurrent HBV infection is associated with rapid progression to cirrhosis and decompensation. Transplant patients may therefore receive life-long hepatitis B immunoglobulin (HBIG), immunosuppressive agents and antiviral drugs such as lamivudine. However, the potential for resistance means that this drug can be used with only limited success in this patient group. Adefovir dipivoxil, associated with lower resistance, might be more suitable (see the sections 'Adefovir dipivoxil' (next column) and 'Treatment resistance' (p. 47).

The following subsections 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.

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 million units (MU) per day or 9–10 MU three times per 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 contraindication to interferon alfa therapy) an initial 12–24-month course of interferon alfa 5–6 MIU three times per 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 contraindication in patients with advanced (decompensated) liver disease. Severe side-effects are rare. However, long-term therapy (e.g. >1 year) can be hard for patients to tolerate.

Lamivudine

In 1998, LAM (Epivir, Zeffix; GlaxoSmithKline), a nucleoside reverse transcriptase inhibitor, was licensed for the treatment of CHB. It is also used to treat HIV in patients with AIDS. The advantage of LAM 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 contraindicated (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 100 mg 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 1 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]

LAM can be used as first-line treatment for some patients, and expert opinion suggests that it is used more commonly than interferon alfa as first-line therapy. 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 and compensated liver disease is LAM (used in approximately 80%). LAM can also be used as dual therapy with interferon alfa in both HBeAg-positive and -negative patients.

Description of new intervention

Adefovir dipivoxil

ADV, a prodrug of adefovir, was launched in 2003 as the first licensed nucleotide for the treatment of CHB. ADV is rapidly converted to adefovir in plasma and tissues with a plasma half-life of 5–7 hours and is excreted in urine. ADV

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 ALT levels and histological evidence of active liver inflammation and fibrosis **or** decompensated liver disease. The recommended dose is 10 mg/day, taken orally.

EASL guidelines recommend that ADV, like LAM, can be used as second-line therapy in patients who have not responded to IFN. ADV can also be used as second-line therapy in patients who have become resistant to LAM (where it might be given as a replacement for LAM or added to ongoing LAM). Expert opinion suggests that many clinicians would use it as first-line therapy but for its cost (around four times more expensive than LAM). Like LAM, it can be used in the treatment of pre- and post-liver transplant patients, and might be more suitable than LAM owing to a lower rate of resistance [see the section 'Treatment resistance' (p. 47)].

In terms of adverse events, ADV 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 3 months.

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

Pegylated interferon alfa-2a (PEG)

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 kDa pegylated interferon-2a (Pegasys; Hoffman-La Roche) and (ii) 12 kDa pegylated interferon-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.

PEG 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 the Southampton Health Technology Assessments Centre (SHTAC).[27] In February 2005, PEG-2a received its marketing authorisation from the EU Commission for the treatment of both HBeAg-positive and -negative CHB in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis. PEG 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] outlined the potential place of PEG as being first-line treatment with reservation of other antiviral agents (e.g. LAM/ADV) for patients who have failed PEG treatment in whom remission is unlikely. It may also be used as dual therapy with LAM and in the retreatment of patients failing IFN. Withdrawal rates due to adverse effects with PEG are reported to be less than with IFN and lower than those observed in hepatitis C.[29]

PEG 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.

Chapter 3
Methods

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

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, QoL, resource use/costs and epidemiology/natural history (see Appendices 1, 2 and 3 for search strategies). The strategies were applied to the following electronic databases:

1. Cochrane Systematic Reviews Database
2. Cochrane Central Register of Controlled Trials
3. NHS CRD (University of York) databases:
   (a) DARE (Database of Abstracts of Reviews of Effects)
   (b) Health Technology Assessment (HTA) database
   (c) NHS EED (Economic Evaluations Database)
4. MEDLINE (Ovid)
5. PreMEDLINE
6. EMBASE (Ovid)
7. EconLit (Silver Platter)
8. National Research Register
9. ISI Web of Science – Science Citation Index
10. ISI Proceedings
11. BIOSIS
12. Clinicaltrials.gov
13. Current Controlled Trials.

Searches for clinical effectiveness, cost-effectiveness, costs of illness, QoL, and epidemiology/natural history studies were carried out for the period from 1995–6 to 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; and 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 NICE were searched for studies that met the inclusion criteria.

Inclusion and exclusion criteria

Studies identified by the search strategy were assessed for inclusion through two stages. First, 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. Second, full text versions of relevant papers were retrieved and an inclusion worksheet (see Appendix 4) 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.

Interventions

1. interventions (alone and in combination with other treatment options):
   (a) PEG
   (b) ADV
2. comparators (alone and in combination with other treatment options):
   (a) PEG (intervention was not compared with itself)
   (b) ADV (intervention was not compared with itself)
   (c) interferon alfa-2a
   (d) interferon alfa-2b

(e) LAM
(f) best supportive care.

Patients

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

Types of studies

1. 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.
2. With the exception of one as yet unpublished RCT, studies presented as conference abstracts 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 'unpublished data').
3. Full economic evaluations of the specified interventions in patients with CHB were included.
4. A range of designs for studies on HRQoL and epidemiology/natural history were considered.

Outcomes

1. The following outcome measures were included:
   (a) survival
   (b) HRQoL
   (c) drug resistance
   (d) time to treatment failure
   (e) histological response (e.g. inflammation/fibrosis – on biopsy)
   (f) biochemical response (e.g. liver function – aminotransferase)
   (g) virological response (e.g. seroconversion rate and viral replication – HBV DNA)
   (h) seroconversion (e.g. HBeAg loss/anti-HBe; HBsAg loss/anti-HBs)
   (i) adverse effects of treatment.

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 5–12.

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.

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 owing to heterogeneity in the interventions and comparators evaluated by the included clinical trials. Where data allowed, clinical and cost-effectiveness were assessed according to patient subtypes (e.g. according to genotypes).

Chapter 4

Clinical effectiveness

Results

Quantity and quality of research available

The initial literature search generated a total of 806 references (152 on the term pegylated interferon alfa, 682 on the term adefovir dipivoxil and 28 which contained both terms). Additional references were added as the review progressed. In total, 1086 titles and abstracts were inspected, of which 164 papers were retrieved. Of these, 155 were excluded according to our criteria, leaving nine included studies.

Of the 155 excluded studies:

- 88 were conference abstracts.
- 21 were non-systematic reviews.
- 29 were general background reviews or guidelines.
- 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 ADV as monotherapy, 16 reported PEG monotherapy, 22 reported ADV with LAM and 17 reported PEG with LAM (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 subgroup 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 'unpublished data').

In terms of the nine included studies:

- Seven were fully published RCTs.
- One was a systematic review.
- One was a pooled subgroup analysis of two of the RCTs.

In addition to these, a conference abstract relating to an additional RCT is presented.

Four of the fully published RCTs evaluated the effectiveness of ADV, 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 of treatment are available.

- Two of these three studies are ongoing with treatment continuing for up to 5 years.[31,32]
- The other reports results at the end of 52 weeks of treatment.[33] This study is continuing treatment in 78 participants for a further 2 years.
- Three of the trials used a dose of 10 mg/day, but one of the monotherapy trials compared doses of 10 and 30 mg/day with placebo (*Table 3*).

A further trial by Sung and colleagues[34] is currently available only as a conference abstract. This Phase II RCT included two arms, comparing the use of LAM plus ADV with LAM monotherapy in previously untreated patients. Results are available (in abstract form only) for 52 weeks of treatment, with the study continued for a further 52 weeks. As there is increasing interest in the role of combination therapy (see NICE's guidance on hepatitis B, via www.NICE.org.uk), and in the absence of fully published RCTs, we included this abstract in our review of clinical effectiveness. Caution is advised as the study has not undergone full critical appraisal.

Three fully published RCTs evaluated the effectiveness of PEG, two for 48 weeks and one for 24 weeks. The 48-week trials compared PEG monotherapy with PEG in combination with LAM and with LAM alone. The latter compared three doses of PEG with IFN.

The key characteristics of the RCTs are shown in *Table 4*. One of the four ADV RCTs[31] and one of the three PEG RCTs[36] included patients with HBeAg-negative CHB. The other five published trials were based on patients who were HBeAg positive. The published trials ranged in size from 59 to 814 participants, with the trial by Marcellin

TABLE 3 *Characteristics of included studies – trial arms*

Study	HBeAg status	No. of participants (*n*), duration of trial (T_d), additional follow-up (F_d) and total duration (total)	Arm 1	Arm 2	Arm 3	Arm 4
ADV studies						
Hadziyannis *et al.*, 2003[31] Study 438	Negative	*n* = 185 T_d = 48 weeks[a] F_d = 0 weeks Total = 48 weeks	ADV 10 mg/d (*n* = 123)	Placebo (*n* = 62)		
Marcellin *et al.*, 2003[32] Study 437	Positive	*n* = 515 T_d = 48 weeks[b] F_d = 0 weeks Total = 48 weeks	ADV 10 mg/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[c] F_d = 0 weeks Total = 52 weeks	LAM 100 mg/d + ADV 10 mg/d (*n* = 46)	LAM 100 mg/d + placebo (*n* = 49)		
Peters *et al.*, 2004[35] Study 461	Positive	*n* = 59 T_d = 48 weeks F_d = 0 weeks Total = 48 weeks	ADV 10 mg/d + placebo (*n* = 19)	ADV 10 mg/d + LAM 100 mg/d (*n* = 20)	LAM 100 mg/d + placebo (*n* = 19)	
Sung *et al.*, 2003[34] (unpublished data)	Positive	*n* = 115 T_d = 52 weeks[d] F_d = 0 weeks Total = 52 weeks	LAM 100 mg/d + ADV 10 mg/d (*n* = 55)	LAM 100mg/d + placebo (*n* = 57)		
PEG studies						
Marcellin *et al.*, 2004[36] Study 241	Negative	*n* = 552, of whom 537 were included in analyses T_d = 48 weeks F_d = 24 weeks Total = 72 weeks	PEG 180 μg/w + placebo (*n* = 177)	PEG 180 μg/w + LAM 100 mg/d (*n* = 179)	LAM 100 mg/d (*n* = 181)	
Cooksley *et al.*, 2003[37] Study 037	Positive	*n* = 194 T_d = 24 weeks F_d = 24 weeks Total = 48 weeks	IFN 4.5 MIU 3 × week (*n* = 51)	PEG 90 μg/w (*n* = 49)	PEG 180 μg/w (*n* = 46)	PEG 270 μg/w (*n* = 48)
Lau *et al.*, 2005[38–40] Study 240	Positive	*n* = 814 T_d = 48 weeks F_d = 24 weeks Total = 72 weeks	PEG 180 μg/w + placebo (*n* = 271)	PEG 180 μg/w + LAM 100 mg/d (*n* = 271)	LAM 100 mg/d (*n* = 272)	

[a] After 48 weeks, patients in the ADV group were re-randomised to receive placebo for 48 weeks or 10 mg ADV for 192 weeks. Patients in the placebo group received 10 mg ADV for a further 192 weeks. Study due to end June 2005 when patients will have received 5 years of treatment.

[b] After 48 weeks patients were reassigned so that the 30-mg ADV group received placebo, the 10-mg ADV group were re-randomised to receive either 10 mg ADV or placebo, and the placebo group received 10 mg ADV. After July 2001, the double-blind phase of the study was terminated and all groups were assigned to receive 10 mg ADV (open label) up to March 2005, when patients will have received 5 years of treatment.

[c] 78 patients continued to receive treatment for a further 2 years (Study 493). Study is ongoing.

[d] Study continued for a further 52 weeks.

and colleagues[32] being the largest published ADV study and that by Lau and colleagues[38–40] the largest PEG study. 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[34,35,37] did not state their funding sources in the published papers, but the remaining studies were sponsored by drug manufacturers.

Summary of key trials

Key points regarding the aims of the trials, their duration and publication status are summarised below.

Adefovir dipivoxil studies

Hadziyannis and colleagues, 2003[31] (Study 438).

1. HBeAg negative.
2. Two arms: ADV 10 mg versus placebo.
3. Fully published results up to 48 weeks of blinded, randomised treatment.
4. After 48 weeks, patients in the ADV group were re-randomised to receive placebo for 48 weeks, or 10 mg ADV for 192 weeks. Patients in the placebo group received 10 mg ADV for a further 192 weeks. The study is due to end in June 2005, when patients will have received 5 years of treatment.

Hadziyannis and colleagues, 2005[41] (long-term continuation of Study 438).

1. After 48 weeks, patients in the ADV arm of Study 438 were randomly assigned to continued ADV therapy or placebo for a further 48 weeks. Patients who had been in the placebo group for the first 48 weeks were switched to ADV for the next 48 weeks.
2. Patients receiving ADV for weeks 49–96 were subsequently offered continued therapy until week 240.
3. Results are reported for the continued ADV group at weeks 96 (n = 79) and 144 (n = 70), the ADV–placebo group at week 96 (n = 40), and the placebo–ADV group at week 96 (n = 60).

Marcellin and colleagues, 2003[32] (Study 437).

1. HBeAg positive.
2. Three arms: ADV10 mg versus ADV 30 mg versus placebo.
3. Fully published results up to 48 weeks of blinded, randomised treatment.
4. After 48 weeks, patients were to be reassigned so that the 30-mg ADV group received placebo, the 10 mg ADV group were re-randomised to receive either 10 mg ADV or placebo and the placebo group received 10 mg 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 10 mg ADV (open label) up to March 2005, when patients will have received 5 years of treatment.
5. Conference abstracts are available with results up to week 144.[42,43]

Perrillo and colleagues, 2004[33] (Study 465).

1. HBeAg positive, LAM resistant.
2. Two arms: LAM + ADV 10 mg versus LAM + placebo.
3. Designed to test the safety and efficacy of adding ADV to ongoing LAM in patients who have developed LAM resistance, versus maintaining them on LAM.
4. Fully published results up to 52 weeks of blinded, randomised treatment.
5. 78 patients continued to receive treatment for a further 2 years (Study 493). Study is ongoing.
6. Conference abstracts are available for extension Study 493 at 104 weeks.[44,45]

Peters and colleagues, 2004[35] (Study 461).

1. HBeAg positive, LAM resistant.
2. Three arms: ADV 10 mg + placebo versus LAM + ADV 10 mg versus LAM + placebo.
3. Designed to test the safety and efficacy of:
   (a) switching LAM resistant patients to ADV monotherapy, versus maintaining them on LAM.
   (b) adding ADV to ongoing LAM in patients who have developed resistance, versus maintaining them on LAM
4. Fully published results up to 48 weeks of randomised treatment.
5. No results published beyond 48 weeks, either as conference abstract or full publication.

Sung and colleagues, 2003[34] (unpublished data).

1. HBeAg positive.
2. LAM + ADV (10 mg) versus LAM + placebo.
3. Designed to test the safety and efficacy of dual therapy versus monotherapy in patients not previously treated.
4. 52-week data available as a conference abstract.

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 years • **HBeAg negative** • Compensated liver disease • Total bilirubin level of no more than 2.5 mg/dl • Prothrombin time no more than 1 s above the normal range • Serum albumin level at least 3 g/dl • Serum creatinine level of no more than 1.5 mg/day • 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 years • Sex: 83% male	*Primary outcomes:* • Histological 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 16–65 years (*NB baseline characteristics table lists age range as 16–68 years*) • **HBeAg positive** • Compensated liver disease • Average age ~33 years	• 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 <6 months 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 years • Sex: 74% male	*Primary outcomes:* • Histological 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:* GlaxoSmithKline; Gilead Sciences *Country:* not stated	• HBsAg + adults receiving ongoing lamivudine therapy for >6 months for CHB • **HBeAg positive** • Compensated liver disease • HBV DNA concentration $\geq 10^6$ 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 years • Sex: 95% male	*Primary outcomes:* • Reduction in HBV DNA *Secondary outcomes:* • ALT normalisation • HBeAg loss and seroconversion • Proportion of patients with undetectable serum HBV DNA • Proportion of patients with YMDD mutant HBV DNA

continued

TABLE 4 *Characteristics of included studies – participants and outcomes (cont'd)*

Study	Methods	Key inclusion criteria	Other patient characteristics	Outcomes
Peters *et al.*, 2004[35] 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 years • HBsAg present for ≥ 6 months • **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 preceding 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 years • 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 from baseline • % of patients with ALT normalisation • 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 • 96% ALT> ULN • 98% HBV DNA positive	*Primary outcomes:* • HBV DNA time-weighted average change from baseline to week 16 ($DAVG_{16}$). *Secondary outcomes:* • ALT normalisation • HBV DNA reduction • HBeAg/HBsAg loss • Incidence of viral breakthrough and YMDD mutant HBV

continued

TABLE 4 *Characteristics of included studies – participants and outcomes (cont'd)*

Study	Methods	Key inclusion criteria	Other patient characteristics	Outcomes
Pegylated interferon alfa studies				
Marcellin *et al.*, 2004[36] 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/ml • A serum alanine aminotransferase level >1 but ≤10 times the ULN	• No decompensated liver disease; no treatment for CHB within the previous 6 mths • 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 years • Sex: 85% male	*Primary outcomes:* • Normalisation of ALT levels • Suppression of HBV DNA to below 20,000 copies/ml *Secondary outcomes:* • HBsAg loss • HBsAg seroconversion • Histological response • Suppression of HBV DNA to below 400 copies/ml • Ranked assessments of necroinflammatory activity and fibrosis • Safety analysis • Resistance analysis
Cooksley *et al.*, 2003[37]	*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 • Average age: ~31 years • Sex: 74% male	*Outcomes:* • Loss of HBeAg • Suppression of HBV DNA levels to <500,000 • Copies/ml • Normalisation of ALT, seroconversion to anti-HBe • Loss of HBsAg • Combined response of HBeAg loss, HBV DNA suppression and ALT normalisation

continued

TABLE 4 *Characteristics of included studies – participants and outcomes (cont'd)*

Study	Methods	Key inclusion criteria	Other patient characteristics	Outcomes
Lau *et al.*, 2005[40]	*Design:* multicentre RCT *Number of centres:* 67 *Country:* 16 countries in North America, South America, Europe, Middle East, Asia and Australasia *Sponsor:* Roche	• HBsAg positive 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 • Sex: 78% male	*Primary outcomes:* • HBeAg seroconversion • HBV DNA <100,000 copies/ml *Secondary outcomes:* • Combines response (HBeAg seroconversion, ALT normalisation and HBV DNA <100,000 copies/ml) • HBsAg seroconversion • Histological response • Adverse events

ULN, upper limit of normal range.

5. Study is ongoing and will continue for total treatment duration of 104 weeks.

PEG studies

Marcellin and colleagues, 2004[36] (Study 241).

1. HBeAg negative.
2. Three arms: PEG + placebo versus PEG + LAM versus LAM.
3. Designed to assess the safety and efficacy of combination therapy in this patient group.
4. Fully published data for 48 weeks partially double-blinded, randomised treatment plus 24 weeks of follow up.
5. No further follow-up published or available as conference abstract.

Cooksley and colleagues, 2003[37] (Study 037).

1. HBeAg positive.
2. Four arms: IFN versus PEG 90 µg/week versus PEG 180 µg/week versus PEG 270 µg/week.
3. Fully published data for 24 weeks of open-label treatment with 24 weeks of follow-up.
4. No further follow-up published or available as conference abstract.

Lau and colleagues, 2005[40] (Study 240).

1. HBeAg positive.
2. Three arms: PEG 180 µg/week + placebo versus PEG 180 µg/week + LAM versus LAM.
3. Designed to compare PEG as combination therapy and monotherapy with LAM.
4. Fully published for 48 weeks of treatment plus 24 weeks of follow-up.

The published RCTs used similar inclusion and exclusion criteria and most defined CHB by the presence of detectable HBsAg for at least 6 months, a serum HBV DNA level of at least 10^5 copies/ml (10^6 in one study[33]) and an ALT level of between one 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.[36,37] Studies with HBeAg-negative participants also specified undetectable HBeAg and detectable anti-HBe.

Three of the ADV studies specified that patients must have compensated liver disease[31, 33] and one[32] specified that participants must have well preserved liver function. The three published PEG studies all excluded patients with decompensated liver disease.

Four of the studies included small proportions of patients with compensated cirrhosis/bridging fibrosis. Three of these were PEG studies: 9% in the study by Cooksley and colleagues,[37] 16% in the study by Lau and colleagues[40] and 27% in the study by Marcellin and colleagues.[36] The only ADV 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 ADV study of HBeAg-negative patients[31] had previously used interferon alfa and less than 10% had previously used LAM. The studies by Peters and colleagues[35] and Perrillo and colleagues[33] included patients who were resistant to LAM. The ADV studies of HBeAg-positive participants specified no prior therapy within 3[32,33] or 6[35] 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[36] which reported on PEG in HBeAg-negative participants stated that 6% had previously used LAM and 8% had previously used interferon alfa. Approximately 12% of participants in the study by Lau and colleagues[40] had previously used LAM and about 12% had previously used IFN.

None of the seven published RCTs included patients co-infected with HIV and six of the studies also excluded patients co-infected with HCV or HDV [see the section 'Effectiveness of treating patients with co-morbidities/co-infections' (p. 54) for details of studies in these patients].

Information on ethnicity was provided by three of the published ADV studies; just under two-thirds of participants were white and approximately one-third were Asian. The unpublished study by Sung and colleagues[34] 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 PEG studies, with 61% in the study by Marcellin and colleagues,[36] 97% in the study by Cooksley and colleagues[37] and 85–97% in the study by Lau and colleagues.[40] 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 years. The mean age of the HBeAg positive participants in one of the adefovir dipivoxil studies[32] was 33 years, but those in the remaining three adefovir

dipivoxil studies had similar mean ages of 43–46 years. The mean age of participants in the unpublished study by Sung and colleagues[34] was 36 years. The mean ages of patients in the two published PEG trials differed by 10 years, with the HBeAg-negative people in Study 241 by Marcellin and colleagues[36] having a mean age of 41 years compared with only 31 years in the HBeAg-positive study by Cooksley and colleagues.[37] The average age of participants in Lau and colleagues' study[40] was 32 years, similar to that in the study by Cooksley and colleagues,[37] but approximately 10 years older than the average age of participants in Study 241.[36]

Between 74 and 95% of participants in the included studies were male. Recent figures from the Health Protection Agency (http://www.hpa.org.uk/infections/topics_az/hepatitis_b/data.htm; accessed 21 October 2004) 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[37] reported the genotype profile of the study population (33% genotype B; 67% genotype C). However, Westland and colleagues[46] reported a pooled analysis of effects by genotype of two of the ADV studies [see the section 'Subgroup comparisons' (p. 44)]. Genotypic analyses of HBV polymerase was performed in the study by Peters and colleagues[35] on patients who had LAM-resistant mutations by sequencing at baseline. All four major patterns of LAM-resistant 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, in the PEG Study 241, Marcellin and colleagues[36] used a serum HBV DNA threshold of 20,000 copies/ml, whereas Cooksley and colleagues' earlier study[37] defined a response as suppression of HBV DNA levels to <500,000 copies/ml.

The primary outcome measure used in two of the ADV trials (Studies 438[31] and 437[32]) was histological 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,[36] in their study of PEG, used ALT normalisation as an additional primary outcome. Cooksley and colleagues[37] also used 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 ADV studies included normalisation of ALT levels as a secondary outcome measure.

Four of the studies of HBeAg-positive participants[32,33,35,37] used HBeAg loss or HBeAg seroconversion as a secondary outcome measure. Other common secondary outcomes were HBV DNA change (for Studies 437 and 438, which did not include this as a primary outcome), and HBsAg loss or seroconversion.[31,35–37]

The primary outcomes in the study by Lau and colleagues[38–40] were HBeAg seroconversion and HBV DNA <100,000 copies/ml.

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,[31,36] 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

TABLE 5 *Quality assessment table*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	ITT analysis	Withdrawals explained
ADV studies – HBeAg negative										
Hadziyannis *et al.*, 2003[31]	Un	Ad	Rep	Ad	Ad	Ad	Par	Ad	In	Par
ADV 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[35]	Un	Un	Rep	Ad	Ad	Ad	Ad	Ad	In	Ad
PEG studies – HBeAg negative										
Marcellin *et al.*, 2004[36]	Un	Ad	Rep	Ad	Ad	Ad	Par	Ad	Par	Ad
PEG studies – HBeAg positive										
Cooksley *et al.*, 2003[37]	Un	Un	Rep	Ad	NA	NA	NA	Ad	Ad	Par
Lau *et al.*, 2005[40]	Un	Un	Ad	Ad	Ad	Un	Un	Ad	Ad	Par

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

colleagues[37] was an open-label study, so assessment of blinding is recorded as 'not applicable' in the table.

All seven published RCTs reported primary outcomes adequately, giving point estimates and measures of variability. However, only the studies by Cooksley and colleagues[37] and Lau and colleagues[40] described an adequate intention-to-treat (ITT) 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.[33,35,36] 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 study by Sung and colleagues[34] is currently only available as conference presentations. Consequently, it was not possible to assess its methodological quality and so it has been excluded from *Table 5*.

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; subgroup 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.

Virological response

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

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 ADV in comparison with placebo:

1. 51% of the ADV treated patients achieved undetectable HBV DNA levels (defined as

TABLE 6 *Virological response (ADV)*

Study, patient type, outcome type	Treatment arms			Difference
Hadziyannis *et al.*, 2003,[31] HBeAg negative, secondary	**ADV 10 mg/d (*n* = 117)**	**Placebo (*n* = 55)**		
HBV DNA mean change (reduction) from baseline at week 48 (log copies/ml)	3.91	1.35		$p < 0.001$
n (%) with undetectable HBV DNA levels	63/123 (51)	0/61 (0)		$p < 0.001$
Perrillo *et al.*, 2004,[33] HBeAg positive, primary	**LAM 100 mg/d + ADV 10 mg/d (*n* = 46)**	**LAM 100 mg/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	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 100 mg/d + ADV 10 mg/d (*n* = 55)**	**LAM 100 mg/d (*n* = 57)**		
HBV DNA (log copies/ml):				
Baseline	8.84	9.17		
$DAVG_{16}$[a]	–4.20	–4.20		
Median change: week 16	–4.82	–5.04		
week 52	–5.41	–4.80		
<200 (LLOD) week 52	21/54 (39%)	23/56 (41%)		
Breakthrough DNA[b]	3/54 (2%)[c]	11/55 (20%)		
Marcellin *et al.*, 2003,[32] HBeAg positive, secondary	**10 mg ADV (*n* = 171)**	**30 mg ADV (*n* = 173)**	**Placebo (*n* = 167)**	
HBV DNA change from baseline (log copies/ml)				
Results at 48 weeks:				
Mean ± SD	–3.57 ± 1.64	–4.45 ± 1.62	–0.98 ± 1.32	
Median	–3.52	–4.76	–0.55	
95% CI	–3.84 to –3.31	–4.72 to –4.19	–1.20 to –0.77	
p-Value	<0.001	<0.001		
Serum HBV DNA <400 copies/ml at 48 weeks:				
n (%)	36 (21)	67 (39)	0	
p-Value	<0.001	<0.001		
Peters *et al.*, 2004,[35] HBeAg positive	**ADV 10 mg/d + placebo (*n* = 19)**	**ADV 10 mg/d + LAM 100 mg/d (n = 20)**	**LAM 100 mg/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	–3.11* ± 0.94 (–3.54 to –2.69)	–2.95* ± 0.64 (–3.23 to –2.66)	0.0 ± 0.28 (–0.14 to 0.13)	*$p < 0.001$
Week 48	–4.00* ± 1.41 (–4.65 to –3.35)	–3.46* ± 1.10 (–3.94 to –2.97)	–0.31 ± 0.93 (–0.74 to 0.12)	*$p < 0.001$

continued

TABLE 6 *Virological response (ADV) (cont'd)*

Study, patient type, outcome type	Treatment arms			Difference
HBV DNA undetectable at week 48 (secondary outcome measure) *n* (%) (<1000 copies/ml)	5 (26)	7(35)	0	$p < 0.005$

CI, confidence interval; SD, standard deviation.
[a] $DAVG_{16}$ ($DAVG_{48}$) 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 copies/ml) divided by the number of days from baseline up to the last included value.
[b] 1 log copies/ml, 2 consecutive occasions.
[c] This percentage appears to be incorrect, but is reproduced here from the conference abstract.

<400 copies/ml) compared with none of the placebo-treated patients at week 48 ($p < 0.001$) (Study 438).[31]
   (a) Hadziyannis and colleagues reported long-term results from an extension to Study 438.[41] After 96 weeks, 50 (71%) of patients on continued ADV therapy had serum HBV DNA of <1000 copies/ml, compared with three (8%) of patients who had switched from ADV to placebo after 48 weeks and 37 (76%) of patients who had switched from placebo to ADV at 48 weeks. The difference between the continued ADV therapy group and the group switching from ADV to placebo was statistically significant ($p < 0.001$). Of the patients who continued ADV therapy for 144 weeks, 53 (79%) had serum HBV DNA levels of <1000 copies/ml.
2. The proportion of patients achieving a serum HBV DNA level of <400 copies/ml at week 48 was 21% (for the 10-mg ADV dose) and 39% (30-mg ADV dose) compared with 0% for placebo-treated patients.[32] Both ADV treatment groups were significantly better than placebo ($p < 0.001$).
   (a) Additional information was provided in a conference abstract.[42] At week 96, 45% of 231 patients who had continued to receive 10 mg of ADV had a serum HBV DNA undetectable by polymerase chain reaction (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 ADV in addition to on-going lamivudine:

1. The percentage achieving an HBV DNA response at both weeks 48 and 52 was 11% for patients treated with LAM monotherapy, compared with 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 reduction.[33]
2. HBV DNA levels were undetectable (<1000 copies/ml) in 26% of ADV + placebo patients and 35% of ADV + LAM patients, in comparison with no patients receiving LAM + placebo ($p < 0.005$).[35]

Response rates were similar for patients treated with PEG-2a monotherapy as for those treated with the combination of PEG-2a and LAM. Both groups had significantly higher rates than patients treated with LAM monotherapy:

1. Marcellin and colleagues[36] (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 LAM monotherapy group).
   (a) First, 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 ($p = 0.003$).
   (b) Second, 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 ($p = 0.001$).

TABLE 7 *Virological response (PEG)*

Study, patient type, outcome type	Treatment arms			Difference
Marcellin *et al.*, 2004,[36] HBeAg negative	**PEG 180 μg/week (*n* = 177)**	**PEG 180 μg/week + LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**	
Primary outcome:				
HBV DNA <20,000 copies/ml[a]				
End of treatment (week 48):				
n (%) of patients	144 (81)	164 (92)	154 (85)	
95% CI (%)	74.8 to 86.8	86.6 to 95.2	79.0 to 89.9	
End of follow-up (week 72):				
n (%) of patients	76 (43)	79 (44)	53 (29)	
95% CI (%)	35.5 to 50.6	36.7 to 51.7	22.8 to 36.5	
p-Value compared with LAM monotherapy:				*p*-Value between PEG groups = 0.849
At week 72*	0.007	0.003		
Odds ratio (95% CI)[b]	1.8 (1.2 to 2.9)	1.9 (1.2 to 3.0)		
Secondary outcome:				
HBV DNA <400 copies/ml				
End of treatment (week 48)				
n (%) of patients	112 (63)	156 (87)	133 (73)	
95% CI (%)	55.7 to 70.4	81.3 to 91.7	66.4 to 79.8	
End of follow-up (week 72):				
n (%) of patients	34 (19)	35 (20)	12 (7)	
95% CI (%)	13.7 to 25.8	14.0 to 26.1	3.5 to 11.3	
p-Value compared with LAM monotherapy	<0.001	<0.001		
Primary outcome:				
Change in HBV DNA				
End of treatment (week 48)				
Total number of patients	166	165	174	
Mean log copies/ml	–4.1	–5.0	–4.2	
95% CI (log copies/ml)	–3.8 to –4.5	–4.7 to –5.3	–3.9 to –4.5	
End of follow-up (week 72)				
Total number of patients	165	170	154	
Mean log copies/ml	–2.3	–2.4	–1.6	
95% CI (log copies/ml)	–1.9 to –2.7	–1.9 to –2.8	–1.2 to –2.0	
Lau *et al.*, 2005,[40] HBeAg positive, primary	**PEG 180 μg/week (*n* = 271)**	**PEG 180 μg/week + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	
HBV DNA <100,000 copies/ml End of treatment (week 48), *n* (%)	142 (52)	233 (86)	169 (62)	Overall treatment effect *p* = 0.007; Peg vs PEG + LAM *p* = 0.652
HBV DNA <100,000 copies/ml End of follow-up (week 72), *n* (%)	86 (32)	91 (34)	60 (22)	
p-Value compared with LAM monotherapy	*p* = 0.01	*p* = 0.003		
Lau *et al.*, 2005,[40] HBeAg Positive, secondary	**PEG 180 μg/week (*n* = 271)**	**PEG 180 μg/week + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	
Mean change from baseline (total *n* assessed)				
Week 48	–4.5 (248)	–7.2 (249)	–5.8 (249)	
Mean change from baseline (total n assessed)				
Week 72	–2.4 (248)	–2.7 (254)	–1.9 (241)	

continued

TABLE 7 *Virologic response (PEG) (cont'd)*

Study, patient type, outcome type	**Treatment arms**						**Difference**
HBV DNA <400 copies/ml, *n* (%)							
End of treatment (week 48)	68 (25)		186 (69)		108 (40)		
End of follow-up (week 72)	39 (14)		37 (14)		14 (5)		
p-Value compared with LAM monotherapy at week 72	<0.001		<0.001				
Cooksley *et al.*, 2003,[37] HBeAg positive	**IFN 4.5 MIU 3 × week (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 to 40]	21 (43) [29 to 58]	18 (39) [25 to 55]	13 (27) [15 to 42]	52 (36)	0.096	0.085
Change in HBV DNA (week 24) Mean log copies/ml	–2.2	–2.83[b]	–3.5	–3.14[b]			

[a] $p = 0.005$ for the overall test of treatment effect.
[b] Estimate via graph reading.

2. Lau and colleagues[40] (HBeAg-positive patients) employed a response threshold of 100,000 copies/ml. At the end of 48 weeks of treatment, 52% of the PEG monotherapy group had a virological of response, compared with 86% of the dual therapy group and 62% of the LAM monotherapy group. 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 ($p = 0.01$).
   (a) Lau and colleagues[40] also reported HBV DNA <400 copies/ml as a secondary outcome measure. This showed a greater difference between groups during treatment, with response rates at end of treatment of 25, 69 and 40% for PEG, PEG + LAM and LAM groups, respectively. By the end of follow-up, response rates had dropped to 14 for each of the PEG groups and 5% for the LAM monotherapy group, a statistically significant difference.

Response rates were higher for patients treated with PEG-2a in comparison with IFN, although not significantly:

1. Cooksley and colleagues[37] measured viral response at <500,000 copies/ml. At follow-up (week 48), 25% of IFN-treated patients had responded, in comparison with 36% for all three PEG doses combined ($p = 0.08$). Response rates for the PEG groups ranged from 27% (270 µg/week dose) to 43% (90 µg/week dose). The difference in response rates between the PEG groups combined versus IFN and between all four treatment groups was not significant.

Changes in HBV DNA levels

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

1. The mean reduction in HBV DNA from baseline to week 48 ($\log_{10}$ copies/ml) was 3.91 for ADV in comparison with 1.35 for placebo ($p < 0.001$) (Study 438).[31]
   (a) Hadziyannis and colleagues reported long-term results from an extension to Study 438.[41] The mean reduction in HBV DNA from baseline to week 96 ($\log_{10}$ copies/ml) was 3.35 ± 1.18 in 70 people who continued ADV therapy, compared with 1.34 ± 1.24 in the group who switched from ADV to placebo ($n = 38$) and 3.71 ± 1.05 in the group who switched from placebo to ADV ($n = 49$). The difference between the continued ADV group and the

group who switched from ADV to placebo was statistically significant ($p < 0.001$). The mean reduction in HBV DNA had increased slightly to 3.42 ± 1.27 in the 67 people who continued ADV therapy to week 144.

2. The mean change [± standard deviation (SD)] in HBV DNA from baseline to 48 weeks (log copies/ml) was –3.57 ± 1.64 (for the 10-mg ADV dose) and –4.45 ± 1.62 (30-mg ADV dose), compared with –0.98 ± 1.32 for placebo-treated patients (Study 437).[32] Differences between both treatment groups and the placebo group were statistically significant ($p < 0.001$).

Decreases in HBV DNA levels were greater for the LAM-resistant patients who received ADV in addition to ongoing LAM, in comparison with those continuing on LAM:

1. The median change in HBV DNA (log copies/ml) from baseline level to week 52 was +0.3 (–6.0 to 5.4) for LAM + placebo, compared with –4.6 (–7.3 to 1.5) for LAM + ADV, $p < 0.001$.[33]
   (a) Additional results are reported in a conference abstract[45] for 78 patients from the original 52-week study 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 LAM-resistant patients who switched to ADV and those who continued with LAM with the addition of ADV. Both were significantly greater compared with those who continued with LAM:

1. 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.[35]
2. Sung and colleagues (Study 468)[34] reported preliminary results of their ongoing RCT 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 versus –5.41 $\log_{10}$ copies/ml for LAM + placebo group). Statistical significance was not reported.

For the two PEG combination therapy trials, patterns were similar to those observed with HBV DNA response rates. There were similar reductions for PEG-2a monotherapy and PEG-2a in combination with LAM, and both had greater reductions than LAM 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:

1. Mean reductions in HBV DNA ($\log_{10}$ 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[36] (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 the PEG and LAM monotherapy groups (–4.1 and –4.2, respectively). Statistical significance was not reported.
2. 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, –2.7 and –1.9 for the PEG, PEG + LAM and LAM groups, respectively[40] (HBeAg-positive patients). Statistical significance was not reported.

Reductions in HBV DNA levels appear greater with PEG-2a in comparison with IFN:

1. 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/week PEG doses, respectively, in comparison with –2.2 for IFN-treated patients. Figures for the 90 and 270 µg/week PEG doses were estimated from the graph in the published article.[37] Statistical significance was not reported.

Virological response – summary

In terms of HBV response and reductions in HBV DNA:

1. ADV was significantly more effective than placebo (in both HBeAg-positive and -negative patients).

2. In LAM-resistant HBeAg-positive patients, the addition of ADV to ongoing LAM was significantly more effective than maintenance with LAM alone. Adding ADV to ongoing LAM was of similar effectiveness to switching to ADV.
3. There was little difference between PEG monotherapy and PEG in combination with LAM, but both were significantly more effective than LAM monotherapy at end of follow-up (both HBeAg-positive and -negative patients).
4. PEG was associated with higher response rates than IFN, but the difference was not always statistically significant (HBeAg-positive patients).
5. Virological response rates decline following cessation of PEG or ADV treatment.

Biochemical response (ALT)

Tables 8 and *9* present the biochemical response for ADV and PEG, 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 ADV in comparison with placebo. A slightly higher response was observed with the 30-mg dose:

1. In Study 438,[31] 72% of ADV-treated patients had normalised ALT levels at week 48 compared with 29% in placebo-treated patients ($p < 0.001$).
2. Hadziyannis and colleagues reported long-term results from an extension to Study 438.[41] At week 96, 47 patients (73%) who received continued ADV therapy had normalised ALT, compared with 12 (32%) in the group of patients who switched from ADV to placebo after 48 weeks and 40 (80%) of the group who switched from placebo to ADV after 48 weeks. The difference between the ADV–placebo group and the ongoing ADV group at 96 weeks was statistically significant ($p < 0.001$). Of the 62 patients who continued ADV for 144 weeks, 43 (69%) had normalised ALT.
3. The proportion of patients with normalised ALT at 48 weeks was 48% (for the 10-mg ADV dose) and 55% (30-mg ADV dose) compared with 16% for placebo-treated patients ($p < 0.001$ for both comparisons) (Study 437).[32]
   (a) Additional information is provided in a conference abstract.[42] At week 96 ($n = 231$), 71% of 231 patients who continued to receive 10 mg of ADV had normalised ALT levels. At week 144, this figure was 81%, of 84 patients.

Response rates were highest for LAM-resistant patients who received ADV in addition to ongoing LAM:

1. The proportion of patients with normalised ALT levels at both weeks 48 and 52 was 9% for patients treated with LAM + placebo, compared with 37% for patients treated with LAM + ADV ($p < 0.003$).[33]
   (a) A conference abstract[45] 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.
2. The study by Peters and colleagues[35] found that response rates for LAM-resistant patients who switched to ADV were similar to those who received ADV in addition to on-going LAM (47 and 53%, respectively). Rates for both groups were significantly higher than for patients who continued with LAM (+ placebo) (5%).
3. Sung and colleagues reported results from Study 468 in a conference abstract.[34] Approximately 70% of the LAM + placebo group had normalised ALT at weeks 48 and 52 compared with 48% of the ADV + LAM group ($p = 0.023$).

By the end of follow-up, response rates for patients treated with PEG monotherapy were similar to those treated with PEG in combination with LAM. Both PEG groups showed significantly higher response rates than those for patients treated with LAM monotherapy at week 72:

1. Marcellin and colleagues[36] 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 LAM 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.
   (a) 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).

TABLE 8 *Biochemical response ALT (ADV)*

Study, patient type, outcome type	Treatment arms			Difference
Hadziyannis *et al.*, 2003,[31] HBeAg negative, secondary	**ADV 10 mg/d (*n* = 116)**	**placebo (*n* = 59)**		
n (%) with normalised ALT levels at 48 weeks	84 (72)	17 (29)		$p < 0.001$
Median decrease from baseline (U/l) at 48 weeks	55	38		$p = 0.01$
Perrillo *et al.*, 2004,[33] HBeAg positive, secondary	**LAM 100 mg/d + ADV 10 mg/d (*n* = 46)**	**LAM 100 mg/d + placebo (*n* = 48)**		
ALT change from baseline (IU/l) at 52 weeks:				
Mean (SD)	–90 (160)	–44 (312)		
Range	–793 to 43	–1643 to 758		
Change from baseline in ALT times the ULN at 52 weeks:				
Median	–1.1	–0.2		
Range	–18.4 to 1.0	–38.2 to 17.6		$p \leq 0.01$
ALT normalisation at both 48 and 52 weeks	37%	9%		$p = 0.003$
Sung *et al.*, 2003[34] (unpublished data)	**LAM 100 mg/d + ADV 10 mg/d (*n* = 55)**	**LAM 100 mg/d (*n* = 57)**		
ALT normalisation weeks 48 and 52	25/52 (48%)	39/56 (70%)		$p = 0.023$
Median change at week 52	–1.80	–1.84		
ALT median (× ULN):				
Baseline	2.79	2.52		
W16	1.16	0.94		
W52	0.81	0.55		
Peters *et al.*, 2004,[35] HBeAg positive, secondary	**10 mg ADV + placebo (*n* = 19)**	**10 mg ADV + 100 mg LAM (*n* = 20)**	**LAM + placebo (*n* = 19)**	
Change in serum ALT level (IU/l), mean ± SD (95% CI)	–87.7 ± 121.7 (–143.9 to –31.5)	–48.6 ± 82.0 (–84.5 to –12.6)	± 30.8 (–4.2 to 14.2)	
Normalisation of serum ALT, *n*/total (%)	9*/19 (47)	10**/19 (53)	1/19 (5)	*$p = 0.004$, **$p = 0.001$
Marcellin *et al.*, 2003,[32] HBeAg positive, secondary	**10 mg ADV (*n* = 171)**	**30 mg ADV (*n* = 173)**	**Placebo (*n* = 167)**	
Change in ALT (IU/l) at 48 weeks:				
Mean ± SD	–92.1 ± 167.2	–74.4 ± 128.4	–23 ± 140.7	
Median	–51	–54	–17	
95% CI	–118.8 to –65.3	–95.6 to –53.3	–45.9 to –0.2	
p-Value	<0.001	<0.001		
Normalisation of ALT at 48 weeks:				
n/total (%)	81/168 (48)	93/169 (55)	26/164 (16)	
p-Value	<0.001	<0.001		

(b) 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 ($p = 0.003$).

2. Lau and colleagues[38–40] (HBeAg-positive patients) reported ALT normalisation rates at end of treatment and end of follow-up. At end of treatment, ALT normalisation was highest in the LAM monotherapy group:
   (a) The proportion of patients with an ALT response at week 48 was 39, 46 and 62% in the PEG, PEG + LAM and LAM groups,

TABLE 9 *Biochemical response (PEG)*

Study, patient type, outcome type	**Treatment arms**			**Difference**
Marcellin et *al.*, 2004,[36] HBeAg negative, primary	**PEG 180 µg/week (*n* = 177)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**	
ALT normalisation				
End of treatment (week 48)				
n (%) of patients	67 (38)	87 (49)	132 (73)	
95% CI (%)	30.7 to 45.4	41.1 to 56.2	65.8 to 79.3	
End of follow-up (week 72)				
n (%) of patients	105 (59)	107 (60)	80 (44)	
95% CI (%)	51.7 to 66.6	52.2 to 67.0	36.8 to 51.8	*Comparison between PEG groups, $p = 0.0915$
p-Value compared with LAM monotherapy*	0.004	0.003		
Odds ratio (95% CI)	1.9 (7.2 to 2.8)	1.9 (1.2 to 2.9)		
Lau et *al.*, 2005,[40] HBeAg positive, secondary	**PEG 180 µg/week (*n* = 271)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	
ALT normalisation at end of treatment (week 48), *n* (%)	105 (39)	126 (46)	168 (62)	
ALT normalisation at end of follow-up (week 72), *n* (%)	111* (41)	106** (39)	76 (28)	Compared with LAM only: *$p = 0.002$ **$p = 0.006$

Cooksley et *al.*, 2003,[37] HBeAg positive	**IFN 4.5 MIU 3 × week (*n* = 51)**	**PEG 90 µg/week (*n* = 49)**	**PEG 180 µg/week (*n* = 46)**	**PEG 270 µg/week (*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 to 40]	21 (43) [29 to 58]	16 (35) [21 to 50]	15 (31) [19 to 46]	52 (36)	0.290	0.153

respectively. By the end of follow-up, this had increased to 41% in the PEG monotherapy group, but had reduced in the dual therapy group (39%) and the LAM monotherapy group (28%). Differences between PEG monotherapy and LAM monotherapy were statistically significant ($p = 0.002$) at the end of follow-up, as were those between the PEG + LAM and LAM monotherapy groups ($p = 0.006$).

Response rates were higher for PEG in comparison with IFN-2a, although not significantly:

1. 25% of IFN-treated patients had responded at follow-up (week 48), in comparison with 36% for all three PEG doses combined ($p = 0.153$). Response rates for the PEG groups ranged from 31% (270 µg/week dose) to 43% (90 µg/week dose). The difference in response rates between the four treatment groups was not significant ($p = 0.290$).[37]

Changes in ALT levels

Some studies reported mean or median changes in ALT levels between baseline and follow-up, in terms of IU/l or U/l. Mean changes in ALT levels were not reported in any of the published PEG trials.

Decreases in ALT levels were generally greater for ADV in comparison with placebo and for the lower dose compared with the higher dose:

1. In Study 438 by Hadziyannis and colleagues,[31] the median decrease in ALT at week 48 was 55 U/l for ADV in comparison with 38 U/l for placebo ($p = 0.01$).
   (a) Hadziyannis and colleagues reported long-term results from an extension to Study 438.[41] At week 96, the median change in serum ALT for the continued ADV group ($n = 71$) was –59 IU/l. This reduced slightly to –54 IU/l in the 67 people who were assessed after continued ADV therapy for 144 weeks. The median change in the group who switched from ADV to placebo ($n = 38$) was –29.5 IU/l, and in the group who switched from placebo to ADV after 48 weeks ($n = 50$) it was –79.5 IU/l. The difference between the ADV–placebo group and the ongoing ADV group at 96 weeks was statistically significant ($p = 0.01$).
2. In the study by Marcellin and colleagues,[32] the mean decrease (± SD) in ALT from baseline to 48 weeks was 92 (±167.2) IU/l for the 10-mg ADV dose and 74 (±128.4) IU/l for the 30-mg ADV dose, compared with 23 (±140.7) IU/l 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 LAM-resistant patients who received ADV in addition to ongoing LAM:

1. In the study by Perrillo and colleagues,[33] the mean (± SD) change in ALT levels from baseline to week 52 was –44 (± 312) IU/l for LAM monotherapy compared with –90 IU/l (± 160) for LAM + ADV (not statistically significant).
2. Peters and colleagues[35] also found a greater mean reduction in ALT levels in LAM-resistant patients receiving ADV (87.7 points) or ADV added to ongoing LAM (48.6 points) compared with a mean increase of 3 points in those receiving lamivudine monotherapy. Statistical significance was not reported.
3. Sung and colleagues[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 of treatment. Statistical significance was not reported.

Marcellin and colleagues[36] (HBeAg-negative patients) reported marked elevations ('flares') in ALT levels during and after therapy. Flares are often observed prior to a response to treatment:

1. Marked elevations in ALT of more than 10 times the upper limit of the normal range (or > 300 IU/l) were observed in a significantly higher proportion of the PEG monotherapy group than the PEG + LAM or LAM monotherapy groups during therapy [12% versus 4% ($p = 0.007$) and 6% ($p = 0.038$), respectively].
2. After therapy, the proportion of people with marked elevations in ALT levels was significantly higher in the LAM monotherapy (14%, $p = 0.03$) or dual therapy (15%, $p = 0.02$) groups than in the PEG monotherapy group (7%). There was a significant association between a marked elevation in ALT during therapy and normalisation of ALT levels at week 72 ($p = 0.01$).

Biochemical response (ALT) – summary
In terms of ALT response:

1. ADV was significantly more effective than placebo (for both HBeAg-positive and -negative patients), but this was only maintained with continued treatment.
2. ADV added to ongoing LAM in LAM-resistant HBeAg-positive patients was significantly more effective than continuing with LAM.
3. There was little difference between PEG monotherapy and PEG in combination with LAM. Two studies reported that PEG treatment (either alone or in combination with LAM) was significantly more effective than lamivudine monotherapy (HBeAg-negative patients) by the end of follow-up.
4. Differences between PEG and IFN responses were not statistically significant.

In terms of changes in ALT levels:

1. ADV was significantly more effective than placebo (for both HBeAg-positive and -negative patients). Improvements in biochemical response were only maintained while treatment continued.
2. Preliminary conference abstract evidence suggests the two regimens to be of similar efficacy in treatment-naïve patients (no significance values reported).

Liver histological response

Four studies reported changes in liver histology:

1. Study 438 by Hadziyannis and colleagues[31] reported liver histology as a primary outcome measure.

2. ADV Study 437[32] by Marcellin and colleagues reported histological improvement as a primary outcome and other histological assessments as secondary outcomes.
3. Two PEG studies by Marcellin and colleagues[36] (HBeAg-negative patients) and Lau and colleagues[38–40] (HBeAg-positive patients) reported histological 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 stated otherwise.

Histological improvement is defined in ADV 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 PEG Study 241 by Marcellin and colleagues,[36] histological response is defined as a reduction from baseline of at least 2 points in the modified (Ishak) histological 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 ADV 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 shows histological improvement rates.

1. Approximately one-third of the placebo group and two-thirds of the ADV group in Study 438[31] (HBeAg-negative patients) experienced histological improvement, with a statistically significant absolute difference of 30% ($p < 0.001$).
   (a) Further results for the subset of patients who received continuous ADV were presented for this study in a conference abstract.[47] The proportion with an improvement in Ishak fibrosis score (defined as a ≥1 point reduction) after 96 weeks of treatment was 53%. At 144 weeks this figure was 63%. At weeks 96 and 144, 5% and 10%, respectively, had worsened on this score.
2. ADV Study 437 (HBeAg-positive participants) found that both the 10-mg and 30-mg ADV groups had a statistically significantly higher rate of histological improvement than the placebo group (53 and 59 versus 25%, $p < 0.001$ for both groups). The proportion of participants in Study 437 showing no histological improvement was also greater in the placebo group than in either of the treatment groups (65 versus 36 and 28% for placebo, 10-mg ADV and 30-mg ADV groups, respectively).
3. The PEG combination therapy studies[36,40] reported the proportion of participants showing histological 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. The PEG group showed a higher percentage of improvers than the PEG + LAM dual therapy group or the LAM group in the study in HBeAg-negative patients,[36] whereas the PEG + LAM group showed the highest percentage of improvers in the HBeAg positive study,[40] followed by the PEG monotherapy group on an ITT basis and the LAM monotherapy group in the analyses of people with paired biopsy samples.
4. Change in Knodell score was reported in ADV Studies 437 and 438, but not in the PEG study (*Table 11*). The ADV 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 and –0.16 in placebo arms. The treatment difference compared with placebo was statistically significant for both the 10- and 30-mg dosage groups ($p < 0.001$).
5. A small change in Knodell fibrosis score was seen for both treatment and placebo groups, ranging from –0.18 to –0.32 for ADV groups and from +0.1 to –0.01 for placebo groups. The treatment difference was statistically significant for the 10-mg ADV group in Study 438 ($p = 0.005$) and the 30-mg ADV group in Study 437 ($p = 0.001$). In Study 437, changes in Knodell fibrosis score between the ADV 10-mg dose group and the placebo group were not significant.
6. Hadziyannis and colleagues reported long-term results from an extension to Study 438.[41] Changes in Knodell score are shown in *Table 12*. Patients who continued ADV therapy for 96 weeks showed very little difference in either component of the Knodell score between weeks 48 and 96. Patients who received ADV until week 48 and placebo from weeks 48 to 96 showed a mean increase of approximately 3 points on the inflammation component between weeks 48 and 96, but no change in fibrosis. Patients who received placebo until

TABLE 10 *Histological improvement (ADV and PEG)*

Study, drug, patient type, outcome type	Treatment arms			Difference
Hadziyannis *et al.*, 2003,[31] ADV, HBeAg negative, primary Study 438	**ADV 10 mg/d (*n* = 121)**	**Placebo (*n* = 57)**		
Histological 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 *et al.*, 2003,[32] ADV, HBeAg positive, primary Study 437	**10 mg ADV (*n* = 168)**	**30 mg ADV (*n* = 165)**	**Placebo (*n* = 161)**	
Histological improvement (Knodell score) at end of treatment (week 48)				
n (%)	89* (53)	98* (59)	41 (25)	*$p < 0.001$ for both groups
No improvement *n* (%)	61* (36)	47* (28)	105 (65)	
Unstratified relative risk	2.1	2.3		
95% CI	1.5 to 2.8	1.7 to 3.1		
Stratum-adjusted relative risk	2.1	2.3		
95% CI	1.6 to 2.8	1.7 to 3.1		
Marcellin *et al.*, 2004,[36] PEG, HBeAg negative, secondary Study 241	**PEG 180 µg/week (*n* = 177)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**	
Histological response (Ishak score) at end of follow-up (week 72)				
Improved *n* (%)	85 (48)	68 (38)	72 (40)	$p = 0.144$ overall
95% CI (%)	40.5 to 55.6	30.9 to 45.5	32.6 to 47.3	
No. of patients with paired biopsy samples:				
n (%) improved	143	143	125	$p = 0.101$ overall
95% CI (%)	85 (59) 50.9 to 67.6	68 (48) 39.1 to 56.1	72 (58) 48.4 to 66.4	
Lau *et al.*, 2005,[40] HBeAg positive, secondary	**PEG 180 µg/week (*n* = 271)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	
All patients				
No. of patients improved/total no. of patients (%) at end of follow-up (week 72)	102/271 (38)	111/271 (41)	93/272 (34)	Overall treatment effect $p = 0.23$
Patients with paired biopsy samples				
No. of patients improved/total no. of patients (%) at end of follow-up (week 72)	102/207 (49)	112/215 (52)	93/184 (51)	Overall treatment effect $p = 0.79$

week 48 and ADV from weeks 48 to 96 showed a mean decrease of approximately 3 points on the inflammation score, and approximately 0.5 points on the fibrosis component.

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 13*).

TABLE 11 *Change in Knodell score (ADV)*

Study, drug, patient type, outcome type	Treatment arms			Difference
Hadziyannis *et al.*, 2003,[31] ADV, HBeAg negative, primary Study 438	**ADV 10 mg/d (*n* = 116)**	**Placebo (*n* = 59)**		
Change in total Knodell score (week 48):	(*n* = 112)	(*n* = 55)		
Mean ± SD	–3.7 ± 3.1	0.4 ± 3.7		$p < 0.001$
Median	–4	1		
Range	–11 to 2	–9 to 8		
Change in Knodell necroinflammatory score (week 48):	(*n* = 112)	(*n* = 55)		
Mean ± SD	–3.4 ± 2.9	0.3 ± 3.2		$p < 0.001$
Median	–3	0		
Range	–9 to 2	–7 to 8		
Change in Knodell fibrosis score at week 48:	(*n* = 112)	(*n* = 55)		
Mean ± SD	–0.3 ± 0.7	0.1 ± 0.9		$p = 0.005$
Median	0	0		
Range	–3 to 1	–2 to 2		
Marcellin *et al.*, 2003,[32] ADV, HBeAg positive, primary Study 437	**10 mg ADV (*n* = 145)**	**30 mg ADV (*n* = 150)**	**Placebo (*n* = 146)**	
Necroinflammatory activity – Knodell Score (week 48):				
Mean ± SD change in score	–2.58 ± 3.22	–3.17 ± 3.30	–0.16 ± 3.06	$p < 0.001$
Median change in score	–2	–3	0	for both
Range of scores	–9 to 6	–9 to 5	–10 to 7	groups
Fibrosis – Knodell score (week 48):				
Mean ± SD change in score	–0.18* ± 0.84	–0.32** ± 0.80	–0.01 ± 0.86	*$p = 0.061$
Median change in score	0	0	0	**$p = 0.001$
Range of scores	–2 to 2	–2 to 2	–3 to 2	

Both ADV studies reported an improvement in treatment groups compared with placebo in terms of necroinflammatory activity and fibrosis assessments:

1. In ADV Study 438, almost twice as many participants in the ADV group as in the placebo group showed an improvement in necroinflammatory activity. Only 3% of the ADV group showed a worsening of necroinflammatory activity, compared with just over half of the placebo group. Approximately 95% of the ADV 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.

2. ADV 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 ADV 10-mg group and 10% of the ADV 30-mg group. The differences for changes in fibrosis assessment were less marked, with 10 and 14% of the ADV 30- and 10-mg dose groups, respectively, and 26% of the placebo group experiencing worsening of fibrosis.

PEG Study 241[36] 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:

1. Just over half of the PEG group reported an improvement in necroinflammatory activity,

TABLE 12 *Changes from baseline in Knodell scores at weeks 48 and 96*[41]

	Continued ADV (*n* = 19)	ADV–placebo (*n* = 8)	Placebo–ADV (*n* = 20)
Overall score			
Baseline	10.02 ± 2.07	12.3 ± 2.25	8.3 ± 3.31
Change week 48	–4.4 ± 2.39	–4.3 ± 1.49	0.9 ± 4.56
Change week 96	–4.7 ± 2.7	–1.4 ± 1.92	–2.4 ± 4.79
Inflammation			
Baseline	8.37 ± 1.50	10.0 ± 1.31	6.40 ± 2.76
Change week 48	–4.2 ± 2.32	–3.8 ± 1.83	0.6 ± 3.78
Change week 96	–4.3 ± 2.71	–0.9 ± 1.96	–2.3 ± 3.93
Fibrosis			
Baseline	1.84 ± 1.17	2.3 ± 1.39	1.9 ± 1.17
Change week 48	–0.2 ± 0.63	–0.5 ± 0.93	0.3 ± 1.17
Change week 96	–0.4 ± 1.12	–0.5 ± 0.93	–0.15 ± 1.27

TABLE 13 *Ranked assessment of change (ADV and PEG)*

Study, drug, patient type, outcome type	Treatment arms			Difference
Hadziyannis *et al.*, 2003,[31] ADV, HBeAg negative, primary Study 438	**ADV 10 mg/d (*n* = 116)**	**Placebo (*n* = 59)**		
Necroinflammatory activity at end of treatment (week 48):				
Improved (%)	80	42		
No change (%)	17	7		Not
Worse (%)	3	51		reported
Fibrosis at end of treatment (week 48):				
Improved (%)	48	25		
No change (%)	47	36		
Worse (%)	4	38		
Marcellin *et al.*, 2003,[32] ADV, HBeAg positive, secondary Study 437	**10 mg ADV (*n* = 150)**	**30 mg ADV (*n* = 145)**	**Placebo (*n* = 145)**	
Necroinflammatory activity at end of treatment (week 48) *n* (%):				
Improved	107 (71)	112 (77)	59 (41)	$p < 0.001$
No change	23 (15)	18 (12)	37 (26)	for both
Worse	20 (13)	15 (10)	49 (34)	groups
Fibrosis at end of treatment (week 48) *n* (%):				
Improved	62 (41)	78 (54)	35 (24)	$P < 0.001$
No change	67 (45)	53 (37)	72 (50)	for both
Worse	21 (14)	14 (10)	38 (26)	groups
Marcellin *et al.*, 2004,[36] PEG, HBeAg negative, secondary Study 241	**PEG 180 µg/week (*n* = 143)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 143)**	**LAM 100 mg/d (*n* = 125)**	
Necroinflammatory activity at end of follow-up (week 72):				
Improved *n* (%)	79 (55)	66 (46)	57 (46)	
Worse *n* (%)	16 (11)	23 (16)	21 (17)	
Fibrosis:				
Improved *n* (%)	21 (15)	18 (13)	22 (18)	
Worse *n* (%)	11 (8)	15 (10)	6 (5)	

TABLE 14 *HBeAg loss/seroconversion (ADV)*

Study, patient type, outcome type	Treatment arms			Difference
Perrillo *et al.*, 2004,[33] HBeAg positive, secondary *n*/total *n* (%)	**LAM 100 mg/d + ADV 10 mg/d (*n* = 40)**		**LAM 100 mg/d + placebo (*n* = 42)**	
HBeAg loss	6/40 (15)		1/42 (2)	
HBeAg seroconversion at week 52	3/40 (8)		1/42 (2)	
Sung *et al.*, 2003,[34] (unpublished data)	**LAM 100 mg/d + ADV 10 mg/d (*n* = 55)**		**LAM 100 mg/d (*n* = 57)**	
HBeAg loss at week 52	10/53 (19%)		11/54 (20%)	
Marcellin *et al.*, 2003,[32] HBeAg positive, secondary	**10 mg ADV (*n* = 171)**	**30 mg ADV (*n* =173)**	**Placebo (*n* = 167)**	
HBeAg Loss at 48 weeks				
n/total *n* (%)	41/171 (24)	44/165 (27)	17/161 (11)	
p-Value	<0.001	<0.001		
HBeAg seroconversion at 48 weeks				
n/total *n* (%)	20/171 (12)	23/165 (14)	9/161 (6)	
p-Value	<0.049	<0.011		
Peters *et al.*, 2004,[35] HBeAg positive, secondary	**ADV 10 mg/d + placebo (*n* = 19)**	**ADV 10 mg/d + LAM 100 mg/d (*n* = 18)**	**LAM 100 mg/d + placebo (*n* = 19)**	
HBeAg status:				
Negative at week 48 *n* (%)	3[a] (16)	3[b] (17)	0 (0)	[a] $p = 0.075$
Rate of seroconversion	2[c] (11)	1[d] (6)	0 (0)	[b] $p = 0.067$
				[c] $p = 0.152$
				[d] $p = 0.304$

compared with 46% of both the LAM group and the PEG + LAM group.
2. 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.
3. 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 ADV studies and two PEG studies reported histological outcome measures:

1. A statistically significant difference between ADV groups and placebo groups was seen in terms of histological improvement.
2. There was no statistically significant difference in histological improvement between the PEG group, the LAM group and the PEG + LAM group.
3. Change in Knodell scores for necroinflammatory activity was significantly better for ADV than placebo. Knodell fibrosis scores were generally better for ADV than placebo, but statistically significant differences were reported by only one study.
4. ADV was better in terms of ranked assessments of change in necroinflammatory activity and fibrosis than placebo. However, this was reported to be statistically significant in only one study. Ranked assessments were broadly similar between the PEG monotherapy group, the LAM monotherapy group and the group using ADV in combination with LAM (significance not reported).
5. Improvements in liver histology from ADV therapy were maintained only while treatment continued.

HBeAg loss/seroconversion

Tables 14 and *15* present HBeAg loss/seroconversion rates in the included trials (HBeAg-positive patients only, by definition) for ADV and PEG, respectively.

TABLE 15 *HBeAg loss/seroconversion (PEG)*

Study, patient type, outcome type	**Treatment arms**						
Cooksley *et al.*, 2003,[37] HBeAg positive	**IFN 4.5 MIU 3 × week (*n* = 51)**	**PEG 90 µg/week (*n* = 49)**	**PEG 180 µg/week (*n* = 46)**	**PEG 270 µg/week (*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 to 40]	18 (37) [23 to 52]	16 (35) [21 to 50]	14 (29) [17 to 44]	48 (34)	0.295	0.127
Seroconversion: *n* (%) [95% CI (%)]	13 (25) [14 to 40]	18 (37) [23 to 52]	15 (33) [20 to 48]	13 (27) [15 to 42]	46 (32)	0.428	0.185

Lau *et al.*, 2005,[40]	**PEG 180 µg/week (*n* = 271)**	**PEG + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	***p*-Value compared with LAM monotherapy**
HBeAg seroconversion (week 48): *n* (%)	72 (27)	64 (24)	55 (20)	$p = 0.003$ for overall test of treatment effect and $p = 0.23$ for comparison between PEG + placebo and PEG + LAM
HBeAg seroconversion (week 72): *n* (%)	87 (32)	74 (27)	52 (19)	
p-Value compared with LAM monotherapy	$p < 0.001$	$p < 0.02$		
HBeAg loss (week 48) *n* (%)	81 (30)	73 (27)	59 (22)	
HBeAg loss (week 72) *n* (%)	91 (34)	77 (28)	57 (21)	
p-Value compared with LAM monotherapy	$p < 0.001$	$p = 0.04$		

In the ADV trials, rates of HBeAg loss and seroconversion were higher in treatment-naïve patients than patients who were resistant to LAM:

1. In the trial by Perrillo and colleagues (HBeAg positive LAM-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]
   (a) Perrillo and colleagues[45] 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 subgroup 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.
2. In the trial by Peters and colleagues[35] (HBeAg-positive LAM-resistant patients) rates of HBeAg loss were marginally higher in the ADV + LAM group (17%) than the ADV + placebo group (16%). Seroconversion rates were highest in the ADV + placebo group (11%) compared with the ADV + LAM group (6%). No patients either lost HBeAg or seroconverted in the LAM + placebo group. None of the differences were statistically significant.
3. In Study 437 by Marcellin and colleagues,[32] HBeAg loss was highest in patients receiving the 30-mg dose of ADV (27%) followed by the 10-mg 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 10-mg ADV group ($p < 0.049$) and for the ADV 30-mg group ($p < 0.011$).

(a) Additional information was provided in a conference abstract.[42] At week 96, 29% of 231 patients receiving 10 mg 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.
(b) Chang and colleagues[43] (in a conference abstract) monitored the durability of seroconversion after discontinuation of ADV (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 >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.

4. 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.

Seroconversion rates were higher for PEG compared with IFN, although not significantly:

1. 25% of IFN-treated patients had seroconverted (week 48), in comparison with 32% for all three PEG doses combined ($p = 0.185$). Rates for the PEG groups ranged from 27% (270 µg/week dose) to 37% (90 µg/week dose). The difference in response rates between the four treatment groups was not statistically significant ($p = 0.428$).[37]

Seroconversion rates were also higher for PEG monotherapy than the combination of PEG and LAM or LAM monotherapy:

1. At the 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.[40] No significance values are reported. Seroconversion rates at end of follow-up (week 72) had increased to 32 and 27% for the PEG and 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).

HBeAg loss/seroconversion – summary

1. ADV was significantly more effective than placebo in treatment-naïve patients.
2. Unpublished data suggest that HBeAg seroconversion associated with ADV is durable up to 1 year after discontinuing treatment.
3. Differences in HBeAg loss/seroconversion rates between ADV, ADV added to LAM or ongoing LAM in patients with resistance to LAM were not statistically significant.
4. Differences between PEG and IFN were not significant.
5. PEG monotherapy and PEG in combination with LAM were both more effective than LAM monotherapy. PEG monotherapy was marginally more effective than PEG in combination with LAM.

HBsAg loss/seroconversion

HBsAg seroconversion is defined as the loss of HBsAg and the presence of anti-HBs antibodies. All three PEG studies and three of the ADV studies reported HBsAg loss or seroconversion rates, in varying detail (studies providing tabulated results are reported in *Table 16*). In addition, ADV 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.

1. The ADV study by Peters and colleagues[35] reported that no participants lost HBsAg during the course of the trial.
2. 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.
3. Perrillo and colleagues[45] reported results in a conference abstract for 78 LAM-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 with no patients in the LAM + placebo group.
4. 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

TABLE 16 *HBsAg loss/seroconversion at end of follow-up (week 72) (ADV and PEG)*

Study, patient type, outcome type	Treatment arms		Difference
Marcellin *et al.*, 2004,[36] HBeAg negative	**PEG 180 µg/week (*n* = 177)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**
HBsAg loss *n* (%)	7 (4)	5 (3)	0
p-Value compared with LAM	$p = 0.007$	–	
HBsAg seroconversion *n* (%)	5 (3)	3 (2)	0
p-Value compared with LAM	$p = 0.029$	–	
Lau *et al.*, 2005,[40] HBeAg positive	**PEG 180 µg/week (*n* = 271)**	**PEG 180 µg/week + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**
End of follow-up (week 72)			
HBsAg loss *n* (%)	9 (3)	11 (4)	2 (<1)
p-Value compared with LAM	$p = 0.033$	$p = 0.012$	
HBsAg seroconversion *n* (%)	8 (3)	8 (3)	0
p-Value compared with LAM	$p = 0.004$	$p = 0.004$	
Sung *et al.*, 2003,[34] (unpublished data)	**LAM 100 mg/d + ADV 10 mg/d (*n* = 55)**	**LAM 100 mg/d (*n* = 57)**	
HBsAg loss at week 52 *n* (%)	0/54	2/55 (4)	

loss or seroconversion was observed in the LAM monotherapy group (*Table 16*). 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 PEG-2a occurred earlier than the response obtained by IFN tends to occur.

5. In their study of HBeAg-positive patients, Lau and colleagues[40] 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.
   (a) 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 with the LAM group were statistically significant.
   (b) No patients receiving LAM experienced HBsAg seroconversion, compared with eight patients (3%) in each of the PEG groups. The results were statistically significant ($p < 0.01$). Differences between both PEG groups compared with the LAM group were statistically significant ($p = 0.004$).
6. Cooksley and colleagues[37] 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.
7. 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 PEG are significantly more likely to respond than patients taking LAM.

Combined outcomes

Table 17 shows the three studies which measured combined outcomes (all PEG studies):

1. Marcellin and colleagues (2004)[36] 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 LAM monotherapy at week 48 than for PEG monotherapy or for PEG in combination with LAM. However, the reverse was the case by week 72, with response rates in LAM monotherapy patients significantly less than in the other two treatment groups.
   (a) 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.

(b) 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 versus LAM, and PEG + LAM versus LAM were statistically significant ($p = 0.011$ and $p = 0.0002$, respectively).
(c) 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.
(d) 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 versus LAM, and PEG + LAM versus. LAM were statistically significant ($p = 0.007$ and $p = 0.003$, respectively).

2. At the end of 48 weeks of treatment, the HBeAg-positive patients in the study by Lau and colleagues[40] were assessed for a combined response in terms of HBeAg seroconversion, ALT normalisation and HBV DNA response. The highest response rate was in the LAM monotherapy group (18%), followed by the dual therapy group (15%) and finally the PEG monotherapy group (10%). By the end of follow-up, the response rates were highest in the PEG monotherapy group (23%), followed by the dual therapy group (21%) and the LAM monotherapy group (10%). These differences at 72 weeks were statistically significant ($p < 0.001$).
3. Cooksley and colleagues[37] 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 three 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 in the IFN arm). The difference in response rates between the four treatment groups was not statistically significant.

Health-related quality of life

The impact of treatment on HRQoL was reported in two studies, both of which were for PEG (Marcellin and colleagues and Lau and colleagues, reported in the manufacturer's submission to NICE[39]). HRQoL was measured using the 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
- 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 PEG monotherapy:

1. During treatment, HBeAg-positive CHB patients experienced a mean reduction of one point each in both PCS and MCS values from baseline.
2. For HBeAg-negative patients, the mean reduction in values was 0.5 and 3 points, respectively.
3. For patients with CHC, mean reductions were 2.5 points and approximately 4.5 points, respectively.
4. 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.
5. Similar small increases were experienced by CHC patients at follow-up in both PCS and MCS.
6. No statistical significance values were reported for these results.

Comparison with LAM:

1. In both trials, HRQoL scores for PEG-treated patients (with or without LAM) returned to levels at least as high as baseline at follow-up.
2. 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, $p < 0.05$).
3. For HBeAg-positive patients, reductions in PCS and MCS scores during treatment were

TABLE 17 *Combined response (PEG)*

Study, drug, patient type, outcome type	**Treatment arms**		
Marcellin *et al.*, 2004,[36] HBeAg negative, secondary	**PEG 180 μg/week (*n* = 177)**	**PEG 180 μg/week + LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**
ALT normalisation and HBV DNA <20,000 copies/ml			
End of treatment (week 48):			
n (%) of patients	63 (36)	87 (49)	125 (69)
95% CI (%)	28.6 to 43.1	41.1 to 56.2	61.8 to 75.7
End of follow-up (week 72):			
n (%) of patients	63 (36)	68 (38)	42 (23)
95% CI (%)	28.6 to 43.1	30.9 to 45.5	17.3 to 30.0
p-Value compared with LAM monotherapy	$p = 0.011$	$p = 0.0002$	
ALT normalisation and HBV DNA <400 copies/ml			
End of treatment (week 48):			
n (%) of patients	47 (27)	82 (46)	109 (60)
95% CI (%)	20.2 to 33.7	38.4 to 53.4	52.7 to 67.4
End of follow-up (week 72):			
n (%) of patients	26 (15)	29 (16)	11 (6)
95% CI (%)	9.8 to 20.8	11.1 to 22.4	3.1 to 10.6
p-Value compared with LAM monotherapy	$p = 0.007$	$p = 0.003$	
Lau *et al.*, 2005,[40] HBeAg positive	**PEG 180 μg/week (*n* = 271)**	**PEG 180 μg/week + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**
HBeAg seroconversion, normalisation of ALT and HBV DNA <100,000 copies/ml:			
n (%) at week 48	27 (10)	42 (15)	50 (18)
n (%) at week 72	62 (23)	56 (21)	28 (10)
p-Value compared with LAM monotherapy at week 72		$p < 0.001$	$p < 0.001$

Cooksley *et al.*, 2003,[37] HBeAg positive	**IFN 4.5 MIU 3 × week (*n* = 51)**	**PEG 90 μg/week (*n* = 49)**	**PEG 180 μg/week (*n* = 46)**	**PEG 270 μg/week (*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)	$p = 0.088$	$p = 0.036$

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'.

4. There was no statistically significant difference in HRQoL between the three treatment arms in the HBeAg-positive study over the 72-week trial period.
5. 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

TABLE 18 *Race and genotype data from studies 437 and 438*

	Study 437 (n^a = 510)	Study 438 (n^a = 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

[a] No.of patients in whom baseline genotyping was possible.

TABLE 19 *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

appear to have been published in a peer-reviewed publication. It is likely that fully published results will emerge in the near future.

Subgroup comparisons

Race and genotype

Westland and colleagues[46] reported a pooled subgroup analysis of race and genotype data from the ADV trials Study 437 and Study 438 (*Table 18*). 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.

HBV genotype is associated with race (*Table 19*); therefore, the different racial mixes of the two trials should be taken into consideration when viewing the combined percentages by genotype in *Table 18*. HBV genotypes C, D and A were the most commonly found types in the pooled analysis of Studies 437 and 438. Some 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 19*).

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 20*). Overall, serum HBV DNA levels were significantly different between genotypes ($p < 0.001$ for HBeAg-positive participants, $p = 0.001$ for HBeAg-negative participants).

1. Among HBeAg-positive participants, serum HBV DNA levels were highest in people with genotype G.
2. 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).
3. 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 *Baseline levels of serum HBV DNA by genotype*

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

TABLE 21 *Reductions in serum HBV DNA (log 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

TABLE 22 *Reductions in serum HBV DNA (log 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

Reductions in serum HBV DNA at week 48 were reported by genotype (*Table 21*) and by race (*Table 22*):

1. 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: $p = 0.931$).
2. There was no significant difference between different racial groups in changes in serum HBV DNA ($p = 0.182$).

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 ADV who had major genotypes A to D, but rates were not significantly different ($p = 0.25$).

Cooksley and colleagues,[37] in their evaluation of PEG, reported additional analyses by genotype. They found that response rates across treatment groups were significantly higher in patients with genotype B than genotype C:

1. Combined response rates (loss of HBeAg, suppression of HBV DNA and normalisation of ALT) were 31% in patients with genotype B compared with 17.5% in those with genotype C ($p < 0.05$).
2. 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).

Lau and colleagues[40] also reported subgroup analyses for the four main genotypes A, B, C and D. Rates of HBeAg seroconversion were highest in the PEG monotherapy groups and were also higher in the dual-therapy groups than in the LAM monotherapy groups. The numbers of people who seroconverted in PEG, PEG + LAM and LAM groups, respectively, were:

- 12 (52%), 4 (22%) and 3 (20%) (genotype A)
- 23 (39%), 24 (29%) and 17 (23%) (genotype B)
- 50 (31%), 43 (28%) and 29 (18%) (genotype C)
- 2 (22%), 2 (18%) and 3 (18%) (genotype D).

Cirrhotic patients

Cooksley and colleagues[37] reported suppression of HBV DNA for a subgroup of 13 patients with cirrhosis or transition to cirrhosis who were treated with PEG. Of this group, seven (54%) lost HBeAg and seroconverted, six (46%) had undetectable HBV DNA and five (38%) had normalised ALT. None of the four patients treated with IFN had a response in any of the outcome measures at the end of follow-up.

Previous treatment history

Lau and colleagues[40] reported HBeAg seroconversion rates for subgroups of patients with different treatment histories. The numbers of people with no previous anti-HBV therapy who seroconverted in the PEG, PEG + LAM and LAM groups were: 66 (31%), 59 (27%) and 42 (20%), respectively. These are very close to the overall seroconversion rates for the whole study population (32, 27 and 19%, respectively). The following seroconversion rates are for PEG, PEG + LAM and LAM groups, respectively:

- 10 (32%), 6 (25%) and 7 (17%) (previous exposure to LAM)
- 77 (32%), 68 (28%) and 45 (20%) (no previous exposure to LAM)
- 13 (43%), 11 (34%) and 4 (12%) (previous exposure to IFN)
- 74 (31%), 63 (26%) and 48 (20%) (no previous exposure to IFN).

Previous exposure to LAM did not result in HBeAg seroconversion rates differing from the overall rate to any great extent. Higher proportions of people previously treated with IFN seroconverted when retreated with PEG monotherapy or PEG + LAM dual therapy than was standard for these treatment groups (standard rates of 32 and 27%, respectively). By comparison, fewer people in the LAM monotherapy group who had previously been treated with IFN seroconverted, compared with the standard rate (19%) for this group.

Baseline HBV DNA

Lau and colleagues[40] reported HBeAg seroconversion rates for subgroups of patients with different baseline HBV DNA levels. The highest rates were seen in patients whose baseline HBV DNA was ≤ 9.07 log copies/ml: 37 (53%), 20 (36%) and 24 (31%) for PEG, PEG + LAM and LAM groups, respectively. Patients with baseline HBV DNA of between 9.07 and 10.26 log copies/ml had seroconversion rates of 39 (28%), 40 (27%) and 20 (16%), respectively. For patients with high baseline HBV DNA (>10.26 log copies/ml), seroconversions were 11 (17%), 14 (21%) and 7 (10%), respectively.

Baseline ALT

1. Cooksley and colleagues[37] reported a subgroup analysis of combined response for 'difficult to treat' patients with low baseline ALT (<2 × ULN) and high pretreatment HBV DNA. A combined response was observed in six (27%) of 22 patients treated with PEG and one (11%) of the nine patients treated with IFN.
2. Lau and colleagues[40] also reported HBeAg seroconversion rates by baseline ALT subgroup (*Table 23*), including results for the subgroup with low baseline ALT (≤ 2 × ULN). Of the 92 patients in this subgroup who were treated with PEG 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 subgroup seroconverted. Seroconversion rates were highest in the group with baseline ALT of over five times the ULN (41% for PEG, 37% for PEG + LAM and 28% for LAM).
3. Seroconversion rates were generally highest among people whose maximum ALT level during treatment was more than five times their baseline level.[40]

Subgroup comparisons – summary

- Reductions in serum HBV DNA levels after 48 weeks of ADV therapy were not significantly different on 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 PEG with IFN.
- PEG groups with genotypes B and C showed significantly higher response rates than IFN groups with these genotypes.
- PEG was more effective than IFN in treating people with cirrhosis or transition to cirrhosis.

TABLE 23 *HBeAg seroconversion rates by baseline ALT level: no. of patients who HBeAg seroconverted/total no. of patients (%)*

Study, patient type, outcome type	Treatment arms		
Lau *et al.*, 2005,[40] HBeAg positive, secondary	**PEG 180 µg + placebo (*n* = 271)**	**PEG 180 µg + LAM 100 mg (*n* = 271)**	**LAM 100 mg (*n* = 272)**
Overall study population	87/271 (32)	74/ 271 (27)	52/272 (19)
Baseline ALT level (× ULN)[a]			
≤ 2	27/92 (29)	19/93 (20)	19/96 (20)
>2 to 5	36/121 (30)	30/111 (27)	20/129 (16)
>5	24/58 (41)	25/67 (37)	13/47 (28)
Maximum ALT level during treatment (× ULN)[a]			
≤ 5	39/149 (26)	35/150 (23)	33/177 (19)
>5 to 10	28/74 (38)	27/86 (31)	16/64 (25)
>10	20/48 (42)	12/35 (34)	3/31 (10)
Maximum ALT level during treatment (× baseline value)			
≤ 5	81/257 (32)	68/255 (27)	49/260 (19)
>5	6/14 (43)	6/16 (38)	3/12 (25)

[a] ULN = 30 IU/l.

- People with 'difficult to treat' low-baseline ALT responded better to PEG than to treatment with IFN. PEG monotherapy was more effective than LAM monotherapy or PEG + LAM dual therapy in this patient subgroup.

Treatment resistance

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

1. At week 48 in the study by Marcellin and colleagues,[36] YMDD mutations were detected in 32 people in the LAM group (18%) and one person in the PEG + LAM group (<1%). This difference was statistically significant ($p < 0.001$).
   (a) Additional information is provided for this study in the form of conference abstracts.[42,43] Two patients receiving ADV (3.1%) developed resistance by 144 weeks.
2. 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 ADV treatment.
   (a) Additional information is provided for this study at weeks 96 and 144.[41] The overall cumulative rate of resistance to ADV among all patients at 48, 96 and 144 weeks was 0, 3 and 5.9%, respectively.
3. Perrillo and colleagues[33] reported YMDD mutations in LAM-resistant HBeAg-positive patients treated with ongoing LAM or ADV + LAM (*Table 24*). 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 versus 96%, $p < 0.001$).

The manufacturer of ADV, in its submission to NICE,[24] reports an overview of resistance rates, summarised from five 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:

1. A total of 629 patients from the five studies were monitored for up to 4 years (a total of 1201 patient-years).
2. A total of 22 patients developed resistance to ADV 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.
3. The annual risk of resistance was calculated as 0, 2.05, 5.10 and 8.06% for years one, two, three and four, respectively.
4. Study 438 in HBeAg-negative patients had higher resistance rates than the averages across the five studies. After 2 years of treatment, 3% of patients developed resistance; 10.3% developed resistance during 3 years of treatment and 17.5% did so during 4 years of treatment.

TABLE 24 *YMDD mutations reported by Perrillo and colleagues*[33]

Study	Treatment arms		
Perillo *et al.*, 2004[33]	**LAM 100 mg/d + ADV 10 mg/d (*n* = 44)**	**LAM 100 mg/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 (%) Wild-type (%)	14/42 (33) 2/42 (5)	2/46 (4) 0 (0)	

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

1. The 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 LAM (notwithstanding those which included ADV or PEG), we report pooled data on LAM resistance, as discussed in a submission to NICE by the manufacturer of ADV.[24] This provides an indirect comparison of resistance rates between the two drugs:

1. Lai and colleagues[48] combined four RCTs and calculated the overall proportion of patients with YMDD variants after 1 year of therapy to be 24%, rising to a cumulative rate of 42% after 2 years, 53% after 3 years and 70% after 4 years. The annual risk was calculated to be approximately 26% per year.
2. Lok and colleagues[49] combined seven trials, and calculated that 16% of patients would have developed M204V/I mutations after 1 year, rising to 36, 56, 75 and 80% after 2, 3, 4 and 5 years, respectively.

In summary, resistance rates are generally 5-fold lower with ADV than LAM. After 4 years of treatment, cumulative rates were 14.5 and 70%, respectively.

Adverse events

Adverse events for ADV studies are reported in *Table 25*. 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 30-mg group than in the ADV 10-mg 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 versus 10%) in the study by Hadziyannis and colleagues,[31] whereas the rates of reporting were similar across groups in the study by Marcellin and colleagues[32] (10% in the 10-mg ADV group, 9% in the 30-mg ADV group and 8% in the placebo group). The serious adverse events reported by Peters and colleagues[35] 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 LAM monotherapy and the LAM + ADV dual-therapy regimes were well tolerated with similar safety profiles. Four serious adverse events (7%) were reported in the LAM monotherapy group and one (2%) in the LAM + ADV group.

Commonly reported adverse events in studies of ADV include pharyngitis, headache, abdominal pain, asthenia and influenza-like symptoms. Other adverse events were experienced by higher

TABLE 25 *Adverse events in ADV studies*

	Hadziyannis *et al.*, 2003[31]		Perrillo *et al.*, 2004[33]		Marcellin *et al.*, 2003[32]			Peters *et al.*, 2004[35]		
	ADV 10 mg/d (*n* = 123)	**Placebo (*n* = 61)**	**LAM 100 mg/d placebo (*n* = 48)**	**LAM 100 mg/d + ADV 10 mg/d (*n* = 44)**	**10 mg ADV (*n* = 171)**	**30 mg ADV (*n* = 173)**	**Placebo (*n* = 167)**	**100 mg LAM + placebo (*n* = 19)**	**10 mg ADV + placebo (*n* = 19)**	**10 mg ADV+ 100 mg LAM (*n* = 20)**
Dose discontinuation for any AE/safety reasons (%)	0	0	NR	NR	2	3	<1	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)

continued

TABLE 25 *Adverse events in ADV studies (cont'd)*

	Hadziyannis et *al.*, 2003[31]		Perrillo et *al.*, 2004[33]		Marcellin et *al.*, 2003[32]			Peters et *al.*, 2004[35]		
	ADV 10 mg/d (*n* = 123)	**Placebo (*n* = 61)**	**LAM 100 mg/d placebo (*n* = 48)**	**LAM 100 mg/d + ADV 10 mg/d (*n* = 44)**	**10 mg ADV (*n* = 171)**	**30 mg ADV (*n* = 173)**	**Placebo (*n* = 167)**	**100 mg LAM + placebo (*n* = 19)**	**10 mg ADV + placebo (*n* = 19)**	**10 mg ADV+ 100 mg LAM (*n* = 20)**
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)

AE, adverse event; NR, not reported.

percentages of participants in the study by Peters and colleagues,[35] 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.

1. Two trials reported higher rates of pharyngitis in placebo groups compared with 10-mg ADV groups, but one of these also reported a higher rate in the 30-mg ADV group than in the placebo group. The small study by Peters and colleagues[35] 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.
2. Reporting of headaches was higher in both 10-mg ADV groups and the 30-mg ADV group than in the placebo groups in ADV Studies 437 and 438,[33,35] but rates of reporting were broadly similar across groups in the small study by Peters and colleagues.[35]
3. Reports of abdominal pain varied, with one of the trials' 10-mg ADV groups reporting higher incidences than the placebo group (15 versus 5%), and another trial reporting similar levels across groups (18, 22 and 19% in 10-mg ADV, 30-mg ADV and placebo groups, respectively). Peters and colleagues[35] reported similar rates across treatment groups in their small study.
4. Reports of asthenia were also mixed, with one trial[31] reporting a higher rate in the placebo group than in the 10-mg ADV group (16 versus 13%) and one trial reporting a lower rate in the placebo group (19%) than in either the 10-mg or 30-mg ADV groups (25 and 26%, respectively).
5. Influenza-like syndrome was reported by a higher percentage of placebo group participants than those in any of the ADV groups, although this difference was small in some cases.

Results of a long-term extension to Study 438[41] showed that the safety profile of ADV up to 144 weeks remained consistent with that seen earlier in the study.

Adverse events for PEG studies are reported in *Table 26*. With the exception of the study by Marcellin and colleagues,[36] tests of statistical significance were not reported. Very few deaths were reported in any of the studies. The three deaths reported in the dual-therapy arm of the study by Lau and colleagues[40] were due to accidents rather than being related to CHB or drug treatment.

Discontinuations for safety reasons were generally very low, but were higher in PEG groups than in LAM or interferon alfa groups. Marcellin and colleagues[36] reported a significant difference between PEG (overall treatment effect) and LAM groups. Dose discontinuations for other reasons were also rare, with no significant difference reported between PEG and LAM groups by Marcellin and colleagues.[36]

Dose modifications for laboratory abnormality were reported in two studies.[36,37]

1. In the study by Marcellin and colleagues,[36] ALT elevation and thrombocytopenia were more common problems in the PEG 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 PEG monotherapy group. It should be noted that some participants had their doses reduced owing to both laboratory abnormalities and adverse events. No dose modifications for laboratory abnormalities or adverse events were reported in the LAM monotherapy group.
2. In the study by Cooksley and colleagues,[37] dose modifications for laboratory abnormalities were approximately two to three times higher in PEG groups than in the IFN 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 PEG groups than in the LAM monotherapy group in the study by Marcellin and colleagues.[36] Although no statistical tests were reported, the same pattern is seen in the study by Lau and colleagues.[40] The total number of participants experiencing at least one adverse event was not reported by Cooksley and colleagues.[37] Serious adverse events were infrequent, but were generally higher in the PEG groups than in the LAM monotherapy group in the study by Marcellin and colleagues.[36] Again, the same pattern was seen in the study by Lau and colleagues.[40] Slightly higher percentages of serious adverse events were reported in the PEG 180- and 270-μg groups than in the IFN group, although the numbers are probably too low to make any meaningful comparison between the groups.

Commonly reported adverse events in studies of PEG include headache, pyrexia, fatigue, myalgia and alopecia:

TABLE 26 *Adverse events in PEG studies*

	Lau *et al.*, 2005[40]			**Marcellin *et al.*,2004[36]**			**Cooksley *et al.*, 2003[37]**			
	PEG 180 μg/week (*n* = 271)	**PEG + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	**PEG 180 μg/week (*n* = 177)**	**PEG 180 μg/week +LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**	**IFN 4.5 MIU 3 × week (*n* = 50)**	**PEG 90 μg/week (*n* = 48)**	**PEG 180 μg/week (*n* = 48)**	**PEG 270 μg/week (*n* = 45)**
Discontinuation for safety reasons[a] *n* (%)	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[b] *n* (%)	9 (3)	6 (2)	12 (4)	2 (1)	3 (2)	4 (2)				
Dose modification[c]										
Total	124 (46)	127 (47)					10%	22–30%		
For										
Laboratory abnormality	99 (37)	102 (38)	0	65 (37)	64 (36)	0				
ALT elevation			0	15 (8)	6 (3)	0				
Neutropenia			0	30 (17)	44 (25)	0				
Thrombocytopenia			0	34 (19)	22 (12)	0				
Dose reduction for any AE *n* (%)	20 (7)	23 (8)	0	13 (7)	23 (13)	0				
Deaths	0	3 (1)[e]	1 (<1)	1(1)	0	0				
At least one AE[a] *n* (%)	240 (89)	240 (89)	152 (56)	155 (88)	155 (87)	86 (48)				
At least one serious[d] 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%

continued

TABLE 26 *Adverse events in PEG studies (cont'd)*

	Lau et *al.*, 2005[40]			Marcellin et *al.*,2004[36]			Cooksley et *al.*, 2003[37]			
	PEG 180 µg/week (*n* = 271)	**PEG + LAM 100 mg/d (*n* = 271)**	**LAM 100 mg/d (*n* = 272)**	**PEG 180 µg/week (*n* = 177)**	**PEG 180 µg/week +LAM 100 mg/d (*n* = 179)**	**LAM 100 mg/d (*n* = 181)**	**IFN 4.5 MIU 3 × week (*n* = 50)**	**PEG 90 µg/week (*n* = 48)**	**PEG 180 µg/week (*n* = 48)**	**PEG 270 µg/week (*n* = 45)**
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)				

[a] $p < 0.001$ for overall test of treatment effect in Marcellin and colleagues.[36]
[b] $p = 0.913$ for overall test of treatment effect in Marcellin and colleagues.[36]
[c] Some patients who required a dose modification had both an adverse event and a laboratory abnormality.
[d] Serious adverse event defined as 'one that presented a clinically significant hazard or resulted in a contraindication or side effect'.
[e] These three deaths were due to accidents, not CHB or drug treatment.

1. Headaches were reported by two to three times as many people receiving PEG as those receiving LAM monotherapy and by approximately 50% more people receiving PEG than by those receiving IFN.
2. Pyrexia was reported by over half of all participants receiving 90 or 180 µg PEG monotherapy or PEG + LAM dual therapy, compared with only 4% of people receiving LAM monotherapy. Reports of pyrexia reached over 70% in participants receiving either IFN or 270 µg PEG.
3. Very few people receiving LAM monotherapy reported myalgia (6% in Marcellin and colleagues' study[36] and 3% in Lau and colleagues' study[40]), whereas over one-quarter of people receiving either 90 or 180 µg PEG monotherapy or dual therapy reported experiencing this. Myalgia was reported by over 40% of people receiving 270 µg PEG or IFN.
4. Fatigue was reported by approximately 40% of people receiving PEG, either as monotherapy or dual therapy, but by less than 20% of people receiving LAM monotherapy. Reporting of fatigue was similar across all treatment arms of the study by Cooksley and colleagues,[37] ranging from 22% in the 180-µg PEG group to 29% in the 90-µg PEG group.
5. Alopecia was rarely seen in people receiving LAM monotherapy, but was reported by 11–14% of people being treated with PEG in the study by Marcellin and colleagues[36] and by 20–29% of the PEG-treated patients in the study by Lau and colleagues.[40] Rates of alopecia increased with dose of PEG from 17 to 44% in the study by Cooksley and colleagues,[37] compared with a reported rate of 24% in the IFN group.

Adverse events – summary

1. Dose discontinuations for safety reasons were low for people receiving ADV. 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 ADV.
2. Dose discontinuations for safety reasons were significantly higher for people receiving PEG than for people receiving LAM monotherapy.
3. The most commonly reported adverse events in the PEG studies were headache, pyrexia, fatigue, myalgia and alopecia. These were all experienced in greater numbers by people receiving PEG than by people receiving LAM monotherapy.
4. People receiving IFN or high-dose PEG (270 µg) had greater incidences of pyrexia or myalgia than people receiving 90 or 180 µg PEG.
5. Fewer people receiving IFN experienced headaches than people receiving PEG.

Evidence from related systematic reviews

Dando and Plosker[50] conducted a systematic review of ADV 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 prespecified 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 10 mg/day ADV (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 ADV group. The review also identified several non-comparative trials assessing the effects of ADV in specific patient populations, such as patients co-infected with HIV, patients with hepatic decompensation and pre- and post-liver transplant patients.

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:

1. Benhamou and colleagues reported up to 4 years of 10 mg/day ADV treatment in patients with LAM-resistant HBV and HIV co-infection in a series of eight conference abstracts.[51–58] ADV was added to the pre-existing anti-retroviral therapy including LAM, and key results are shown in *Table 27*.

TABLE 27 *Results of ADV 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 copies/ml)	–3.97*	–4.80*	–5.55*	–5.62*
HBV DNA <1000 copies/ml *n* (%)	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 normalisation (%)	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.

(a) 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.
(b) 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 period ($p < 0.0001$).
(c) 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.
(d) Two patients seroconverted to anti-HBe by week 48.
(e) There were no serious adverse events related to ADV throughout the study period.

2. Four other abstracts[59–62] mentioned people co-infected with HIV, but did not present detailed results for this patient group.
3. 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.

Treatment for pre- and post-operative liver transplant patients

We did not identify any fully published RCTs evaluating ADV in pre- and post-liver transplant patients. However, expert opinion suggests that 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 in conference abstract form:

1. 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).[63,64] 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 normalised 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.
2. Schiff and colleagues[65] 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).
3. Perrillo and colleagues[33] conducted an open-label evaluation of ADV (10 mg/day) in combination with ongoing LAM (100 mg/day) 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 9 for full tabulated details of this study).
   (a) 92% of patients achieved an HBV DNA response at weeks 48 and 52 (response defined as serum HBV DNA level ≤ 10^5 copies/ml or ≤ 2 log reduction from baseline HBV DNA level at weeks 48 and 52); median HBV DNA (log copies/ml) decreased from 8.6 at baseline to 3.2 at follow-up.
   (b) Of the 68% who were HBeAg positive at baseline, 30% lost HBeAg at follow-up and 4% (one of 27) seroconverted.
   (c) Median ALT levels (× the upper limit of normal) reduced from 1.9 at baseline to 0.9 at follow-up; and the proportion with ALT normalisation at follow-up was 53%.
4. An observational study[66] investigated the incidence of ADV resistance in liver transplantation patients (n = 114). After 2 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.
5. Barcena and colleagues[67] reported the results of a retrospective observational study in a conference abstract. The study included 39 transplant patients with HBV resistant to LAM who were treated with ADV (mean age 54 years, 22/39 were HBeAg positive, mean time from transplant to beginning of ADV treatment was 5 years). Approximately 46% negativised DNA. ALT levels decreased significantly (p = 0.002) and 21.4% reached normal ALT ranges (32% in HBV-positive patients, without HCV co-infection). No seroconversions, deaths or serious adverse events occurred.
6. A number of small observational studies have reported that ADV therapy is associated with biochemical, virological and clinical improvements in post-liver transplant patients.[68–71] For example:
   (a) Ahmad and colleagues[72] reported results for six patients and found that an average of 5 months of ADV treatment decreased HBV DNA levels by a mean of >3 $\log_{10}$ copies/ml. One patient normalised ALT.
   (b) Foxton and colleagues[73] found that ADV significantly suppressed HBV replication in three preoperative and three postoperative liver transplant patients with LAM-resistant HBV.
7. Several non-systematic reviews have examined the evidence base for treatment of pre- and post-liver transplant patients and noted that ADV is a promising treatment for LAM-resistant HBV in post-liver transplant patients.[68,74–76]
8. 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 ADV. 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 LAM and other agents (e.g. 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 ADV:

1. 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.[77]
2. A non-systematic review suggested that combined therapy of HBIG and LAM is more effective in preventing recurrent HBV than either treatment used as monotherapy, decreasing recurrence rates to 0–18% in some studies.[75] Drug resistance led to breakthrough infections in up to 25% of patients.
3. Another non-systematic review suggested that post-transplant prophylaxis with HBIG has significantly reduced HBV recurrence rates, but that HBIG is ineffective in patients with pre-transplant viraemia.[74] Long-term administration is expensive and potentially associated with emergence of escape HBV mutants.

Ethnicity

One conference abstract was identified which specifically reported on ethnicity. Lim and colleagues[78] reported the combined results of two RCTs (n = 338 HBeAg positive, n = 184 HBeAg negative). 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. Some 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 normalisation at week 48.

Clinical effectiveness – summary

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

The majority of the fully published RCTs report outcomes measured at the end of 48 weeks of treatment (for the PEG studies results are also presented 24 weeks after end of treatment, i.e. week 72). Some of the ADV studies are ongoing with treatment up to 5 years. With the exception of Study 438,[41] 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.

HBV DNA

Reductions in HBV DNA to low or undetectable levels were associated with all active treatments. In general, ADV was significantly more effective than placebo (21–51% compared with 0%, respectively), and when added to LAM in patients with LAM resistance it was more effective than ongoing LAM (35–85% compared with 0–11%, respectively). Reductions in HBV DNA are only maintained if ADV treatment is continued, and long-term therapy is likely to be required.[41]

In the three PEG trials, the general trend was for PEG monotherapy and PEG + LAM dual therapy to be of similar efficacy, and both were significantly superior to LAM monotherapy. For HBeAg-positive patients, end of follow-up HBV DNA response rates were 32, 34 and 22%, respectively. 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 PEG in comparison with IFN (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 ADV monotherapy after 1 year's treatment were in the range 48–72% in comparison with 16–29% for placebo (statistically significant). Results from a long-term study (up to 144 weeks) indicate that treatment needs to be continued if biochemical response is to be maintained.[41] In LAM-resistant patients, significantly higher response rates were observed for patients given ADV in addition to LAM, compared with those who continued with LAM (37 versus 9%). Response rates for LAM-resistant patients who switched to ADV (+ placebo) were significantly higher than rates in patients who continued on LAM (+ placebo).

For the three PEG studies, PEG monotherapy and PEG + LAM dual therapy were of similar efficacy and both were superior to LAM monotherapy. For HBeAg-positive patients, end of follow-up response rates were 41, 39 and 28%, respectively. 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 PEG monotherapy and dual-therapy treated patients, but decreased in LAM monotherapy patients.

ALT response rates (measured 24 weeks after 24 weeks of treatment) were also higher for all doses of PEG-2a in comparison with IFN. However, this difference was not statistically significant.

Liver histological response

Four of the included studies reported liver histology results (two ADV studies and two PEG studies, one with HBeAg-positive and one with HBeAg-negative patients in each case). All four studies reported improvements in liver histology following treatment, expressed in terms of changes in Knodell and Ishak scores.

ADV was more effective than placebo in terms of histological improvement (where the proportion of patients treated with ADV 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). Results from a long-term study (up to 96 weeks) indicate that treatment needs to be continued if improved liver histology is to be maintained.[41]

In the PEG studies, histological improvements were observed for all three treatments (in the range 48–59% based on paired biopsy samples), with no significant differences between groups. Similarly, there were improvements in terms of ranked assessment of change reported in one study, 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 ADV and 37% for PEG.

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

Significantly higher rates were observed for PEG monotherapy, and PEG in combination with LAM therapy compared with LAM monotherapy (32, 27 and 19%, respectively). Rates increased between end of treatment and follow-up (but not for LAM monotherapy, where there was a slight decrease).

Seroconversion rates were higher for all doses of PEG in comparison with IFN. However, the 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 two of the PEG combination therapy trials (HBeAg-positive and -negative patients), seroconversion rates were similar for patients treated with PEG monotherapy and dual therapy with LAM monotherapy (in the range 2–3%). No patients treated with LAM monotherapy seroconverted in either trial. Differences between mono and dual PEG therapies compared with LAM were significant.

Combined outcomes
Three studies employed combined measures of effect, all of them evaluating PEG.

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 PEG monotherapy and with the combination of PEG with LAM. Rates in both groups were significantly greater than LAM 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 PEG-treated patients compared with IFN (24 versus 12%, $p = 0.03$).

The combined response in the third study was based on HBeAg seroconversion, normalisation of ALT and HBV DNA <100,000 copies/ml. The response rates were significantly higher for both PEG monotherapy and PEG + LAM dual therapy compared with LAM monotherapy (23 and 21 versus 10%, $p < 0.001$).

Health-related quality of life
QoL was reported as an outcome in only two of the included trials, both of them on PEG 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 PEG and patients treated with LAM.

During treatment, CHB patients experienced lower mean reductions in physical and mental health values than did patients with CHC (based on an indirect comparison). Therefore, PEG does not appear to reduce QoL in CHB patients to the same extent as observed in CHC patients. Fully published results are awaited.

Adverse events
Dose discontinuations for safety reasons were low for patients receiving ADV. 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 ADV-treated patients.

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

Patient subgroups
Data on subgroups of treated patients were limited. In terms of genotype, results were mixed. One pooled analysis of two ADV trials found no significant difference in treatment effects according to genotype. Another study (evaluating PEG versus IFN) 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 subgroup of cirrhotic patients were reported in one trial (PEG). Response was only observed in PEG-treated patients (as opposed to IFN) 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. PEG with and without LAM).

For patients co-infected with HIV, the addition of ADV to existing anti-retroviral therapy (including LAM) significantly reduced 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 ADV administered pre- and post-transplant was associated with reductions in HBV DNA, ALT and 3-year survival rates in excess of 80%.

Chapter 5
Economic analysis

Introduction

The aim of this chapter is to assess the cost-effectiveness of PEG and ADV compared with existing treatments (IFN and LAM) or best supportive care in adults with CHB in England and Wales. The economic analysis comprises:

- a systematic review of the literature on the cost-effectiveness of PEG and of ADV
- a review of the manufacturers' submissions (cost-effectiveness section) to NICE
- presentation of our economic model and cost-effectiveness evaluation.

Systematic review of the literature

Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations comparing PEG and/or ADV with existing treatments (IFN and LAM) or no treatment (best supportive care) in adults with CHB. The details of the search strategy are documented in Appendix 2. 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 PEG and/or ADV versus existing treatments (IFN and LAM) or no treatment (best supportive care) in adults with CHB. 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 CHB.

Results of the systematic review: cost-effectiveness

A total of 1951 publications relating to cost-effectiveness in hepatitis B were identified through our searches. Only one of these was a fully published economic evaluation. No additional publications were identified from the manufacturers' submissions and further discussion with the industry teams confirmed that no full reports of economic evaluation of PEG or ADV have been published. The fully published economic evaluation that was identified reports the cost-effectiveness of ADV as a salvage strategy for CHB patients who have developed LAM resistance.

Kanwal and colleagues, 2005.[79] Recognising the high cost of ADV compared with LAM, this US-based analysis considered a hybrid strategy that would take advantage of the comparatively low cost and durable on-treatment effectiveness of LAM and that would be responsive to the high level of resistance observed with long-term LAM therapy. A Markov model was used to estimate the cost-effectiveness of this 'salvage strategy' compared with current practice of either interferon alfa or LAM therapy alone for a cohort of 40-year-old patients with CHB with raised ALTs, but without cirrhosis. Unlike other cost-effectiveness analyses published to date, this evaluation was not limited 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 MU of interferon alfa, three times per week, for 6 and 12 months for HBeAg-positive and HBeAg-negative patients, respectively
2. 100 mg of LAM daily continued until sustained virological response was achieved
3. 100 mg of LAM daily continued until resistance develops, at which point treatment changes to 10 mg of ADV daily (salvage therapy).

Transition probabilities were derived from a systematic review of the literature and treatment and health state costs were obtained from Medicare and the Red Book.

Undiscounted lifetime costs for the three treatment strategies were US$18,607, $20,915 and $28,362 for interferon alfa, LAM and ADV salvage, respectively, and the undiscounted outcomes in terms of life-years were 34.7, 37.2 and 38.9, respectively. 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 (ICER) for the salvage strategy was $14,204 per life-year gained. Sensitivity analysis showed that ADV salvage became the dominant strategy if ADV costs were halved (or, alternatively, LAM costs were doubled) and where >60% of the treatment cohort consisted of people with HBeAg-negative CHB.

Hepatitis B antiviral therapy: published economic evaluations

In the absence of published economic evaluations of PEG and ADV, this section presents a brief review of economic evaluations of other antiviral therapies for the treatment of CHB. We present an overview of methods used to model disease progression, to estimate benefits/outcome and to estimate costs.

Summary of methods

Six fully published economic evaluations of antiviral interventions for CHB were found,[16,80–84] although two of these[81,84] 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 antiviral therapy (IFN and LAM) presented models for disease progression in patients with HBeAg-positive disease and excluded those with HBeAg-negative CHB from their analysis. As a result of this, the principal treatment end-point was 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.[80] In all evaluations, the effect of this was to reduce the rate of progression to compensated cirrhosis, owing to the lower transition probability from the HBeAg seroconverted state to compensated cirrhosis compared with that from active CHB (i.e. prior to seroconversion) to compensated cirrhosis. This applies to all the antiviral agents being evaluated – although the estimates for the exact proportion of patients seroconverting and the durability of seroconversion vary between studies and between agents that were evaluated.

There may also be benefits from HBeAg seroconversion through a lower transition probability to HCC,[85] although not all evaluations took this into account. Two evaluations[80,81] did not allow the transition from the HBeAg seroconverted state to HCC, whereas the other maintained the same risk of developing HCC from CHB and HBeAg seroconversion, but applied a substantially lower risk for HBsAg-seroconverted patients.[16]

Evaluations of lamivudine[81–84] 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 LAM-treated patients was 1.8% compared with 7.1% for placebo and 9.5% for interferon alfa. Where evaluations included this effect, it was assumed to occur only after the first year of treatment; after that, LAM provided no benefit against progression to cirrhosis.

All published evaluations assumed that patients who stop therapy, do not respond or 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 CHB. Where studies were 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 were developed and estimates of health state costs were 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 were undertaken in each of the evaluations to cost the interventions being investigated. Studies differed in the comprehensiveness of these costings. Most included estimates of both the cost of drugs and monitoring patients while on treatment,[16,80,81,83,84] although they vary substantially in the detail provided to allow comparison of their assumptions in costing treatment; one study limited their costings of the interventions to drug costs only.[82]

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 variations in variables that impacted on the effectiveness of interventions (eligibility for treatment and rate of progression to cirrhosis[81,83,84]) 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.

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 USA developed a decision analytic model to synthesise evidence on the natural history of CHB and the effect of a 16-week course of interferon alfa-2b compared with standard care. Patients entered the model aged 35 years 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 ITT basis and that these would therefore include patients with dose reductions and who discontinued treatment owing 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 1 year of treatment were assumed to follow the same course of disease as untreated patients.

Screening for HCC was excluded from the model, owing to uncertainty over the benefits of screening in a North American population.[86] Despite this, screening for HCC remains a core component of clinical guidelines for monitoring CHB patients during and post-treatment.[3,87,88] Liver transplantation was also excluded on the assumption that few decompensated patients could benefit given the then limited supply of donor organs, but also owing to the high risk of re-infection with CHB. Subsequent research using LAM and ADV as prophylaxis for patients undergoing liver transplantation suggests that these agents can significantly reduce the risk of re-infection for patients on immunosuppression and, although 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 with 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 with 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 the Section 'Health-related quality of life for patients with chronic hepatitis B' (p. 70)]. 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 or exactly how these values were elicited.

The costs of interferon alfa therapy were based on a treatment course of 10 MU, three times per

week, for 16 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 CHB 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 HCC 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 CHB 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 US$4000 for compensated and $18,000 for decompensated cirrhosis) was due to the assumed frequency of hospitalisation (once every 2 years for compensated cirrhosis and once every 5 months for decompensated cirrhosis). The annual cost for the hepatocellular state was lower than for decompensated cirrhosis owing to a lower unit cost for hospitalisation despite a slightly higher frequency of hospitalisation (once every 4 months for HCC compared with once every 5 months for decompensated cirrhosis).

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[80] 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 alpha.

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, although 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 HCC. Mortality from liver disease, in the model, occurred only from the decompensated cirrhosis health state in this model, whereas current opinion suggests that excess mortality should be modelled for the compensated cirrhosis state and possibly also the chronic hepatitis B state, although at a substantially lower rate than for decompensation.[3,89,90] 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 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 with those adopted in other evaluations which have excess mortality rates for decompensation at 39 and 56% for HCC.

The model took no account of spontaneous responses in the untreated cohort. All patients in the untreated cohort remained in the CHB 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 MU, three times per week, for 16 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 the first interferon alfa injection and training in administering the drug, and for eight follow-up visits. Costs for untreated patients were based on two outpatient 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) every 2 months. The assumptions underlying the health state costs for this model are generally less resource intensive than those adopted by Wong and colleagues,[16] 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 USA

A decision tree model was developed to determine the costs and outcomes of interferon alfa and LAM in treating patients with CHB over a 1-year time horizon.[82] 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 end-points 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 LAM monotherapy with interferon alfa therapy and with LAM and interferon alfa combination therapy.[91] The rates used, 17.5% for patients receiving LAM and 18.8% for patients receiving IFN, 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 LAM[92,93] by combining the numbers of patients who seroconverted while on placebo. Three out of 70 placebo-treated patients in one trial[92] and four out of 69 in the other[93] 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 LAM-treated patients this was 2.2%. The rates of progression to cirrhosis in the combined trial populations were 12.1% (four out of 33 patients) for interferon alfa and 7.4% (seven out of 94) for placebo. Owing to the small numbers of patients in this analysis and a lack of a 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 that the time horizon for the evaluation was defined at the outset to be 1 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 end-points 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 LAM are equally durable. Durability of seroconversion has been estimated to be between 60 and 80% for LAM and between 80 and 90% for interferon alfa.[3] A recent meta-analysis of patient-level data on long-term follow-up (up to 3 years) for patients treated with LAM or

interferon alfa reported a relative risk of relapse of 4.6 for LAM compared with interferon alfa.[94]

The only costs included in this evaluation were the direct costs of a treatment course of 10 MU, three times per week, for 16 weeks of interferon alfa (US$5589.10) and 52 weeks of a regimen of LAM at 100 mg/day ($1580.80). 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 1-year's LAM 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 or with long-term outcomes.

Orlewska, 2002: The cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B in Poland
Orlewska[83] 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 LAM were available and only varied according to whether interferon alfa or LAM was the first-choice treatment for eligible patients. In the third, only interferon alfa was available. The final scenario was one where no antiviral 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 1-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 years, with moderately raised ALT levels, but had not progressed to cirrhosis. Some 60% of the population was female and all patients were assumed to be interferon alfa naïve.

Rates of seroconversion for LAM (18%) and interferon alfa (19%) were taken from an RCT comparing LAM monotherapy with interferon alfa therapy and with LAM and interferon alfa combination therapy.[91] The spontaneous seroconversion rate was based on the rate for untreated patients in a placebo-controlled trial of LAM. The annual probability of progression to cirrhosis was based on an adjustment to a pooled analysis of data from three clinical trials.[95] The reported proportions of 1.8, 7.1 and 9.5% for LAM, placebo and interferon alfa, respectively (which included both seroconverted and non-seroconverted patients in the denominators) were adjusted upward to 2, 8 and 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 the 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 owing to the similarity of this estimate to that presented by Wong and colleagues.[16]

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

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 years 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 LAM treatment. A greater

danger of bias in the study results from assuming that the treatment effect estimated at 1 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 antiviral agents.[96] The durability of HBeAg seroconversion following LAM treatment appears to be lower than in interferon alfa-treated patients.[94]

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 24 weeks (which was the usual clinical practice in Poland) and 52 weeks of a regimen of LAM at 100 mg/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 11 specialist consultations during the year in which treatment occurred, compared with LAM-treated patients who required eight specialist consultations during the first year of treatment. Patients not receiving any antiviral therapy were assumed to have the same schedule of specialist consultations as the LAM-treated patients. For both interventions, drugs represented the majority of the costs of antiviral therapy. Drug costs comprised 70% of the total cost of IFN treatment and 79% of the total cost of LAM 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 LAM separately. To test sensitivity to the interferon alfa drug cost, a dosage of 10 MU for 4 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 LAM 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[81,84] developed a two-stage decision analytic model to compare three treatment scenarios for patients with CHB in Australia. The treatment options included in the three scenarios were as follows:

- Scenario 1 included treatment with either interferon alfa or LAM.
- Scenario 2 included only treatment with interferon alfa.
- Scenario 3 included no antiviral 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 1-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), CHB, compensated cirrhosis, decompensated cirrhosis, HCC and death. HBsAg seroconversion and liver transplant states were excluded from the model owing to their infrequent occurrence.

The population of patients entered into the model were 70% male with an average age of 30 years, 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 the normal range (ULN). The model structures adopted in both publications[81,84] are identical, as are the input data, other than that the second paper contains trial-based HBeAg seroconversion rates for up to 4 years of LAM treatment whereas only 3 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 ULN 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[82] and Orlewska.[83] However, Crowley and colleagues used a pooled analysis which only included patients with ALT levels greater than or equal to twice the upper limit of the ULN, reported as comprising 60% of trial participants. These patients were selected as being the group in which durable response to antiviral therapy is most likely to occur.

The HBeAg seroconversion rates applied in the 1-year model were 28.7% for LAM and interferon alfa (a weighted average of the observed seroconversion rates of 30 and 24% for LAM 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 LAM trials. The seroconversion rates for LAM at 2, 3 and 4 years used in the model were 18.7, 39.6 and 22.9%, respectively. These were based on the longer term results for patients in the clinical trials meeting the ALT inclusion criterion and correspond to cumulative rates of 42, 65 and 73%, respectively. Continued treatment with LAM 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 LAM, reactivated disease within 1 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 and colleagues,[16] 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[3,97,98] and long-term follow-up of LAM-treated patients,[99,100] which show reactivation of CHB in a proportion of patients who seroconvert.

Pooled data from the three LAM trials were also used to derive estimates of the effect of LAM on the rate of progression to cirrhosis for the subgroup 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 LAM and interferon alfa/no treatment, respectively. In the long-term model, LAM 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 and colleagues[16]). 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 colleagues[16]) 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 and 39% for decompensated cirrhosis and 84.3% for HCC.

One scenario omitted from this analysis was the option to use LAM 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 CHB would not be retreated. However, discussion with UK specialists suggests that it is normal practice to reinitiate treatment in patients whose disease reactivates. The meta-analysis by van Nunen and colleagues[94] suggests that patients who have previously reactivated disease after seroconverting are less likely to achieve a durable response when retreated, although 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 16 weeks of interferon alfa and a variable-length regimen of LAM at 100 mg/day. LAM 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 6 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 10 specialist consultations during the year in which treatment occurred compared with LAM 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 2 months after treatment ceased, whereas LAM-treated patients were seen monthly for the first 4 months of treatment then reviewed at 6 months. Patients not receiving any antiviral therapy were assumed to have the same schedule of specialist consultations as the LAM-treated patients. For the second 6 months of year one, all patients were seen every 3 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 LAM treatment. The next largest components were laboratory tests and pathology at 20% of the total for interferon alfa and 32% of the total for LAM 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 HCC patients. 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 US$3000 for compensated cirrhosis and $13,500 for decompensated cirrhosis) was due to the assumed frequency of hospitalisation (once every 2 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 of PEG and/or ADV identified only one economic evaluation. This was a US Markov model comparing ADV as salvage therapy to interferon alfa or LAM. The ICER for ADV salvage therapy was US$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 LAM. 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, although 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 end-points. 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 antiviral treatment. None included patients with HBeAg-negative CHB.
- A number of treatment scenarios were modelled, including interferon alfa and LAM (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

TABLE 28 *Health state utilities used in previous economic evaluations in CHB*

Health state	Wong *et al.*, 1995[16a]	Dusheiko and Roberts, 1995[80a]	Crowley *et al.*, 2000, 2002[81,84a]	Mild Hepatitis C Trial[102b]
HBeAg seroconverted	0.931	0.90	0.783	NA
Chronic hepatitis:		0.80		NA
No treatment	0.893		0.692	
IFN treatment	0.777		0.467	
LAM treatment			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

NA, not applicable.
[a] Derived utilities based on clinician opinion.
[b] Used patient data on health state classification using EQ-5D and tariff values from the general population.[103]

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, although 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.

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 CHB (see Appendix 2 for details of the search strategy). The literature search identified one published study reporting on health state values/utilities for patients with CHB,[101] discussed in the section 'Health state values/utilities' (below). There is little information in general on QoL 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 28* 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.[102]

Health state values/utilities

Owens and colleagues[101] derived utility scores for asymptomatic, mildly symptomatic and severely symptomatic 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 and also contained a section to assess QoL 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 approach does not follow the principles of the time trade-off technique as described by Torrance and colleagues.[104]

The 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 that for AIDS (the most severe HIV state), although 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 QoL 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 QoL in CHC and CHB patients recruited in the liver clinic at St Mary's Hospital, London.[105] This paper (reviewed below) suggested that CHB 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 with utility values for similar states derived from patients.

Supporting information on quality of life associated with chronic hepatitis B

Two studies have reported on HRQoL for CHB patients who were not on antiviral therapy, using a generic QoL instrument (SF-36). Foster and colleagues[15] investigated sequential CHC and CHB patients attending outpatient clinics at St Mary's Hospital, London. Patients with cirrhosis or other significant chronic conditions were excluded, as were any patients who were on antiviral medication (or had been within 6 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.[106] Scores for HCV patients were significantly reduced compared with the general population norms. Scores for patients with HCV and HBV were compared to determine whether the reduction in QoL 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 the general health and mental health dimensions 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 QoL.

Pojoga and colleagues[17] investigated 66 consecutive patients with chronic viral hepatitis within 6 months of referral to tertiary centres in Romania who were not receiving antiviral treatment. Patients with cirrhosis or alcoholic liver disease were excluded from the study population, which consisted of 27 patients with CHB, 38 patients with CHC and one patient with both CHB and CHC. Scores on the SF-36 for all hepatitis patients were compared with 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 Foster and colleagues' study[15] and other studies concerned with QoL in chronic viral hepatitis,[107,108] no significant correlations were found between patients' transaminase levels and QoL as assessed by the SF-36.

These studies suggest that economic evaluations of interventions for CHB need to take account of the reduction in patients' QoL 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 QoL. The limited evidence available suggests that the impact on QoL for CHB infection is not as great as for CHC, when in the asymptomatic state. However, there is no evidence of a difference in the impact of CHB and HCV on QoL once patients have progressed to cirrhotic and decompensated disease.

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 PEG relative to currently available treatments for patients with CHB, 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, that is, patients with HBeAg-negative CHB are not excluded. The comparators are clearly identified as IFN, LAM, ADV 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 CHB, while only LAM 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.

Estimation of benefits

Model structure/structural assumptions

Separate state transition models were developed to model disease progression and treatment effects in HBeAg-positive and -negative CHB. These were structurally similar to models used in previous economic evaluations that have included long-term models of disease progression[81,84] and are consistent with published studies of the natural history of CHB infection.[3,89,97]

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 HCC with condition-specific excess mortality risks), but differed in the definition of response to treatment. As with previous economic evaluations of antiviral treatment for CHB, the primary therapeutic aim modelled for patients with HBeAg-positive disease was HBeAg seroconversion. Since this end-point 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 CHB health state. No short-term effect of antiviral therapy on progression to compensated cirrhosis, such as that estimated in recent economic evaluations of LAM,[81,83,84] has been included. The models do not take any explicit account of LAM or ADV 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[16] and Crowley and colleagues[81,84] excluded liver transplantation from their models owing to uncertainty over outcomes for this subgroup 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 antiviral 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 owing to the comparatively small number of patients who achieve this. This exclusion is unlikely to have a significant impact on comparisons between PEG and other antiviral 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 QOL as 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. LAM and ADV-treated patients who respond are maintained on consolidation therapy for 6 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 IFN and PEG 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 PEG-treated patients reporting side-effects which are likely to impact on patients' QoL (e.g. pyrexia, fatigue and headache) than those treated with LAM in the Phase III trial.[38] An adjustment to the QoL scores for patients while on treatment, similar to those adopted in previous economic evaluations involving interferon alfa,[16,81,84] 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 on patients' QoL and also substantial excess mortality. The cycle length of 1 year is also appropriate given the comparatively slow rate of progression of disease.

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.[81,84] Both of these evaluations excluded liver transplantation, so a third source[109] 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 CHB to compensated cirrhosis (0.06 and 0.09 for HBeAg-positive and -negative patients, respectively) and from CHB 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 and these are discussed in turn below.

Pegylated interferon alfa and conventional interferon alfa

Three comparisons of PEG and IFN are reported:

- The first uses seroconversion rates for PEG and IFN reported by Cooksley and colleagues[37] [as discussed earlier in the section 'Results' (p. 15)] based on 24 weeks of treatment with each agent.
- The second uses the seroconversion rate and treatment duration reported by Lau and colleagues[40] [see the section 'Results' (p. 15)] for PEG against those for IFN reported by Cooksley and colleagues.[37] The seroconversion rates for PEG are almost identical (hence life expectancy/QALYs are almost identical, as are the costs of treating disease progression). The only difference is that, owing to an extra 24 weeks of treatment, PEG treatment costs double. The purpose of this comparison appears to be to provide an evaluation of PEG at its licensed dosage and treatment duration.
- An additional comparison uses a 9-MU dose of IFN for 24 weeks, but uses the seroconversion rate reported by Cooksley and colleagues,[37] against the seroconversion and treatment duration for PEG reported by Lau and colleagues.[40] This simply increases the cost of IFN therapy and therefore reduces the ICER for PEG. The purpose of this comparison appears to be to provide an evaluation of PEG at its licensed dosage and treatment duration against the normal dosage and duration of treatment on IFN in the treatment of HBeAg-positive CHB.

The probability of relapse from HBeAg seroconversion for both PEG and IFN was taken from a recent meta-analysis of patient-level data on the durability of seroconversion following treatment.[94] However, the meta-analysis did not contain any patients treated with PEG. 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 PEG and LAM:

- The first was based on seroconversion rates observed 24 weeks after the end of 48 weeks of treatment as reported by Lau and colleagues.[40]
- The second extends the treatment period for LAM to 4 years, by applying HBeAg seroconversion rates reported in the literature.[110]

The seroconversion rates used for years 2–4 in the longer term analysis are comparatively low. Cumulative rates for HBeAg seroconversion on LAM therapy are typically quoted in the range of 27–35% at 2 years and above 40% at 3 years. The seroconversion rates used by Crowley and colleagues in their cost-effectiveness study were substantially higher at 28.7% at 1 year, 42% at 2 years, 65% at 3 years and 73% at 4 years. These rates apply to CHB patients with ALT levels at greater than or equal to twice the ULN and were estimated for a subset of patients included in clinical trials of LAM.[91–93]

A probability of reactivation of CHB of 0.35, based on the meta-analysis by van Nunen and colleagues,[94] was applied to the seroconversion rate observed for 48 weeks of treatment. This is

TABLE 29 *Age-specific utilities for healthy population, state-specific decrements and estimated health state utilities*

		HBeAg	CHB	CC	DC	HCC	LT	PostLT
Age (years)	**Utility**	**–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

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

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 4 year model. This was done on the basis that longer term LAM treatment provides a more durable response. However, it appears that this value was 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 was conducted as if assuming that all patients were treated for the full 4 years – including those who seroconverted. However, the model assumptions state that seroconverted patients were maintained on a consolidation treatment of LAM for 6 months, then ceased therapy (provided that they remained in the seroconverted state).

Pegylated interferon alfa and adefovir dipivoxil
Two comparisons are made between PEG and ADV:

- The first was based on the seroconversion rate observed after 48 weeks of ADV treatment in a placebo-controlled clinical trial[32] compared with that in the RCT of PEG reported by Lau and colleagues.[40]
- The second comparison extended the treatment period for ADV to 4 years, by applying reported HBeAg seroconversion rates for ADV derived from the literature[42] (this is a conference abstract reporting long-term follow-up of patients in Study 437).

Only 3 years of data are available for ADV so that the seroconversion rate for the fourth year of treatment was assumed to be the same as that for LAM. No attempt was made to model the effect of ADV resistance in this comparison. It was assumed that a proportion of the patient drop-out in the long-term studies of ADV reflected resistance. The durability of seroconversion with ADV was assumed to be the same as for IFN and PEG (92%).

Pegylated interferon alfa and best supportive care
The final comparison uses the seroconversion rate for PEG reported by Lau and colleagues[40] compared with 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 antiviral 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[16] and Crowley and colleagues[81,84]) was used to estimate disease progression in this scenario.

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 CHB, 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 CHB, 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 Wong and colleagues' study, as discussed earlier, values reported in another economic evaluation (by Bennett and colleagues:[109] decision analysis on interferon alfa treatment for CHC) for

TABLE 30 *Health state costs from the 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]	Bottom-up costing by assumption
DC	7,855	Bottom-up costing by assumption
HCC	7,980	NICE Hepatitis C HTA report, 2003
Liver transplant	46,551	NICE Hepatitis C HTA report, 2003
Post-liver transplant	1,677	Bottom-up costing by assumption

[a] "Response" in the 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 LAM.

the year in which the transplant took place and for QoL 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.

For the cost-effectiveness analysis, age-specific utility weights reported by Kind and colleagues[111] 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 29*).

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 antiviral treatment were estimated separately from the health state costs used to estimate the lifetime costs of the medical management of CHB.

The drug costs for interferon alfa-based interventions were based on a treatment course of 4.5 MU/0.5 ml three times per week (giving a weekly cost of £67.80), for 24 weeks of IFN and 180 µg/0.5 ml per week (giving a weekly cost of £132.00) for either 24 or 48 weeks for PEG. Drug costs for LAM were based on either a 48- or 208-week regimen at 100 mg/day (weekly cost £19.52). On progression to seroconversion, patients continued on LAM for a 6-month consolidation treatment. Drug costs for ADV were based on a dose of 10 mg/day (weekly cost £73.50) for a fixed period of either 48 or 208 weeks. There is no indication in the submission whether ADV-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 reviewed in the section 'Results of the systematic review: cost-effectiveness' (p. 61) costed a higher intensity of monitoring during the first 6 months of treatment and although 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, suggest that IFN and PEG treatment require a higher intensity of medical management than do LAM or ADV treatment and such costs should be included in any comparison.

Health state costs for the submission (*Table 30*) 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, which suggest that patients in these categories should be reviewed every 6–12 months during which time their serological status/HBV DNA should be assessed and a screen for HCC should be undertaken. A protocol-based costing similar to that developed for the CHB health state may have been a more appropriate option for these states.

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

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 ADV relative to current available treatments for patients with CHB. The analysis presented in the submission differs from the published evaluations we reviewed in the section 'Results of the systematic review: cost-effectiveness' (p. 61) 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 antiviral treatment (best supportive care)
- LAM first-line with no second-line treatment
- LAM first-line with ADV as second-line treatment
- ADV as first-line with LAM 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 HCC.

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 1-year cycle length, partly because 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. Although 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 permit a more efficient solution than methods requiring the simulation of several thousand individual patients.

Estimation of benefits

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,[16,81,84] and was consistent with published studies of the natural history of CHB infection.[3,89,97] The model has 12 health states incorporating an immunotolerant state which precedes the active CHB state. The immunotolerant state was not included in other evaluations, which took the starting state for the evaluation as CHB as this is the health state in which patients would present for antiviral 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 antiviral treatment for CHB, 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 antiviral 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 24–36 years (median 31 years) whereas for HBeAg-negative disease the range is 36–45 years (median 40 years).[89]

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.[89]

Supporting data

A systematic review was conducted to identify relevant clinical effectiveness studies for ADV and LAM. 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 CHB health state. No short-term effect of antiviral therapy on progression to compensated cirrhosis, such as that estimated in the published economic evaluations of LAM,[81,84,112] has been included.

The estimates of treatment effects after 1 year of treatment with LAM were taken from two placebo-controlled clinical trials,[92,93] which showed a relative risk of 3–3.7 for HBeAg seroconversion and of 2.7–4.1 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 1 year of treatment with ADV for patients with HBeAg-positive disease were taken from a placebo-controlled clinical trial[32] [Study 437, as discussed in the section 'Results' (p. 15)], which showed a relative risk of HBeAg seroconversion of 2 and a relative risk of ALT normalisation of 3. A slightly lower relative risk of 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 the section 'Results' (p. 15)].

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

- 'viral suppression'
- active CHB
- compensated cirrhosis
- decompensated cirrhosis
- HCC
- 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 LAM 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 4 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.

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 unity, a rescaling 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. Although 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 transition 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, although it may be expected that these are correlated in terms of both 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.

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 QoL 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 CHB, derived from ratings by a clinical expert panel. For compensated cirrhosis, decompensated cirrhosis and HCC, the health state utilities used are those derived for the Mild Hepatitis C trial[102] which used the EQ-5D health state questionnaire and values from a published tariff.[103] Finally, the health state values used for the liver transplant state are taken from a study reporting on QoL 3 months after liver transplantation, which used the EQ-5D health state questionnaire.[113]

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 antiviral 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 outpatient 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 HCC (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 CHB 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[102] – 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.[114]

The drug costs for ADV were based on a dose of 10 mg/day (£315.00 per 30-tablet pack or £3835.13 per patient-year) and for LAM were based on a dose of 100 mg/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, whereas 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 the early stages of treatment. As discussed in the section 'Hepatitis B antiviral therapy: published economic evaluations' (p. 62), previous evaluations costed a higher intensity of monitoring during the first 6 months of treatment. Although 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.

Comparison of cost-effectiveness results presented in industry submissions

Table 31 presents the cost-effectiveness results reported in the Roche submission to NICE for PEG-2a. A number of scenarios are modelled, the majority for HBeAg-positive patients, including an indirect comparison between PEG and ADV.

TABLE 31 *Cost-effectiveness of PEG (Roche submission)*

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

TABLE 32 *Cost-effectiveness of ADV (Gilead submission)*

Comparison	Cost/QALY (£)
LAM first line, no treatment second line (LAM–NT) vs no treatment (NT)	3,109
LAM first line, ADV second line (LAM–AD) vs no treatment (NT)	6,651
ADV first line, LAM second line (AD–LAM) vs no treatment (NT)	8,185
LAM first line, ADV second line (LAM–AD) vs LAM first line, no treatment second line (LAM–NT)	9,201
ADV first line, LAM second line (AD–LAM) vs LAM first line, no treatment second line (LAM–NT)	11,435
ADV first line, LAM second line (AD–LAM) vs LAM first line, ADV second line (LAM–AD)	29,359

Table 32 presents the cost-effectiveness results reported in the Gilead submission to NICE for ADV, based on a number of scenarios comparing drug-switching regimes following development of treatment resistance.

The cost per QALY estimates are generally highest when ADV 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 compared PEG as first-line treatment against interferon alfa, LAM and ADV. In contrast, Gilead omitted interferon (pegylated or otherwise) from their model. They assumed that a proportion of patients would receive interferon alfa as first-line treatment, and that only those failing to respond would then receive LAM or ADV. 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 probably PEG) 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. LAM and ADV would then be used in patients who had not responded or who had relapsed.

Chapter 6

SHTAC cost-effectiveness analysis

SHTAC cost-effectiveness model

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

We developed a model to estimate the cost-effectiveness of PEG-2a and of ADV compared with IFN, LAM and best supportive care in a UK cohort of adults with CHB. The perspective of the cost-effectiveness analysis is that of the NHS and personal social services.

Strategies/comparators

The scope for the appraisal, as issued by NICE, states that the interventions to be considered are ADV and PEG-2a. The comparators for these interventions are current standard practice, (non-pegylated) interferon alfa-2a/2b, LAM and non-drug treatment strategies, all of which are indicated for patients with CHB 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 ADV as the intervention and LAM and best supportive care as comparators.

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 CHB 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 CHB (see Appendix 3 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.

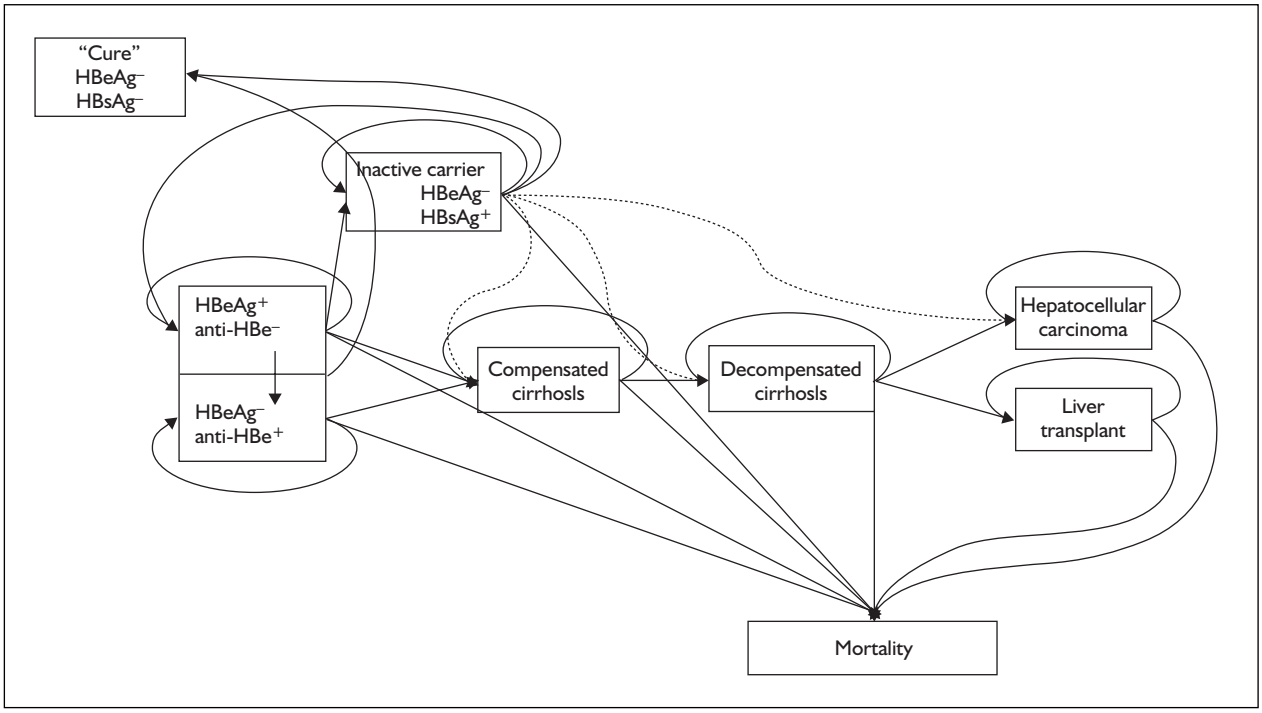

FIGURE 3 *State transition diagram for natural history model in chronic hepatitis B*

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 HCC).
- 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 CHB 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 CHB state. For patients with HBeAg-negative disease, it has been assumed that patients may move spontaneously into remission (with normalisation of ALT and low serum DNA), but it is uncommon for spontaneous remission to be sustained.[89,115]

The diagram indicates that individuals may progress to HCC 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 progress to decompensated liver disease only 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 CHB without cirrhosis; previous evaluations have not included an estimate of excess mortality risk for CHB. However, natural history studies have estimated that this risk may be as high as 2%.[3]

A Markov state transition model was 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 antiviral 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 antiviral drug therapies, the natural history transition probabilities are modified to take account of treatment effects described in the section 'Effectiveness data' (p. 85) and intervention costs as described in the section 'Intervention costs' (p. 88) are included. As stated earlier, the principal effect of antiviral 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 1 year, with a half-cycle correction applied. The subtree 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 subtree are accessible from each starting state. For example, individuals with CHB are assumed not to progress directly to decompensated disease and 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 subtree to be attached to other locations in the tree as shown in *Figure 4*. These copies of subtrees are labelled as clones in the figure with the number and name indicating which cloned subtree has been attached at which node. The advantage of using cloned subtrees is that only one 'master' copy needs to be maintained rather than requiring maintenance of numerous identical subtrees.

Moving to the left of the 'progression' subtree, a second subtree 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 subtree.

The treatment options open to patients who have become resistant are that they may continue on

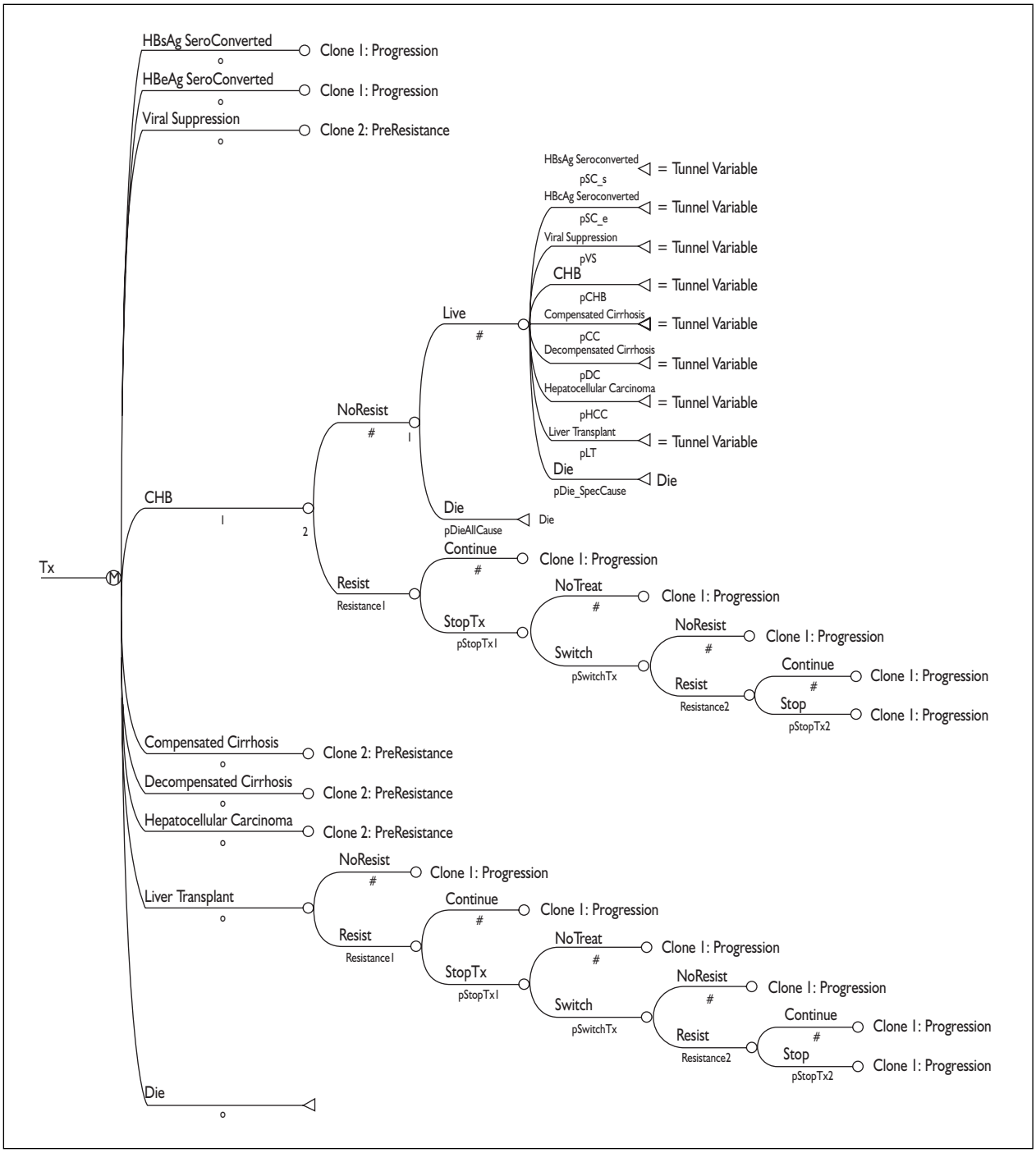

FIGURE 4 *Markov tree used to model patient outcome and treatment costs (# indicates a residual probability, i.e. one minus the sum of the other probabilities at the node)*

treatment, although 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 antiviral treatment (receiving best supportive care from then onwards) or, if other antiviral 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 LAM and ADV, the two antiviral agents for which resistance has been shown to

TABLE 33 *Defining characteristics of tunnels within health states in Markov cycle tree*

Tunnel within health state	Tunnel characteristics (based on patient characteristics of type of CHB 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 antiviral 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 antiviral 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

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, although there are no therapeutic benefits assumed from continued treatment, or stop all antiviral treatment (receiving best supportive care from then onwards). The 'pre-Resistance' subtree is cloned to each of the health states in which patients are eligible to receive active antiviral treatment (compensated cirrhosis, decompensated cirrhosis, HCC and liver transplantation) as shown in *Figure 4*.

Given that patients with HBeAg-positive and -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 -negative disease (given the difference in cohort age and 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 QoL 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 QoL 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 1 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 33*.

Separate tunnels were defined for HBeAg-positive and -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. LAM and ADV) and in which drug resistance has been observed, tunnel states were defined for HBeAg-positive and -negative patients to show whether they were resistant to either drug and whether they were continuing or had stopped therapy.

Baseline cohort of adult chronic hepatitis B patients

Baseline characteristics of CHB patients at the time of diagnosis are taken from natural history studies:

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

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 CHB but have not progressed to cirrhosis.

Data sources

Effectiveness data

We have reported on the findings from our systematic review on the clinical effectiveness of PEG-2a and ADV (Chapter 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 [see the section 'Systematic review of the literature' (p. 61)].

Tables 34 and *35* 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 transition probabilities are modified owing to the treatment effects discussed below in each of the treatment models.

Table 36 summarises the treatment effects that replace the natural history transition probabilities for HBeAg-positive patients indicated in *Table 34*, within the treatment models. HBeAg seroconversion rates for up to 1 year of treatment with PEG-2a (32%) were taken from the Phase III RCT[38] and from a randomised Phase II study for IFN[37] (see Chapter 4). HBeAg seroconversion rates for LAM and ADV were based on seroconversion rates from the Phase III RCTs[32,38] and from reports of seroconverted patients in studies with up to 4 years of follow-up[110,124,125] and 3 years of follow-up on clinical trial patients for ADV.[42] 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.[94] The estimated relapse rate for LAM-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 ADV the proportion not maintaining HBeAg seroconversion (9%) was taken from the conference abstract reviewed in the section 'HBeAg loss/seroconversion' (p. 38). In the absence of information in the durability of HBeAg seroconversion following treatment with PEG-2a, the value for reactivation for IFN (9%) was used. For non-seroconverted patients receiving LAM, the transition rate from CHB 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 LAM.[95]

For HBeAg-negative patients (*Table 37*) the proportions of patients normalising ALT were taken from Phase III RCTs[31,36] for PEG-2a (59% at end of follow-up), LAM (73% at end of treatment) and ADV (72% at end of treatment). Review articles have reported biochemical response rates for IFN of 50%[115,121,126] and relapse following end of treatment of 60–70%. For LAM and ADV 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 LAM-treated patients, an 80% reactivation rate is applied in the year in which resistance develops and effective treatment ceases.[127–129] In the absence of long-term follow up data on ADV in this group of patients, the same assumptions as for LAM were applied. For PEG-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 IFN. The impact of this estimate on the cost-effectiveness of PEG

TABLE 34 *Transition probabilities for natural history model for patients with HBeAg-positive chronic hepatitis*

Health state		Transition probability		
From	**To**	**Value**	**Source**	**Treatment effect**
HBsAg	HBsAg	R[a]		
	HCC	0.00005	Wong *et al.*[16]	
HBeAg	HBsAg	0.02	EASL[3]	
	HBeAg	R		
	CHB	0.03[b]	Wong *et al.*[16]	
	CC	0.01	Fattovich *et al.*,[97] Liaw *et al.*,[116] Crowley *et al.*[81,84]	
	HCC	0.001	Wong *et al.*[16]	
CHB	HBsAg	0.0175	Wong *et al.*,[117] Wong *et al.*[16]	
	HBeAg	0.09	Wong *et al.*,[16] Crowley *et al.*,[81] Fattovich[89]	Yes
	CHB	R		
	CC	0.05	Fattovich *et al.*,[97] EASL,[3] Liaw *et al.*[116]	Yes[c]
	HCC	0.005	Wong *et al.*,[16] Di Bisceglie *et al.*[118]	
	Dead	0.0035	Gilead submission	
CC	HBeAg	0.09	Wong *et al.*,[16] Crowley *et al.*[81]	Yes
	CC	R		
	DC	0.05	Crowley *et al.*,[81] Fattovich *et al.*[97]	Yes
	HCC	0.025	Wong *et al.*,[16] Crowley *et al.*[81]	
	Dead	0.051	Crowley *et al.*,[81,84] Lau *et al.*[119]	
DC	DC	R		
	LT	0.03	Bennett *et al.*,[109] Shepherd *et al.*[120]	
	HCC	0.025	Assume same as CC	
	Dead	0.39	Wong *et al.*,[16] Crowley *et al.*[81]	Yes
HCC	HCC	R		
	LT	0		
	Dead	0.56	Wong *et al.*,[16] Lavanchy[121]	
LT	LT	R		
	Dead	0.21	Bennett *et al.*[109]	Yes
LT	LT	R		
	Dead	0.057	Bennett *et al.*[109]	Yes

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

[a] R 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.

[b] 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.

[c] This effect has only been demonstrated for LAM and applies only in the first year of treatment.[81,83,95]

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.

Health state values/utilities

A systematic search of the literature was undertaken [see the section 'Health-related quality of life for patients with chronic hepatitis B' (p. 70)], which identified one study reporting health state utilities for asymptomatic and symptomatic CHB. Owing to methodological weaknesses in this study,[101] it was decided not to use the values reported. We believe that 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 HRQoL as healthy individuals. Consequently, published age-specific QoL weights for healthy populations were applied to patients in these health states. Utility values for other health states were estimated relative to these values. Using values adopted in the economic evaluation by Wong and colleagues[16] the QoL

TABLE 35 *Transition probabilities for natural history model for patients with HBeAg-negative chronic hepatitis*

Health state		Transition probability		
From	**To**	**Value**	**Source**	**Treatment effect**
HBsAg	HBsAg	R[a]		
	HCC	0.00005	Wong *et al.*[16]	
Respond	HBsAg	0.0175	Wong *et al.*[117] Wong *et al.*[16]	
	CHB	0.029		
	CC	0.01	Assume same as HBeAg SC → CC	
	HCC	0.005	Assume same as CHB → HCC	
	Dead	0.0035	Assume same as CHB → Dead	
CHB	HBsAg	0.005	Fattovich[89]	
	Respond	0.14	Lai *et al.*[48]	Yes
	CHB	R		
	CC	0.09	EASL[3]	
	HCC	0.005	Wong *et al.*,[16] Di Bisceglie *et al.*[118]	
	Dead	0.0035	Gilead submission[24]	
CC	CC	R		
	DC	0.05	Crowley *et al.*,[81] Lavanchy,[121] Fattovich *et al.*[123]	Yes
	HCC	0.025	Wong *et al.*,[16] Di Bisceglie *et al.*,[118] Crowley *et al.*[81]	
	Dead	0.051	Crowley *et al.*,[81,84] Lau *et al.*[119]	
DC	DC	R		
	LT	0.03	Bennett *et al.*,[109] Shepherd *et al.*[120]	
	HCC	0.025	Assume same as CC	
	Dead	0.39	Wong *et al.*,[16] Crowley *et al.*[81]	Yes
HCC	HCC	R		
	LT	0.0		
	Dead	0.56	Wong *et al.*,[16] Lavanchy[121]	
LT	LT	R		
	Dead	0.21	Bennett *et al.*[109]	Yes
LT	LT	R		
	Dead	0.057	Bennett *et al.*[109]	Yes

[a] See *Table 34*.

TABLE 36 *Effectiveness of treatment (%) (HBeAg-positive patients)*

Transition	Conventional interferon	PEG	LAM	ADV
CHB to HBeAg seroconverted	25	32	18	18
CHB to compensated cirrhosis			2	
			This effect applies in first year of treatment	
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 37 *Effectiveness of treatment (%) (HBeAg-negative patients)*

Transition	IFN	PEG	LAM	ADV
CHB to response	50	59	73	72
CHB to compensated cirrhosis			2	
	This effect applies in first year of treatment			
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

weight for the CHB 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 CHC and liver transplant patients, whose health state utilities were determined using the EQ-5D,[102,130] 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 HCC
- –0.55 for patients undergoing liver transplant
- –0.32 for post-transplant patients.

The validity of applying health state valuations developed for CHC patients to CHB 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 HRQoL had not found any studies suggesting that aetiology of liver disease had any impact on QoL with progressive liver disease.

Discounting of future benefits

A discount rate of 1.5% was 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%).

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 discussions 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 CHB health states was used to develop health state costs. Second, 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.

Intervention costs

The frequency and intensity of monitoring of patients being treated with IFN, PEG-2a, LAM and ADV was identified based on clinical guidelines and discussions 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, whereas 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 per year. Two of these (occurring at months 3 and 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 months 6 and 12 in the management cycle) were detailed examinations involving assessment of HBeAg and HBsAg serology and screening for HCC using abdominal ultrasound and the 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 antiviral therapy were performed by the consultant whereas 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 IFN would be seen 10 times during a 24-week treatment period. This corresponds to weekly visits for the first month of treatment, then fortnightly for the second month and thereafter monthly visits. Full blood counts, liver function tests, urea and electrolytes and blood clotting tests are assessed at each consultation. Every 3 months a more detailed assessment is undertaken during which HBeAg and HBsAg serology, HBV DNA and thyroid function are assessed. During the detailed assessments, patients are also screened for HCC using abdominal ultrasound and the α-fetoprotein test. Standard consultations are assumed to take 30 minutes whereas the detailed assessments require 1 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 IFN, the costs of drugs also need to be assessed. Drug costs were calculated for a dosage of a 9-MU prefilled syringe, self-administered by patients three times per week (unit cost £45.19) for HBeAg-positive patients and a 4.5-MU prefilled syringe, self-administered by patients three times per week (unit cost £22.60) for HBeAg-negative patients. Unit costs were taken from the BNF, No. 49 (March 2005). This corresponds to a weekly cost of £135.57 and a total drug cost of £3253.68 for a 24-week course of treatment for HBeAg positive patients. For HBeAg-negative patients the corresponding costs are £67.80 and £3254.40 for a 48-week course.

Patients on PEG would be seen 16 times during a 48-week course of treatment, corresponding to weekly visits for the first month of treatment, then fortnightly for the second month and thereafter monthly for the remainder of treatment. As for IFN, 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 3 months, during which HBeAg and HBsAg serology, HBV DNA and thyroid function are assessed in addition to screening for HCC using abdominal ultrasound and the α-fetoprotein test. Standard consultations are assumed to take 30 minutes whereas the detailed assessments require 1 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 µg/0.5 ml, 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 £6338.88.

Patients on LAM or ADV are seen 11 times during a year of treatment, corresponding to monthly visits, but with no visit during month 11. 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 and HBV DNA are assessed with screening by the 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 HCC 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 LAM 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 £1095.36. Drug costs for ADV 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.

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 (*Table 38*).

TABLE 38 *Health state costs adopted for the economic evaluation*

Health state	Cost (£)
HBsAg seroconverted	0
HBeAg seroconverted	267
ALT normalisation	537
CHB	537
Compensated cirrhosis	1,138
Decompensated cirrhosis	9,120
HCC	8,127
Liver transplant	36,788
Post-liver transplant	1,385

The previous section describes the schedule and content of consultations for patients in the CHB and seroconverted health states for patients receiving each of the antiviral interventions and for the best supportive care comparator. Health state costs for compensated cirrhosis, decompensated cirrhosis and HCC were taken from the observational study conducted during an HTA-funded trial in mild hepatitis C[102] with costs for liver transplantation and post-liver transplantation taken from a Department of Health-funded study of the costs of liver transplantation.[114]

Discounting of future costs

A discount rate of 6% was 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%).

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 CHB and HBeAg-negative CHB. For the interventions being assessed in this report comparisons are made with their closest comparator (for PEG this is with IFN and for ADV it is with LAM) 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 is modelled. For example, a typical treatment strategy would be interferon alfa used as first-line treatment with LAM or ADV 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 QALYs and the incremental costs determined in the cohort analysis. We identify the estimated costs of antiviral therapy separate from the medical costs incurred by managing progressing liver disease.

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 *Tables 34*, *35* and *36* and for health state costs in *Table 38*. Distributions are also assigned to the health state utilities described in the section 'Health state values/utilities' (p. 86) 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 a 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 variations 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 antiviral therapy and the model adopted for this evaluation.

SHTAC cost-effectiveness model – summary of methods

1. We devised a Markov state transition model to estimate the cost-effectiveness of ADV and PEG-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 HRQoL in CHB and also clinical effectiveness and cost-effectiveness of antiviral treatment.
2. The model includes eight health states (CHB, HBeAg seroconversion/remission, HBsAg

TABLE 39 *Cost-effectiveness of interventions and comparators (all patients)*

	Cost (£)	Discounted years of life expectancy	Discounted QALYs	ICER (£)
Best supportive care	8,555	22.29	17.07	
IFN	12,609	22.98	17.75	5,994[a]
PEG	15,745	23.51	18.26	6,119[b]
LAM	12,286	23.36	18.08	3,685[c]
ADV	29,918	24.55	19.15	16,569[d]

[a] Comparing IFN with best supportive care.
[b] Comparing PEG with IFN.
[c] Comparing LAM with best supportive care.
[d] Comparing ADV with LAM.

seroconversion, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant and death). Twelve 'tunnel' states take into account previous treatment history (e.g. switching drugs when resistance develops).
3. 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 years and 75% of whom are male, and HBeAg-negative disease, who have a mean age of 40 years and 90% of whom are male.
4. The model has a lifetime horizon, with a cycle length of 1 year (with half cycle correction applied).
5. Short-term outcomes include HBeAg seroconversion (for HBeAg-positive patients) and ALT normalisation (for HBeAg-negative patients).
6. Published age-specific QoL 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 the published literature.
7. 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.
8. Costs were discounted at 6% and benefits at 1.5%.

Cost-effectiveness results

Cost-effectiveness findings are presented for two separate groups: (1) patients with HBeAg-positive CHB and with HBeAg-negative CHB and (2) overall cohort of CHB patients having the age and sex characteristics reported in the literature and described in the section 'Baseline cohort of adult chronic hepatitis B patients' (p. 85). Discounted costs, identifying the contribution to total costs of antiviral 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 with their closest comparator. For IFN the closest comparator is best supportive care and for PEG it is IFN. For LAM the closest comparator is best supportive care and for ADV it is LAM.

Costs and outcomes modelled for a cohort containing patients with HBeAg-positive and -negative disease for each of the interventions are presented in *Table 39*. Additionally, incremental cost per QALY ratios are shown for each intervention relative to their closest comparator. Costs are discounted at 6% and health outcomes at 1.5%.

These comparisons are based on a 24-week course of treatment with IFN for patients with HBeAg-positive disease and IFN for 48 weeks for patients HBeAg-negative disease. A course of treatment with PEG is 48 weeks for both HBeAg-positive and -negative patients, whereas there is no fixed treatment course for LAM and ADV (although the EASL guideline recommends at least 1 year of treatment[3]). In the model we assumed that treatment with LAM or ADV, once started, is continued until HBeAg seroconversion occurs, drug resistance develops or the patient dies. Patients who undergo HBeAg seroconversion with LAM or ADV treatment are maintained on consolidation therapy for 6 months.

TABLE 40 *Cost-effectiveness of interventions and comparators (HBeAg-positive patients)*

	Cost (£)	Discounted years of life expectancy	Discounted QALYs	ICER (£)
Best supportive care	7,402	25.27	20.08	
IFN	11,359	25.78	20.58	7,936[a]
PEG	14,704	25.99	20.78	16,166[b]
LAM	10,909	26.32	21.08	3,489[c]
ADV	25,224	27.35	22.02	15,289[d]

[a] Comparing IFN with best supportive care.
[b] Comparing PEG with IFN.
[c] Comparing LAM with best supportive care.
[d] Comparing ADV with LAM.

TABLE 41 *Cost-effectiveness of interventions and comparators (HBeAg-negative patients)*

	Costs (£)	Discounted years of life expectancy	Discounted QALYs	ICER (£)
Best supportive care	11,247	15.32	10.05	
IFN	15,524	16.45	11.14	3,922[a]
PEG	18,172	17.72	12.36	2,162[b]
LAM	15,499	16.46	11.08	4,131[c]
ADV	40,870	18.01	12.44	18,620[d]

[a] Comparing IFN with best supportive care.
[b] Comparing PEG with IFN.
[c] Comparing LAM with best supportive care
[d] Comparing ADV with LAM.

Tables 40 and *41* report the modelled costs and outcomes for each intervention for HBeAg-positive and -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 with HBeAg-positive patients. This more than offsets the 8-year difference in mean age between HBeAg-positive and -negative patients that was assumed for the baseline cohort. In each group of patients ADV is associated with the greatest costs – typically double those for PEG and three times those for other treatment options. However, these increased costs are associated with substantial health gains – of the order of two QALYs compared with best supportive care and one QALY compared with LAM.

These may not be the most clinically relevant comparisons. Additional intervention strategies were modelled using interferon alfa as first-line intervention with LAM or ADV for those patients who do not respond to interferon alfa. We also modelled a set of sequential treatment strategies for PEG as first-line with LAM or ADV for those patients who do not respond. The final strategy in each comparison is referred to as ADV salvage, in which patients receive interferon alfa as first-line treatment and LAM is provided for those who do not respond to interferon alfa. Patients who develop resistance to LAM then have ADV added to their treatment. The costs of these intervention strategies, their outcomes and ICERs are reported in *Table 42*. 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.

As with the comparison of intervention costs in monotherapies, all intervention strategies that include ADV are substantially more costly than those that do not. However, these are also associated with health gain, in the range 2–3 QALYs when compared with best supportive care, or around one QALY when compared with the interventions including active antiviral therapy. In all of these cases, the ICERs are well within the range that would conventionally be regarded as being cost-effective.

TABLE 42 *Cost-effectiveness of sequential treatment strategies (all patients)*

Strategy	Cost (£)	Discounted years of life expectancy	Discounted QALYs	ICER (£)
Best supportive care	8,555	22.29	17.07	
IFN	12,609	22.98	17.75	5,994
IFN followed by LAM	15,159	23.76	18.45	3,604[a]
IFN followed by ADV	27,442	24.81	19.40	8,987[b]
IFN followed by LAM with ADV salvage	27,740	25.00	19.56	11,402[c]
PEG	15,745	23.51	18.26	6,119
PEG followed by LAM	18,053	24.20	18.88	6,766[d]
PEG followed by ADV	28,907	25.13	19.71	4,649[e]
PEG followed by LAM with ADV salvage	28,976	25.28	19.83	4,452[f]

[a] Comparing IFN followed by LAM with IFN alone.
[b] Comparing IFN followed by ADV with IFN alone.
[c] Comparing IFN followed by LAM, and ADV salvage with IFN followed by LAM.
[d] Comparing PEG followed by LAM with IFN followed by LAM.
[e] PEG followed by ADV with IFN followed by ADV.
[f] Comparing PEG followed by LAM and ADV salvage with IFN followed by LAM and ADV salvage.

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

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

Sensitivity analysis

Deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around model structure and for variations 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 the section 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 were addressed using probabilistic sensitivity analysis, which is reported later in this section.

Table 43 reports the results of the sensitivity analysis for the overall cohort of patients, including those with HBeAg-positive and -negative disease, for the comparison of each drug reported in *Table 40*. *Table 43* is divided to distinguish between analyses undertaken due to uncertainties in the model structure, 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 antiviral therapy for CHB on the cost-effectiveness estimates.

TABLE 43 *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: £2220 rather than £1138	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 IFN	6,541	5,919	3,685	16,569
Utility effect of interferon treatment – 33% reduction while on IFN	7,609	5,597	3,685	16,569
Relapse for HBeAg-negative patients treated with PEG is same as IFN (60%)	5,994	15,640	3,685	16,569
Relapse for HBeAg-negative patients treated with PEG 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 ADV and PEG costs by 20%	5,994	5,222	3,685	13,006
Reduce ADV and PEG costs by 30%	5,994	3,105	3,685	11,225

Previous economic evaluations, discussed in the section 'Systematic review of the literature' (p. 61), have excluded a number of state transitions from their analyses, either owing to an absence of data or owing 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

TABLE 44 *HBeAg seroconversion rates for lamivudine and adefovir used in sensitivity analysis*

Treatment year	Lamivudine	Adefovir dipivoxil
1	0.19	0.12
2	0.16	0.18
3	0.16	0.18
4	0.16	0.18

patients are non-cirrhotic and would therefore be able to achieve HBeAg seroconversion (although 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 LAM or ADV. 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 LAM. However, the ICER 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 ADV owing 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 LAM.

The impact of two other transitions that are commonly excluded from disease progression models was investigated. Excluding transitions from the HBeAg seroconverted state to HCC 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 ADV owing to its lower resistance profile compared with LAM, 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.

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 ICER 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 ADV has the effect of increasing the cost-effectiveness estimate. Over the range of values used in the sensitivity analysis, the incremental costs (compared with LAM treatment) decreased by 25% whereas incremental QALYs decreased 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 QoL – had comparatively little impact on cost-effectiveness of interventions. However, varying the assumption over the relapse rate for PEG 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 IFN (60%) was applied and also a value mid-way between that adopted by the manufacturer and that for IFN (45%).

In the model for the base case analysis, the effectiveness of LAM and ADV 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 LAM and ADV compared with placebo, and on reported seroconversion rates in long-term follow-up studies compared with 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 44* shows the HBeAg seroconversion rates used in this analysis.

We conducted two sensitivity analyses on LAM and ADV HBeAg seroconversion rates:

- Rates observed in the trials and long-term follow-up studies were applied directly in the model for treatment years 1–4 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 1–4 and the seroconversion rate reverted to the spontaneous rate for all subsequent years. This was the assumption applied in Crowley and colleagues' analysis of LAM.[81,84]

The result of these analyses is to increase the ICER for LAM, compared with best supportive care, slightly (from £3685 to £4223 per QALY for the model extrapolating a treatment effect beyond year 4, and £4728 per QALY for the model in which no extrapolation was applied). The effect on the ICER for ADV is much greater, increasing from £16,569 in the base case to £21,363 for the model that extrapolates beyond 4 years and £50,168 for the model with no extrapolation. The two principal causes of this are:

- The low HBeAg seroconversion rate for ADV in year 1 (12%) compared with the spontaneous rate assumed in the model (9%). In the trial, the seroconversion rate with ADV was double that in the placebo arm [see the section 'HBeAg loss/seroconversion' (p. 38)].
- The high resistance rate for LAM means that comparatively few patients would be treated beyond 4 years in the base case analysis, whereas the low resistance profile for ADV means that patients may be maintained on treatment for a longer period. In the analysis using trial seroconversion rates directly beyond year 4, 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 45 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 ICERs reported are not referenced to a common base, but are derived from a comparison of each strategy to its closest comparator (see *Table 42* for a list of comparators). For example, each strategy which includes PEG is compared with the equivalent strategy that includes IFN. This means that the ICERs for sequential strategies including PEG generally appear to be low as they reflect only the impact of replacing IFN with PEG 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 ICER for strategies including ADV, whereas the results appear to be little influenced by variation in transitions from the HBeAg seroconverted state to HCC or to HBsAg seroconversion.

Changing the discount rates applied to costs and health outcomes has a similar effect as before, greatly increasing the ICER for strategies including ADV.

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 ICERs for strategies that include PEG and ADV. One striking observation from this analysis is that variation in the rate of resistance to ADV over a range of +2 to +8% has very little impact on the ICER.

The ICERs for PEG appear to be particularly sensitive to variation in the relapse rate for HBeAg-negative patients who achieve a response (by normalising ALTs) following treatment.

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 38* for base case analysis). *Table 46* 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 ICERs based on the values generated in the probabilistic analysis.

Figure 5 shows the cost-effectiveness acceptability curves (CEACs) for LAM, ADV and best

TABLE 45 *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 £2220 rather than £1138	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 PEG is same as IFN (60%)	3,604	8,987	11,402	17,472	19,481	20,519
Relapse for HBeAg-negative patients treated with PEG is 45%	3,604	8,987	11,402	10,623	10,063	10,485
Reduce PEG costs by 20%	3,604	8,987	11,402	3,802	624	Dominant
Reduce ADV costs by 20%	3,604	7,312	9,733	6,766	5,637	5,328
Reduce ADV and PEG costs by 20%	3,604	7,312	9,733	3,802	1,612	760
Reduce ADV and PEG costs by 30%	3,604	6,474	8,899	2,320	94	Dominant

IFN + LAM, IFN followed by LAM;
IFN + ADV, IFN followed by ADV;
IFN + LAM + ADV, IFN followed by LAM with ADV salvage for LAM patients who develop resistance;
PEG + LAM, PEG followed by LAM;
PEG + ADV, PEG followed by ADV;
PEG + LAM+ ADV, PEG followed by LAM with ADV salvage for LAM patients who develop resistance.

supportive care. The curves indicate the probability that a given intervention is optimal compared with the other illustrated interventions. This suggests that LAM is a cost-effective option at lower threshold levels of willingness-to-pay for health outcomes, but as the threshold is increased ADV is increasingly likely to be the optimal intervention.

TABLE 46 *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	
IFN	12,655	12,064	14,240	17.77	17.29	19.24	5,920
PEG	15,782	15,211	17,341	18.30	17.80	19.73	5,945
LAM	12,336	11,740	13,982	18.09	17.61	19.53	3,744
ADV	30,082	28,849	33,676	19.13	18.62	20.64	17,078

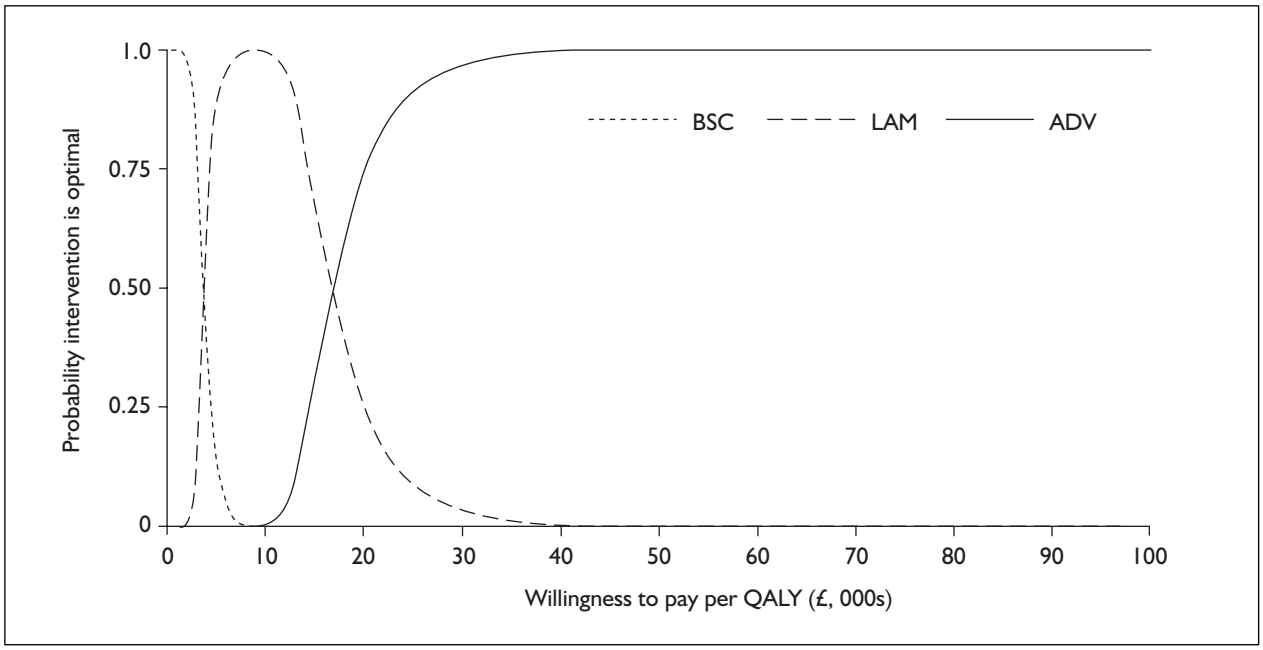

FIGURE 5 *CEACs for best supportive care (BSC), LAM and ADV*

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

Figure 7 shows the CEACs for best supportive care, IFN and PEG for patients with HBeAg-positive disease. In this case the balance between the probability of IFN and PEG is less clear than would be suggested by *Figure 6*. This partly reflects the assumption that the durability of HBeAg seroconversion following treatment with PEG is the same as for IFN, as was discussed in the section 'Sensitivity analysis' (p. 93). This means that for HBeAg-positive patients the only benefit from treatment with PEG is the increased HBeAg seroconversion rate observed in trials of PEG [see the section 'HBeAg loss/seroconversion' (p. 38)].

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

Table 47 reports the mean cost and outcomes and ICERs for the sequential treatment strategies from the probabilistic analysis. The mean discounted QALYs from this analysis are almost identical with the base case values (see *Table 41* for base case analysis). However, the mean costs are slightly higher than in the base case analysis.

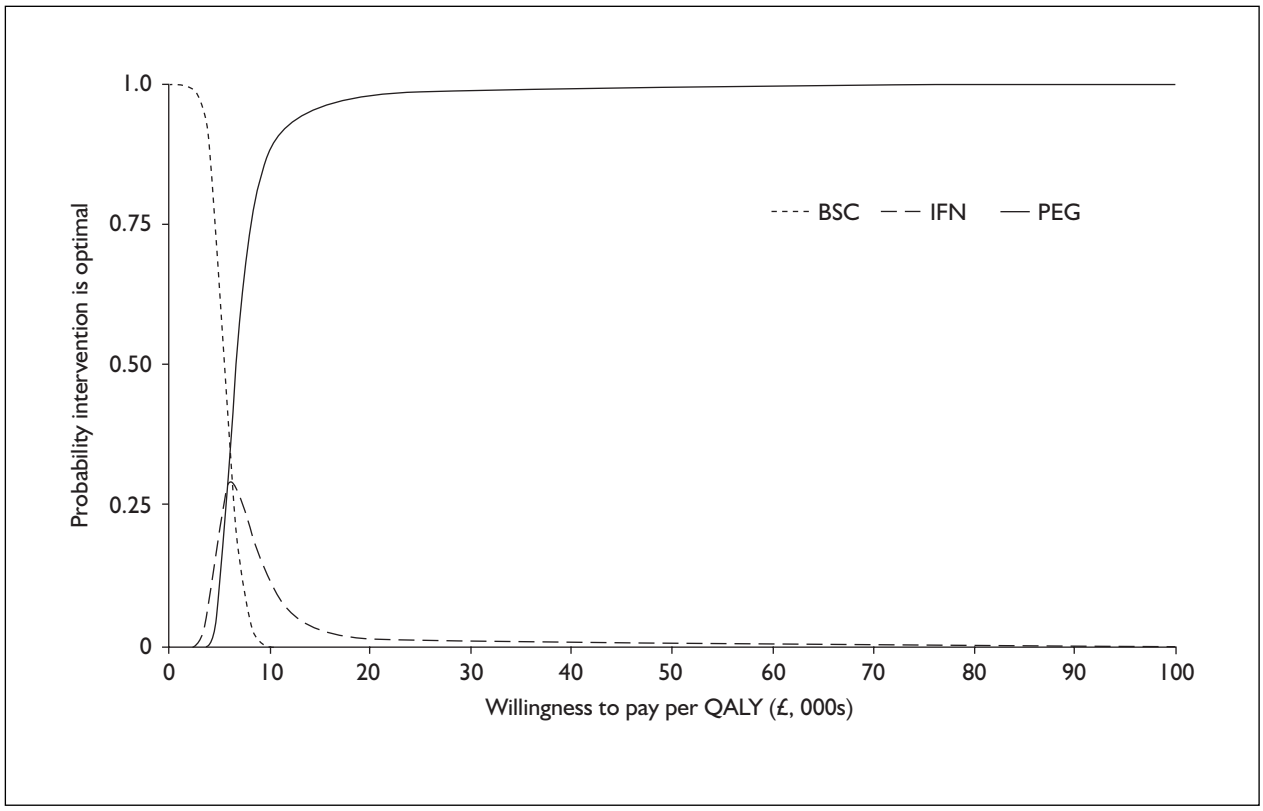

FIGURE 6 *CEACs for best supportive care (BSC), IFN and PEG*

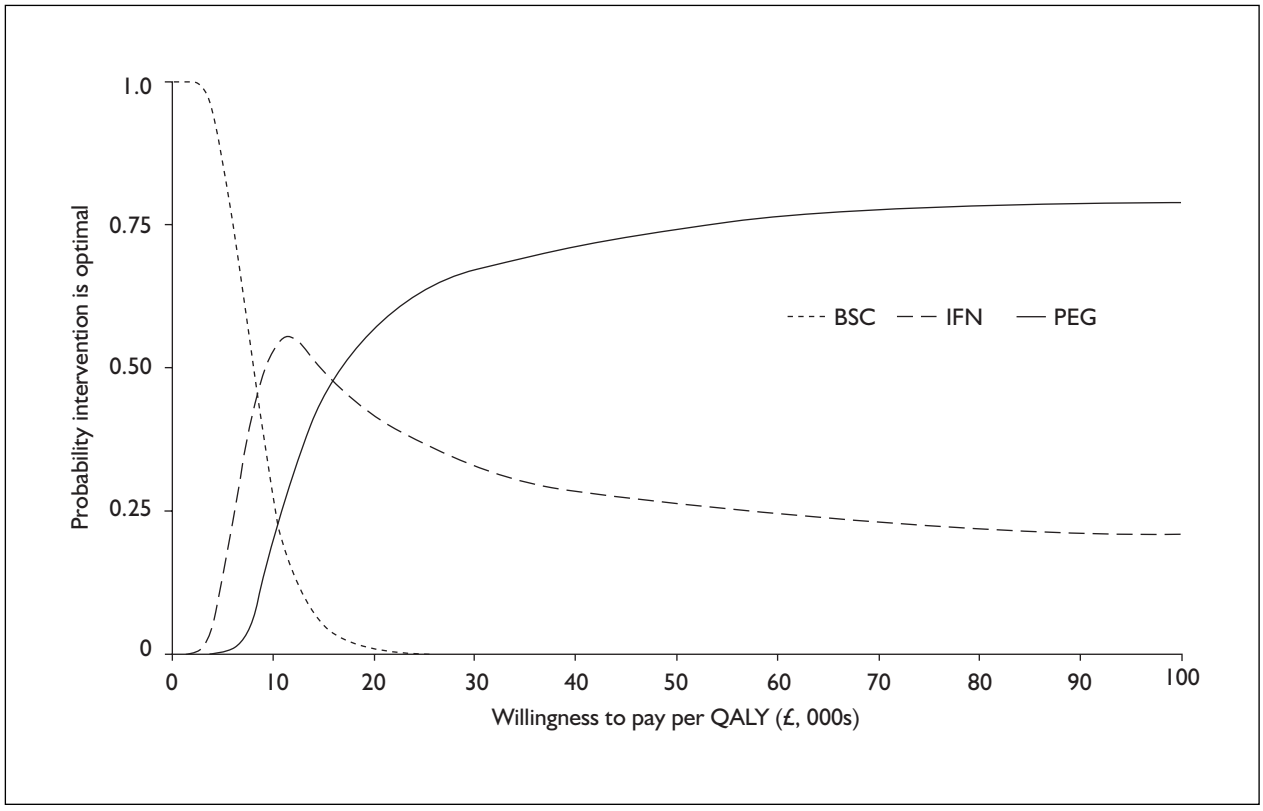

FIGURE 7 *CEACs for best supported care (BSC), IFN and PEG in patients with HBeAg-positive disease*

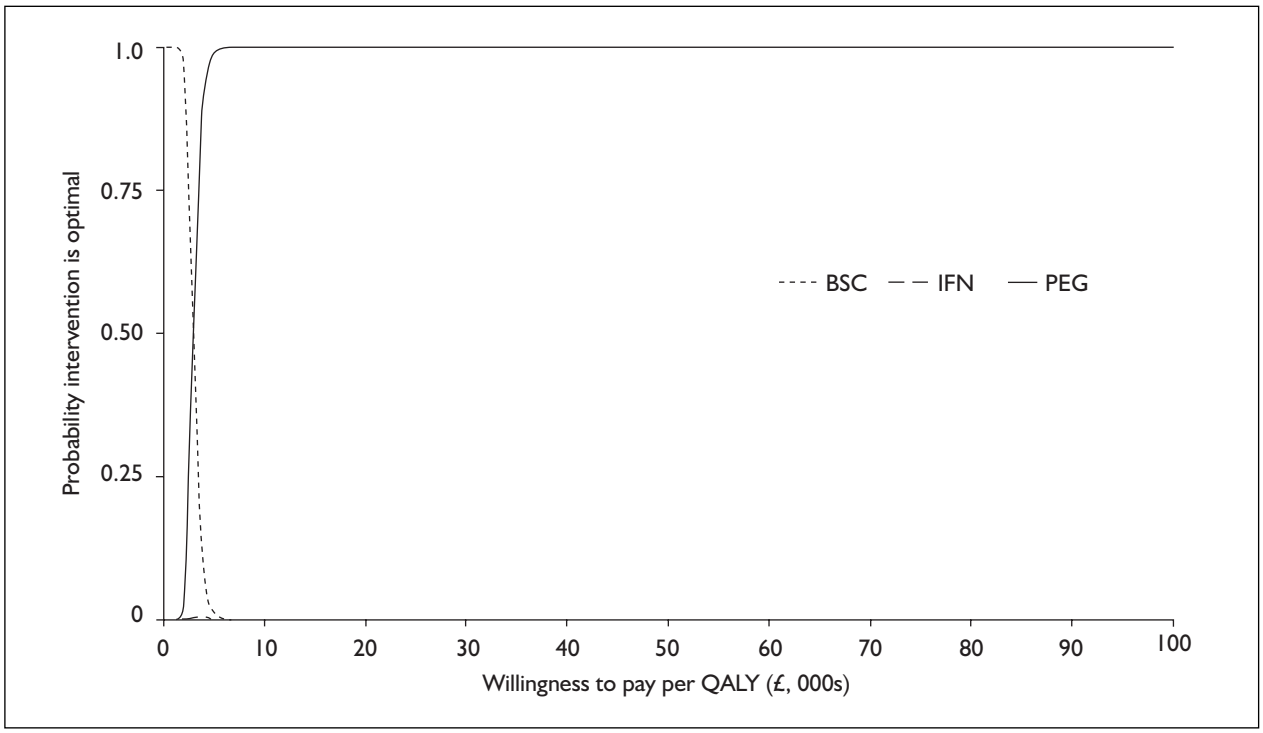

FIGURE 8 *CEACs for best supportive care (BSC), IFN and PEG in patients with HBeAg-negative disease*

TABLE 47 *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 (£)
IFN	12,635	11,679	14,401	17.76	16.44	19.1	5,818
IFN followed by LAM	15,172	14,155	17,170	18.46	17.07	19.89	3,596
IFN followed by ADV	27,490	25,492	31,151	19.39	17.88	20.78	9,120
IFN followed by LAM with ADV salvage	27,826	25,504	32,110	19.55	17.99	20.91	11,677
PEG	15,771	14,838	17,581	18.27	16.9	19.81	6,124
PEG followed by LAM	18,068	17,032	20,150	18.89	17.41	20.37	6,764
PEG followed by ADV	28,954	26,365	33,207	19.7	18.14	21.19	4,623
PEG followed by LAM with ADV salvage	29,059	26,335	33,997	19.83	18.26	21.28	4,424

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

For a summary of the results of our cost-effectiveness analysis, refer to the Executive summary.

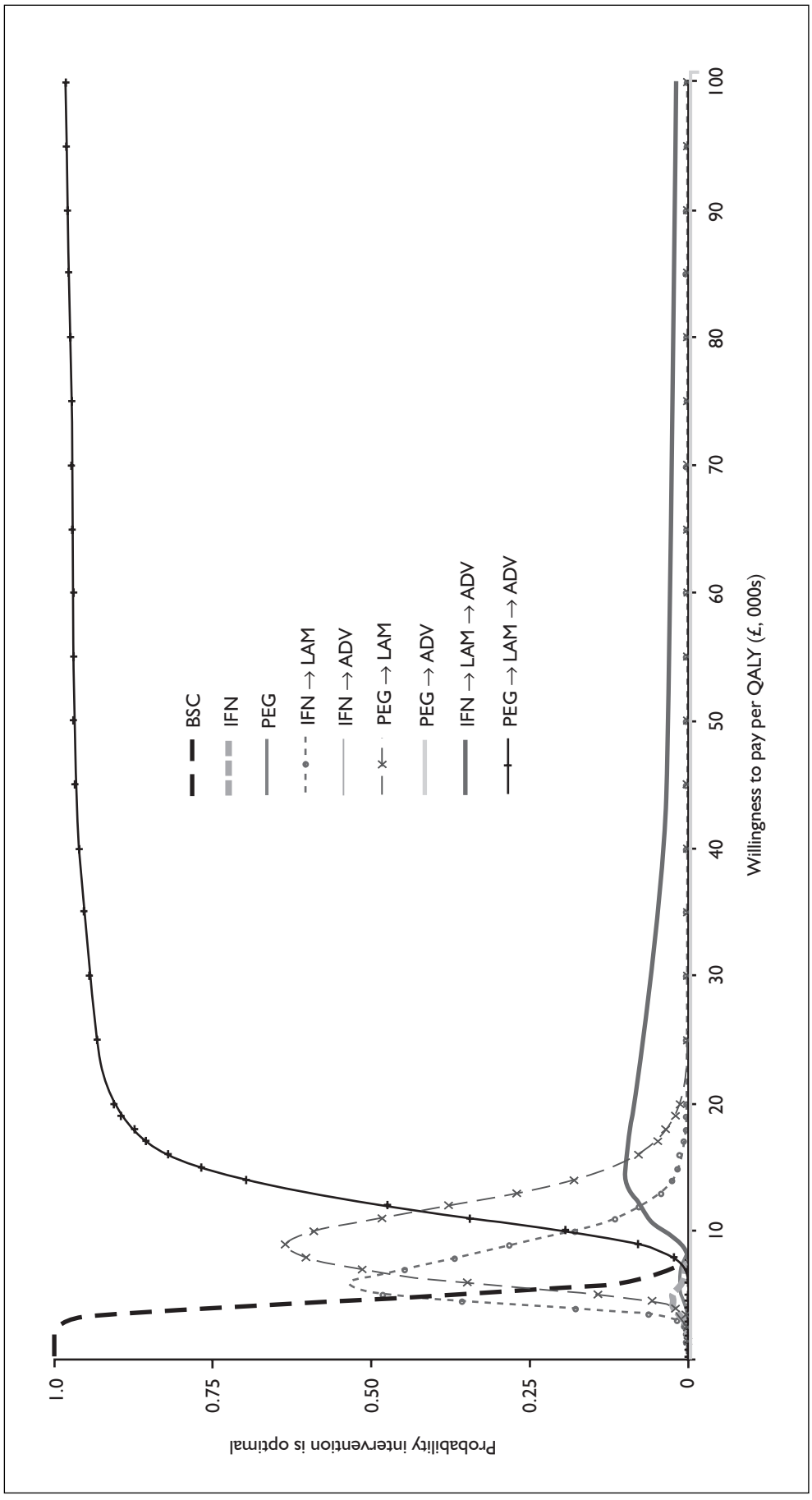

FIGURE 9 *CEACs for sequential treatment strategies*

Chapter 7

Implications for other parties

The availability of safe and effective treatment has positive benefits for people with CHB and their families. The introduction of PEG and ADV increases the treatment options available and gives patients greater choice. The fact that PEG requires only one injection per week instead of three for IFN is more convenient and reduces disruption to the lives of patients and their partners and families.

There are implications for the sexual partners of patients undergoing treatment and for IDUs 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 antiviral 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 ADV 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 antiviral treatment on sexual partners.

The issuing of NICE guidance and the likely increased availability of antiviral therapy for hepatitis B may also help to reduce the stigma associated with infectious diseases such as hepatitis. Hopwood and Southgate[131] reviewed the international sociological literature on hepatitis C and reported that people living with hepatitis are often subjected to social stigma and discrimination, particularly if acquired through injecting drug use or sexual contact. It was 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 homogeneous 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 to work in only 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.

Chapter 8

Factors relevant to the 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 PEG and ADV are in current use, to varying extents. Existing NICE guidance on the use of PEG 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 PEG 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 antiviral 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 (MCHNs). 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 allow the planning and adoption of best clinical practice and to permit comparison of patient outcomes across the country. It is envisaged that there will be 10–15 MCHNs in the UK, each responsible for between one and five 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 antiviral 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 have 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[39] 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 antiviral 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 antiviral treatment in mild disease (NICE is 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 necroinflammation 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 PEG and ADV 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.

Chapter 9
Discussion

Clinical effectiveness

The evidence base for the clinical effectiveness of PEG-2a comprises three RCTs (including one yet to be fully published). For ADV there are four fully published RCTs (of which three are subject to 5-year extension) and one ongoing 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 LAM) 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 1 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 subgroups and long-term outcomes.

The results of the RCTs show that treatment with both PEG-2a and ADV is associated with improvements on a number of outcome measures. Rates of HBeAg seroconversion reached 14% for ADV and 37% for PEG. 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 ADV 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 PEG. 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 antiviral therapy can be compared with the average spontaneous seroconversion rate of 1–2% in untreated Western patients.[3]

Biochemical responses were observed in the form of reductions in ALT, 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 ADV and 60% for PEG.

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 ADV-treated patients and in up to 92% in patients treated with PEG.

Favourable changes were also observed in liver histology (i.e. necroinflammation and fibrosis) with around two-thirds of patients achieving a histological 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 PEG-treated patients in one study attained both a virological and a biochemical response.

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

favours adding ADV to ongoing LAM, rather than withdrawing LAM altogether. This is on the grounds of a reduced potential for resistance.

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

The evidence also demonstrates the superiority of PEG over IFN, a similar scenario to that observed in the treatment of hepatitis C.[29,120] 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, PEG may replace IFN. 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 PEG, results from the two RCTs to evaluate this modality suggest that both PEG monotherapy and PEG in combination with LAM are generally superior to LAM monotherapy in both HBeAg-positive and -negative patients. There appeared to be little difference in effectiveness between the PEG mono and combination therapies, suggesting little additional benefit for using combination therapy.

Results of trials evaluating IFN and LAM, reviewed by Van Nunen and colleagues, are mixed.[132] One of the included studies (Schalm and colleagues[91]) reported similar HBeAg seroconversion rates after 16 weeks of treatment with interferon alfa and LAM (22 and 19%, respectively). The rate for combination therapy was significantly higher (36%, based on the per-protocol analysis). In contrast, another trial[127] reported similar seroconversion rates for combination therapy and placebo (12 and 13%, respectively), with the highest rates in the LAM 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 LAM 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 IFN than in PEG 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 ADV 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 ADV 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 of particular importance for ADV, 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 ADV than LAM (7 versus 56% after 3 years of 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 the section 'Research needs' (p. 111)].

In contrast to the ADV trials, studies of PEG 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 1 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 PEG 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 of follow-up are not currently available; however, an individual patient data meta-analysis of relapse rates (defined as reappearance of HBeAg in serum) following treatment with IFN, LAM and a combination of the two has been published.[94] Three-year cumulative Kaplan–Meier relapse rates were 32, 54 and 23%, respectively. High pretreatment HBV DNA, low ALT and male sex were independent predictive factors of post-

treatment relapse. It could be assumed that relapse rates for PEG would be similar, if not lower. Longer term data are therefore needed.

Cost-effectiveness

Our systematic review of cost-effectiveness studies of antiviral treatments for CHB 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 ADV. No published economic evaluations were found for PEG. 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,[39] the ICER for PEG compared with IFN for HBeAg-positive patients was estimated as between £2663 and £13,921 per QALY, depending on the duration of treatment and dosage of IFN. No comparison of PEG with IFN for HBeAg-negative patients was reported. However, compared with best supportive care, the ICER was £1467 and compared with 4 years of treatment with LAM the ICER was £1886.

The ICER of ADV ranged from £6651 to £29,359 depending on whether ADV 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 LAM followed by second-line ADV provided in patients with LAM resistance against best supportive care. The ICER comparing this strategy against lamivudine alone was £9201.

Our analysis estimated a cost per QALY of £5994 for interferon alfa compared with a best supportive care for a cohort of CHB patients (including both patients with HBeAg-positive and those with HBeAg-negative disease). For PEG compared with interferon alfa the ICER was £6119. For LAM therapy the ICER, when compared with best supportive care, was £3685 and for ADV compared with LAM the ICER was £16,569. These average ratios across HBeAg-positive and -negative patients hide some important differences. Generally, the ICER for interferon (pegylated or non-pegylated) was higher for HBeAg-positive than for HBeAg-negative patients, whereas the reverse was the case for LAM and ADV. In each of the comparisons the lifetime costs associated with IFN and LAM treatment were similar, although they differ in estimated effectiveness and hence cost-effectiveness. In all the comparisons ADV 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 antiviral treatment was provided, interferon alfa (non-pegylated or pegylated) was the first-line treatment with either LAM or ADV provided as second line. ICERs varied from £3604 to £11,402.

Strategies including PEG were more effective than strategies using IFN, but were also more costly, with ICERs of £4500–6800 per QALY. Strategies including ADV 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 -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 with 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 ADV 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.

Assumptions, limitations and uncertainties

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

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, whereas interferon alfa (including PEG) is currently a first-line treatment in some areas, in others LAM is the first choice (despite EASL guidelines recommending first-line interferon alfa). Expert opinion also suggests that ADV would be used more, possibly as first-line treatment, if it were less expensive. Although 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 ADV following resistance to LAM.

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 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 EASL and the American Association for the Study of the Liver. These are likely to be fully published in due course. (Note: 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 ADV 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.

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 antiviral interventions in CHB. 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 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 international, multicentre 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 4 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 CHB 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 CHC 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 HCC 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 QoL than CHC, 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 CHC, were used. The validity of applying these values to patients with CHB may be questioned. The utility value adopted for compensated cirrhosis was similar to that adopted for other recent economic evaluations of antiviral treatment for CHB. However, the values used for decompensated cirrhosis and HCC were higher than those used in most previous evaluations.

Research needs

PEG and ADV 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 subgroups, 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 is 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 antiviral treatment on HRQoL requires evaluation. We did not identify any fully published studies of HRQoL of patients taking ADV and only limited, unpublished data on patients taking PEG.
- There is a lack of published evidence on the effectiveness of PEG in LAM non-responders and in IFN non-responders. The manufacturer reports that relevant studies are under way.
- More evidence of the effectiveness of ADV in combination with LAM in patients not previously treated (as opposed to patients resistant to LAM) is required. A Phase II RCT is in progress and fully published results are awaited.
- We did not identify any direct comparisons between ADV and PEG. 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 PEG-2b (PegIntron, Viraferon Peg, Schering-Plough) as a treatment for CHB[133] (currently not licensed in the UK for hepatitis B). A recently published RCT[133] reported its benefit, with HBV genotype an important predictor of treatment response. An open-label RCT reported the effects of staggered combination

treatment with PEG-2b and LAM in HBeAg-positive patients.[40,134] The results indicate that treatment with PEG-2b and LAM dual therapy may lead to a higher rate of virological response than LAM monotherapy.

- 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 LAM-resistant HBV infection in HIV-co-infected patients.[135,136] Entecavir has been shown to be well tolerated and has a similar safety profile to LAM. Ongoing studies of efficacy are in progress. Neither of these drugs is 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.

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

- LAM and hepatitis B immune globulin for preventing hepatitis B recurrence after liver transplantation
- ADV for CHB
- Acupuncture for CHB virus infection.

Chapter 10
Conclusions

The conclusion of this systematic review and economic evaluation is that ADV and PEG are both 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 HCC. 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 ADV or PEG. 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 £5994 and £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 LAM would be the optimal strategy at lower threshold values of willingness to pay. As the threshold increases, the sequential treatment strategy of PEG, followed by LAM with ADV 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.

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 presenting with more advanced disease (e.g. cirrhosis, decompensation and pre- and post-liver transplant) and also subgroups of patients, particularly those with co-infections and co-morbidities.

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Expert Advisory Group

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Contribution of authors

Jonathan Shepherd (Principal Research Fellow) prepared the protocol and assisted with the inclusion criteria and data extraction and drafted the report. Jeremy Jones (Senior Research Fellow) prepared the protocol and assisted with the inclusion criteria and data extraction and drafted the report. Andrea Takeda (Research Fellow) prepared the protocol and assisted with the inclusion criteria and data extraction and drafted the report. Peter Davidson (Visiting Fellow) assisted with the inclusion criteria and drafted the report. Alison Price (Information Scientist) carried out the literature search.

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136. Van Bommel F, Wunsche T, Mauss S, Reinke P, Bergk A, Schurmann D, *et al.* Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. *Hepatology* 2004;**40**:1421–5.

Appendix 1

Clinical effectiveness search strategy

Search strategy for clinical effectiveness – ADV and PEG-2a for the treatment of chronic hepatitis B

Database: Ovid MEDLINE

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 2

Cost-effectiveness and quality of life search strategies

Cost effectiveness

Database: Ovid MEDLINE

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

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 3

Epidemiology search strategy

Epidemiology

Database: Ovid MEDLINE

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 4

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**	**EXCLUDE (Discuss)**	**Results of Discussion:**

Appendix 5

Data extraction – Cooksley *et al.*, 2003[37]

Extracted by: JS. Date: 22 January 2005.

Reference and design	Intervention	Participants	Outcome measures
Cooksley *et al.* 2003[37] Multi-centre trial ($n = 18$) Phase II RCT Open label Australia; New Zealand; Taiwan; Thailand; China Funding: not stated	*Group A:* $n = 51$ IFN-2a 4.5 MIU 3 × week 24 weeks *Group B:* $n = 49$ PEG-2a 90 μg: once weekly 24 weeks *Group C:* $n = 46$ PEG-2a 180 μg: once weekly 24 weeks *Group D:* $n = 48$ PEG-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 the ULN • Biopsy demonstrating CHB liver disease *Exclusion criteria:* • not previously treated with interferon alfa • nucleoside or nucleotide analogue (e.g. LAM, lobucavir and ADV) 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 times the ULN • serum α-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 antineoplastic 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 and range): mean age across groups 29–32 (range 18–69) Ethnic groups: 97% Asian	• loss of HBeAg • suppression of HBV DNA levels to <500,000 • copies/ml • normalisation 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

continued

Reference and design	Intervention	Participants	Outcome measures
		Compliance: 95% of patients completed 24 weeks of treatment *Baseline measurements:* Log 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) Log 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 antiviral 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 to 40]	21 (43) [29 to 58]	18 (39) [25 to 55]	13 (27) [15 to 42]	52 (36)	0.096	0.085
HBeAg loss:							
n (%) [95% CI (%)]	13 (25) [14 to 40]	18 (37) [23 to 52]	16 (35) [21 to 50]	14 (29) [17 to 44]	48 (34)	0.295	0.127
Seroconversion:							
n (%) [95% CI (%)]	13 (25) [14 to 40]	18 (37) [23 to 52]	15 (33) [20 to 48]	13 (27) [15 to 42]	46 (32)	0.428	0.185
ALT normalisation:							
n (%) [95% CI (%)]	13 (25) [14 to 40]	21 (43) [29 to 58]	16 (35) [21 to 50]	15 (31) [19 to 46]	52 (36)	0.290	0.153
Combined response:							
n (%) [95% CI (%)]	6 (12) [5 to 24]	13 (27) [15 to 41]	13 (28) [16 to 44]	9 (19) [9 to 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

continued

Adverse events	Group A (n = 50)	Group B (n = 48)	Group C (n = 45)	Group D (n = 48)
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 proportions of patients who prematurely discontinued study medication for safety reasons were 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%). Neutropenia 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 270-μg PEG groups).
- 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 copies/ml during weeks 1–4, compared with 0.76 log copies/ml in the IFN group.
- The greatest drop in mean log HBV DNA from baseline to end of treatment was 3.5 log copies/ml with PEG 180 μg compared with 2.2 log 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/week and 3.14 for PEG 270 μg/week.
- 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 copies/ml, 56 and 38% respectively. In the group with baseline HBV DNA of 8.50–10.99 log copies/ml, 36 and 24% respectively; and in the group of patients with HBV DNA titres >11.0 log 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- and 180-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 p. 300 provides these data, although no significance values are provided.
- *Method of data analysis:* An ITT analysis was undertaken on the 194 individuals randomised. For the safety analysis the number analysed was 191 [three patients (one each randomised to IFN and 90- and 180-μg doses of PEG) did not receive study drug because of pregnancy, jaundice and treatment with LAM within 6 months of study entry, respectively]. Response rates and corresponding 95% CIs 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."

continued

- *Attrition/drop-out:* 95% of patients completed the 24 weeks of treatment and 97% of all patients completed the 24 weeks of follow-up. 22 patients on PEG and 9 patients on IFN with screening ALT >2 × ULN but whose baseline ALT levels had fallen below 2 × 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?	NA
6. Was the care provider blinded?	NA
7. Was the patient blinded?	NA
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were losses to follow-up completely described?	Partial

NA, not applicable, since the trial was reported to be open label.

Appendix 6

Data extraction – Hadziyannis *et al.*, 2003[31] (Study 438)

Extracted by: AT. Date: 10 November 2004. Checked by JS. Updated 7 January 2005. Extra information on long-term results extracted by AT, 1 July 2005.

Reference and design	Intervention	Participants	Outcome measures
Hadziyannis *et al.*, 2003[31] Trial design: multicentre RCT Number of centres: 32 Country: Greece (also Canada, Israel, France, Italy, Austria, Taiwan and Singapore) Funding: Gilead Sciences	*Group A:* *n* = 123 Drug 1: ADV Dose: 10 mg/day Duration: 48 weeks *Ongoing phase:* Drug 2: ADV or placebo (random reassignment) Group A1 *n* = 80 drug: ADV dose: 10 mg/day Duration: 48 weeks Group A2 *n* = 40 Drug: placebo Duration: 48 weeks 3 of the original group A did not receive treatment during the second 48 weeks *Group B:* *n* = 62 Drug 1: placebo Duration: 48 weeks *Ongoing phase:* Group B1 *n* = 60 Drug 2: ADV Dose: 10 mg/day Duration: 48 weeks	HBeAg status: negative Total randomised: 185 No. in each group (2:1 ratio): A, *n* = 123; B, *n* = 62[a] [a] One patient never received treatment and was excluded from all analyses *Inclusion criteria:* • aged 16–65 years with HBeAg-negative CHB 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/ml and an ALT level between 1.5 and 15 times the ULN) • patients had to have a total bilirubin level of no more than 2.5 mg/dl, a prothrombin time that was no more than 1 s above the ULN, a serum albumin level that was at least 3 g/dl, a serum creatinine level of no more than 1.5 mg/day and an adequate blood count *Exclusion criteria:* • a coexisting serious medical or psychiatric illness • immune globulin, interferon 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 α-fetoprotein level of at least 50 ng/ml • evidence of a hepatic mass • liver disease that was not due to hepatitis 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 (years): mean ± SD (range) / 46 ± 9.8 (18–65) / 45 ± 10.4 (22–65) Male: no. (%) / 102 (83) / 50 (82) Race: no. (%) White / 82 (67) / 40 (66) Black / 5 (4) / 1 (2) Asian / 36 (29) / 20 (33)	Primary outcomes: histological 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 Long-term follow-up: primary end-points were changes from baseline in serum HBV DNA and ALT levels at week 96 Secondary end-points: % of patients with undetectable serum HBV DNA; % of patients with normalised ALT; % of patients with HBsAg seroconversion; adverse events

continued

Reference and design	Intervention	Participants			Outcome measures
	People receiving ADV for weeks 49–96 were subsequently offered continued therapy until week 240	Weight (kg): mean± SD (range)	75 ± 11.5 (50–111)	73 ± 15.4 (46–135)	Length of follow-up: weeks 96 and 144
		ALT:			
		Mean ± SD (U/l)	143.5 ± 125.3	149.9 ± 195.2	
		Median (U/l)	93	100	
		Range (U/l)	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	
		Median	2.3	2.4	
		Range	0.7–17.3	0.7–33.9	
		HBV DNA (logcopies/ml)[a]:			
		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. (%)[b]			
		Interferon	48 (39)	28 (46)	
		Lamivudine	10 (8)	4 (7)	
		Famciclovir	7 (6)	7 (11)	
		[a] Values were log-transformed with use of a base 10 scale. [b] Some patients had received more than one type of medication. Losses to follow-up: 1 placebo patient 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 Full baseline data are provided for groups A1, A2 and B1. No significant differences between the 3 groups are reported. (full table can be extracted if necessary)		

continued

Outcome	Group A (ADV) (n = 117)	Group B (placebo) (n = 55)	Difference
HBV DNA mean change from baseline at week 48 (log copies/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 Figure 2 show changes through time at 4-weekly intervals, but not data extracted at this stage as treatment end-points already taken from tables.			

Long-term response	Continued ADV group		ADV–placebo group	Placebo–ADV group
Long-term virological response	Week 96 (n = 79)	Week 144 (n = 70)	Week 96 (n = 40)	Week 96 (n = 60)
No. of patients assessed	70	67	38	49
Change in serum HBV/DNA (log copies/ml) Mean ± SD Median	–3.35 ± 1.18 –3.47	–3.42 ± 1.27 –3.63	–1.34 ± 1.24 –1.09	–3.71 ± 1.05 –3.85
Interquartile range	–4.20 to –2.59	–4.23 to –3.11	–2.19 to –0.40	–4.31 to –3.18
p-Value compared with continued treatment at week 96	–	NA	<0.001	0.12
Serum HBV DNA <1000 copies/ml: n/total (%)	50/70 (71)	53/67 (79)	3/38 (8)	37/49 (76)
p-Value compared with continued treatment at week 96	–	NA	<0.001	0.68
ALT at 48 weeks n (%) with normalised ALT levels	n = 116 84 (72)		n = 59 17 (29)	$p < 0.001$
Median decrease from baseline (U/l)	55		38	$p = 0.01$
Long-term biochemical response	Week 96 (n = 79)	Week 144 (n = 70)	Week 96 (n = 40)	week 96 (n = 60)
No. of patients assessed	71	67	38	50
Change in serum ALT (IU/l) Mean ± SD Median	–98 ± 118.4 –59	–97 ± 120.13 –54	–63 ± 131.0 –29.5	–130 ± 213.2 –79.5
Interquartile range	–115 to –27	–121 to –28	–68 to 18	–134 to –46
p-Value compared with continued treatment at week 96	–	NA	0.01	0.21
Normalisation of ALT n/total (%)[a]	47/64 (73)	43/62 (69)	12/38 (32)	40/50 (80)
p-Value compared with continued treatment at week 96	–	NA	<0.001	0.51
Comments: [a] Patients with baseline ALT levels that exceeded the upper limit of the normal range were included in the analysis				
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)

continued

Long-term response	Continued ADV group	ADV–placebo group	Placebo–ADV group
Change in total Knodell score:	(*n* = 112)	(*n* = 55)	$p < 0.001$
Mean ± SD	–3.7 ± 3.1	0.4 ± 3.7	
Median	–4	1	
Range	–11 to 2	–9 to 8	
Change in Knodell necroinflammatory score:	(*n* = 112)	(*n* = 55)	$p < 0.001$
Mean ± SD	–3.4 ± 2.9	0.3 ± 3.2	
Median	–3	0	
Range	–9 to 2	–7 to 8	
Change in Knodell fibrosis score at week 48:	(*n* = 112)	(*n* = 55)	$p = 0.005$
Mean ± SD	–0.3 ± 0.7	0.1 ± 0.9	
Median	0	0	
Range	–3 to 1	–2 to 2	
Ranked assessment (%):			
Necroinflammatory activity			
Worse	3	51	Not reported
No change	17	7	
Improved	80	42	
Fibrosis			
Worse	4	38	
No change	47	36	
Improved	48	25	

Comments: Primary analysis based on 178 patients (97%) with assessable baseline liver-biopsy specimens. 167 (91%) had assessable pre- and post-treatment liver-biopsy specimens. *p*-Values were calculated with the Wilcoxon rank-sum test.

Changes from baseline in Knodell scores at weeks 48 and 96	**Continued ADV group (*n* = 819)**		**ADV–placebo group (*n* = 8)**		**Placebo–ADV group (*n* = 20)**	
	Week 48	**Week 96**	**Week 48**	**Week 96**	**Week 48**	**Week 96**
Overall:						
Baseline	10.02 ± 2.07		12.3 ± 2.25		8.3 ± 3.31	
Change	–4.4 ± 2.39	–4.7 ± 2.7	–4.3 ± 1.49	–1.4 ± 1.92	0.9± 4.56	–2.4 ± 4.79
Inflammation:						
Baseline	8.37 ± 1.50		10.0 ± 1.31		6.40 ± 2.76	
Change	–4.2 ± 2.32	–4.3 ±2.71	–3.8 ± 1.83	–0.9 ±1.96	0.6 ±3.78	–2.3 ± 3.93
Fibrosis:						
Baseline	1.84 ± 1.17		2.3 ± 1.39		1.9 ± 1.17	
Change	–0.2 ± 0.63	–0.4 ± 1.12	–0.5 ± 0.93	–0.5 ± 0.93	0.3 ± 1.17	–0.15± 1.27

Adverse events (AE)	***n* = 123**	***n* = 61**
Dose discontinuation for any AE	0	0
Dose reduction for any AE	0	0
Severe (grade 3 or 4) AE *n* (%)	7 (6)	6 (10)
Serious AE	4[a] (3)	4[b] (7)
AE *n* (%):		
Any AE	94 (76)	45 (74)
Headache	29 (24)	10 (16)
Pharyngitis	23 (19)	14 (23)
Abdominal pain	18 (15)	3 (5)
Asthemia	16 (13)	10 (16)
Influenza-like syndrome	13 (11)	13 (21)
Back pain	12 (10)	4 (7)
Pain	10 (8)	6 (10)

continued

Adverse events (AE)	***n* = 123**	***n* = 61**
Increased cough	10 (8)	4 (7)
Insomnia	6 (5)	4 (7)
Dyspepsia	6 (5)	2 (3)
Rhinitis	6 (5)	1 (2)

Comments:
[a] Hip abscess, transient ischaemic attack, acute hepatitis, sialadenitis.
[b] Perianal abscess, pain after liver biopsy, dengue fever, renal colic.
None of the serious AEs were considered to be related to treatment.

Adverse events occurring in at least 10% of patients – long-term	**Week 49 to week 96**			**Continued ADV group**	
	Continued ADV group (*n* = 79) [*n* (%)]	**ADV–Placebo group (*n* = 40) [*n* (%)]**	**Placebo–ADV group (*n* = 60) [*n* (%)]**	**Baseline to week 48 (*n* = 79) [*n* (%)]**	**Baseline to week 96 (*n* = 70) [*n* (%)]**
Any event	58 (73)	32 (80)	41 (68)	67 (85)	60 (86)
General:					
Headache	12 (15)	4 (10)	5 (8)	23 (29)	19 (27)
Abdominal pain	16 (20)	7 (18)	5 (8)	22 (28)	20 (29)
Asthenia	8 (10)	6 (15)	3 (5)	15 (19)	15 (21)
Flu-like syndrome	6 (8)	4 (10)	5 (8)	14 (18)	14 (20)
Back-pain	4 (5)	5 (12)	3 (5)	9 (11)	9 (13)
Pain	4 (5)	2 (5)	4 (7)	11 (14)	12 (17)
Accidental injury	4 (5)	2 (5)	2 (3)	6 (8)	8 (11)
Digestive:					
Diarrhoea	6 (8)	4 (10)	1 (2)	8 (10)	6 (9)
Dyspepsia	4 (5)	5 (12)[a]	1 (2)	7 (9)	7 (10)
Respiratory:					
Pharyngitis	14 (18)	8 (20)	8 (13)	23 (29)	25 (36)
Increased cough	3 (4)	4 (10)	2 (3)	6 (8)	7 (10)
Bronchitis	2 (3)	1 (2)	1 (2)	6 (8)	9 (13)
Metabolic and nutritional:					
Increased ALT levels	2 (3)[b]	6 (15)[a]	1 (2)	3 (4)	3 (4)
Musculoskeletal:					
Arthralgia	6 (8)	5 (13)[a]	1 (2)	7 (9)	6 (9)

Comments:
[a] $p < 0.05$ compared with the placebo–ADV group.
[b] $p < 0.05$ compared with the ADV–placebo group.
The study drug was discontinued because of adverse events in 2 patients in the continued-ADV group (a protocol-defined increase in serum creatinine levels of ≥ 0.5 mg/dl and HCC) and in 3 patients in the ADV–placebo group (jaundice, elevated ALT and a skin disorder).
The safety profile over 144 weeks remained consistent with that seen earlier in the study.

Additional outcomes
Resistance: The polymerase–reverse-transcriptase domain of the HBV polymerase gene was sequenced from serum samples obtained at baseline 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.
Long-term serological response: HBsAg seroconversion occurred in one patient in the continued ADV group at week 72, and one in the placebo–ADV group at week 68 (approximately 20 weeks after the start of treatment with ADV).

continued

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. Laboratory 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. For the long-term follow-up paper, baseline demographic characteristics and those related to hepatitis B infection were not statistically different among the 3 groups.
- *Method of data analysis* (ITT, point estimates given? CIs given?): "Statistical analyses included all patients who received at least one dose of study drug." The analysis of histological end-points included a subgroup of this population that had an assessable baseline 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 CIs, significance tests and resulting *p*-values were 2-sided, with an α level of 0.05. SDs are given for all mean values.
- For the long-term follow up paper, statistical analyses included all patients who received at least one dose of the study drug in the second 2 weeks. All tests for significance and resulting *p*-values were 2-sided with a 0.05 level of significance.
- *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 baseline Knodell scores of <2 and would therefore be counted as having no response and that 8% would have missing biopsy specimens at baseline and would thus be excluded from the primary efficacy analysis.
- *Attrition/drop-out:* 1 placebo patient 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. For the long-term follow-up paper, one person in group A1 (i.e. continuation of ADV) withdrew from the study before taking medication in the second 48 weeks.

General comments

- Generalisability: Male and female patients 16–65 years of age who had HBeAg-negative CHB 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 subgroups e.g. genotype, ethnicity, gender.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown[a]
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[b]
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate[c]
10. Were losses to follow-up completely described?	Partial

[a] Paper does not report actual method of randomisation.
[b] Just 'double blind' in text and no further description of procedures or nature of the placebo.
[c] As not all outcomes were reported for all patients.

Appendix 7

Data extraction – Marcellin *et al.*, 2003[32] (Study 437)

Extracted by: ST. Checked by: AT. Date: 24 January 2005.

Reference and design	Intervention	Participants	Outcome measures
Marcellin *et al.*, 2003[32] Trial design: Double-blind RCT Number of centres: 78 Country: North America, Europe, Australia, South East Asia Funding: Supported by Gilead Sciences	*Group A:* *n* = 172 ADV Dose: 10 mg/day Duration: 48 weeks *Group B:* *n* = 173 ADV Dose: 30 mg/day Duration: 48 weeks *Group C:* *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 (10 mg ADV) Randomised: *n* = 172; 1 took no study medication leaving *n* = 171 Baseline biopsy available for: *n* = 168 Group B (30 mg 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 and female patients 16–65 years (note: baseline characteristics list age range as 16–68 years) • hepatitis Be antigen-positive CHB 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 or other immune or cytokine-based therapies with possible activity against HBV disease within 6 months before screening • organ or bone marrow transplantation • recent treatment with systemic corticosteroids, immunosuppressants or chemotherapeutic agents • serum α-fetoprotein level of $\geq$50 ng/ml • evidence of hepatic mass • liver disease not due to hepatitis B • prior therapy >12 weeks with nucleoside or nucleotide analogue with activity against HBV • seropositivity for HIV or hepatitis C or D virus	Primary outcomes used: Histological improvement, defined as: Reduction of $\geq$2 points in Knodell necroinflammatory sore with no concurrent worsening of Knodell fibrosis score 48 weeks 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 ALT level • Proportion of patients with loss or seroconversion of HbeAg Length of follow-up: 48 weeks

continued

Reference and design	Intervention	Participants	Outcome measures

Baseline measurements:

	Placebo (*n* = 167)	10 mg ADV (*n* = 171)	30 mg ADB (*n* = 173)
Age: (years)			
median (range)	35 (16–66)	32 (16–65)	32 (17–68)
Male: *n* (%)	119 (71)	130 (76)	129 (75)
Race: *n* (%)			
White	60 (36)	60 (35)	64 (37)
Black	3 (2)	8 (5)	5 (3)
Asian	101 (60)	102 (60)	101 (58)
Other	3 (2)	1 (1)	3 (2)
ALT:			
Mean ± SD U/l	139 ± 131	139 ± 154	124 ± 9.6
Median U/l	94	95	92
<ULN *n* (%)	3 (2)	3 (2)	4 (2)
>ULN *n* (%)	164 (98)	168 (98)	169 (98)
Multiples of ULN:			
Mean ± SD	3.4 ± 3.1	3.4 ± 4.0	3.0 ± 2.3
Median	2.4	2.3	2.3
HBV DNA log copies/ml[a]:			
Mean ± SD	8.12 ± 0.8	8.25 ± 0.9	8.22 ± 0.84
Median	8.33	8.40	8.34
Total Knodell score:			
Mean ± SD	9.65 ± 3.45	9.01 ± 3.33	9.55 ± 3.33
Median (range)	10 (1–17)	9.5 (0–17)	10 (0–16)
Knodell necroinflammatory activity:			
Mean ± SD	7.83 ± 2.89	7.37 ± 2.75	7.84 ± 2.82
Median (range)	8 (1–14)	7 (0–14)	8 (0–12)
Knodell fibrosis score:			
Mean ± SD	1.83 ± 1.12	1.64 ± 1.09	1.71 ± 1.06
Median (range)	1 (0–4)	1 (0–4)	1 (0–4)

[a] Values were log-transformed with use of a base 10 scale.

Compliance: not reported.

Treatment history: subjects were excluded if on interferon or other drugs with possible activity against HBV disease <6 months before screening, but study states 123 (24%) had received treatment with interferon alfa.

Patient characteristics: all with compensated liver disease.

continued

Outcome	**Placebo (*n* = 167)**	**10 mg ADV (*n* = 171)**	**30 mg ADV (*n* = 173)**
HBV DNA change from baseline (log copies/ml) results at 48 weeks:			
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 48 weeks			
n (%)	0	36 (21)	67 (39)
p-Value		<0.001	<0.001
HbeAg seroconversion, results at 48 weeks:			
n/total *n* (%)	9/161 (6)	20/171 (12)	23/165 (14)
p-Value		<0.049	<0.011
Comments: Seroconversion defined as loss of HbeAg and concurrent gain of antibody against HbeAg at 48 weeks.			
HbeAg loss, results at 48 weeks:			
n/total *n* (%)	17/161 (11)	41/171 (24)	44/165 (27)
p-Value		<0.001	<0.001
Comments: Patients positive for HbeAg at baseline were included in the analysis.			
Change in ALT IU/l (at 48 weeks):			
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
Normalisation of ALT, at 48 weeks:			
n/total *n* (%)	26/164 (16)	81/168 (48)	93/169 (55)
p-Value		<0.001	<0.001
Comments: Patients with baseline ALT levels that exceeded the ULN were included in the analysis.			
Other viral response outcomes[a]	**Placebo**	**10 mg ADB**	**30 mg ADV**
Number of patients[b]	***n*** = 161	***n*** = 168	***n*** = 165
Histological 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 (no. of patients)[c]	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[d]		<0.001	<0.001
Ranked assessment (no. of patients)[c]	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[d]		<0.001	<0.001
Fibrosis:			
Knodell score (no. of patients)[c]	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[d]		0.061	0.001

continued

Other viral response outcomes[a]	Placebo	10 mg ADB	30 mg ADV
Ranked assessment (no. of patients)[c]	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[d]		<0.001	<0.001

Comments: Relative risks and *p*-values for comparison with placebo group.

Histological 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 did not satisfy this definition were considered not to have histological improvements. Patients with missing or unassessable data at week 48 considered not to have histological improvement in comparison between each ADV group and placebo.

[a] All figures are at 48 weeks.
[b] Number of patients with assessable liver-biopsy specimens at baseline.
[c] Number of patients with assessable liver-biopsy specimens at baseline and week 48.
[d] *p*-Values for comparisons of 10-mg or 30-mg group with placebo.

Adverse events	Placebo *n* = 167	10 mg ADV *n* = 171	30 mg ADV *n* = 173
Discontinued study prematurely (%)	8	7	8
Incidence of severe (grade 3 or 4) clinical adverse event: (%)	8	10	9
Dose discontinuation for any adverse event[a] (%)	<1	2	3
Adverse events experienced by at least 10% of ADV 30-mg 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 ALT aspartate aminotransferase levels; weight loss; rash	Nausea, abdominal pain, headache, fanconi-like syndrome, amblyopia, myocardial infarction
Serum creatinine level at week 48	No significant change	No significant change	Median increase 0.2 mg/decilitre (18 μmol/l) 8% of patients had an increase of 0.5 mg/decilitre (44 μmol per litre) or greater ($p < 0.001$). The maximal reported serum creatinine level was 1.8 mg per decilitre (159 μmol per litre) in a patient in the 30 mg group.

continued

Comments: Adverse events included (10 mg ADV) increased ALT or aspartate aminotransferase levels; weight loss, rash (30 mg ADV) nausea, abdominal pain, headache, fanconi-like syndrome, amblyopia, myocardial infarction and (placebo) nausea. Adverse events reported by at least 10% of 30 mg ADV group.

In all cases renal function normalised with dose reduction or interruption of treatment.

Resistance profile ($n = 381$): no mutations occurred at higher than background frequencies (<1.6%).
Seven 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 p. 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 10 mg ADV/day; patients in 10-mg group randomly assigned to receive either continued treatment with 10 mg/day or placebo. All patients in 30-mg 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 information 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 information 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 baseline liver-biopsy specimens were prospectively excluded from primary efficacy analysis; Patients with missing or unassessable data at 48 weeks were considered not to have had responses. (so not ITT, then). 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 10 mg ADV and placebo (further information given); study had 79% power to detect absolute difference of 10% (16 vs 6%) in rate of seroconversion between 10-mg ADV group and placebo, assuming that 10% of patients would have missing values (which were counted as treatment failures).
- *Attrition/drop-out* (percentages given?): Patients with missing or unassessable baseline liver-biopsy specimens were prospectively excluded from primary efficacy analysis; patients with missing or unassessable data at 48 weeks were considered not to have had responses.

General comments

- Generalisability (inclusion/exclusion criteria defined?): Patients were male and female, aged 16–65 years, with chronic hepatitis 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 ITT analysis?	Inadequate
10. Were losses to follow-up completely described?	Partial

Appendix 8

Data extraction – Marcellin *et al.*, 2004[36] (Study 241)

Extracted by: AT. Date: 11 November 2004. Checked by: JS. Updated: 7 January 2005.

Reference and design	Intervention	Participants	Outcome measures
Marcellin *et al.*, 2004[36] Trial design: multicentre RCT, partially double-blind. Number of centres: 54 Country: 13 countries, mainly in Asia and Europe Funding: Roche	*Group A:* *n* = 177 PEG-2a Dose: 180 μg once weekly Duration: 48 weeks Placebo Dose: NA Duration: 48 weeks *Group B:* *n* = 179 PEG-2a Dose:180 μg once weekly Duration: 48 weeks LAM Dose: 100 mg daily Duration: 48 weeks *Group C:* *n* = 181 LAM Dose: 100 mg 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 patients from a single centre were excluded owing to irregularities in study conduct *Inclusion criteria:* • adult patients negative for HBeAg and positive for anti-HBe antibody and hepatitis B surface antigen (HBsAg) for at least 6 months, with an HBV DNA level of >100,000 copies/ml, a serum ALT level >1 but ≤10 times the ULN • findings on a liver biopsy within the previous 24 months consistent with the presence of CHB, with evidence of prominent necroinflammatory activity *Exclusion criteria:* • decompensated liver disease • a coexisting serious medical or psychiatric illness • a neutrophil count of <1500/mm^3, a platelet count of <90,000/mm^3, a serum creatinine level >1.5 times the ULN • a history of alcohol or drug abuse within 1 year before entry • treatment for CHB within the previous 6 months • co-infection 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: (years) 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/l)[a]: 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	Primary outcomes used: normalisation of ALT levels; suppression of HBV DNA to below 20,000 copies/ml. ALT measured at local laboratories following standard procedures, HBV DNA measured at one of 3 central laboratories. Secondary outcomes used: proportion of patients with HBsAg loss; HBsAg seroconversion (defined by loss of HBsAg and presence of anti-HBs antibody); histological response (reduction of at least 2 points in the modified histological activity index); suppression of HBV DNA to below 400 copies/ml; ranked assessments of necroinflammatory activity and fibrosis Also safety analysis and resistance analysis Length of follow-up: 48 weeks of treatment plus 24 weeks of follow-up.

continued

Reference and design	Intervention	Participants	Outcome measures

	A (n = 177)	B (n = 179)	C (n = 181)
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
Bridging fibrosis or cirrhosis *n* (%)	54 (31)	40 (22)	53 (29)
Prior use of LAM *n* (%)	7 (4)	15 (8)	9 (5)
Prior use of interferon alfa *n* (%)	11 (6)	18 (10)	14 (8)

[a] The ULN is 30 IU/l.

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 <20,000 copies/ml[a]:			
End of treatment (week 48):			
No. of patients (%)	144 (81)	164 (92)	154 (85)
95% CI (%)	74.8 to 86.8	86.6 to 95.2	79.0 to 89.9
End of follow-up (week 72):			
No. of patients (%)	76 (43)	79 (44)	53 (29)
95% CI (%)	35.5 to 50.6	36.7 to 51.7	22.8 to 36.5
p-Value compared with Group C[b]	0.007	0.003	
Odds ratio (95% CI)	1.8 (1.2 to 2.9)	1.9 (1.2 to 3.0)	
HBV DNA <400 copies/ml:			
End of treatment (week 48):			
No. of patients (%)	112 (63)	156 (87)	133 (73)
95% CI (%)	55.7 to 70.4	81.3 to 91.7	66.4 to 79.8
End of follow-up (week 72):			
No. of patients (%)	34 (19)	35 (20)	12 (7)
95% CI (%)	13.7 to 25.8	14.0 to 26.1	3.5 to 11.3
p-Value compared with Group C	<0.001	<0.001	
Change in HBV DNA:			
End of treatment (week 48):			
Total no. of patients	166	165	174
Mean log copies/ml	–4.1	–5.0	–4.2
95% CI (log copies/ml)	–3.8 to –4.5	–4.7 to –5.3	–3.9 to –4.5
End of follow-up (week 72):			
	* Total no. of patients	165	170 154
Mean log copies/ml	–2.3	–2.4	–1.6
95% CI (log copies/ml)	–1.9 to –2.7	–1.9 to –2.8	–1.2 to –2.0

Comments:
[a] $p = 0.005$ for overall treatment affect.
[b] Virological response Group A compared with Group B is $p = 0.849$.
Graphs in Figure 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.

continued

Outcome	Group A (*n* = 177)	Group B (*n* = 179)	Group C (*n* = 181)
ALT normalisation[a]:			
End of treatment (week 48):			
No. of patients (%)	67 (38)	87 (49)	132 (73)
95% CI (%)	30.7 to 45.4	41.1 to 56.2	65.8 to 79.3
End of follow-up (week 72):			
No. of patients (%)	105 (59)	107 (60)	80 (44)
95% CI (%)	51.7 to 66.6	52.2 to 67.0	36.8 to 51.8
p-Value compared with Group C[b]	0.004	0.003	
Odds ratio (95% CI)	1.9 (7.2 to 2.8)	1.9 (1.2 to 2.9)	
Comments:			
During therapy, marked elevations in ALT (>10 times the ULN, or more than 300 IU/l) were observed in a significantly higher % of Group A patients (12%) than Group B patients (4%) or Group C patients (6%) ($p = 0.007$ and $p = 0.038$, respectively). % of patients 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 normalisation of ALT levels at week 72 ($p = 0.01$).			
[a] $p = 0.003$ for the overall test of treatment effect.			
[b] Biochemical response Group A compared with Group B is $p = 0.0915$.			
Graphs in Figure 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 normalisation and HBV DNA <20000 copies/ml:			
End of treatment (week 48):			
No. of patients (%)	63 (36)	87 (49)	125 (69)
95% CI (%)	28.6 to 43.1	41.1 to 56.2	61.8 to 75.7
End of follow-up (week 72):			
No. of patients (%)	63 (36)	68 (38)	42 (23)
95% CI (%)	28.6 to 43.1	30.9 to 45.5	17.3 to 30.0
p-Value compared with Group C	0.011	0.0002	
ALT normalisation and HBV DNA <400 copies/ml:			
End of treatment (week 48):			
No. of patients (%)	47 (27)	82 (46)	109 (60)
95% CI (%)	20.2 to 33.7	38.4 to 53.4	52.7 to 67.4
End of follow-up (week 72):			
No. of patients (%)	26 (15)	29 (16)	11 (6)
95% CI (%)	9.8 to 20.8	11.1 to 22.4	3.1 to 10.6
p-Value	0.007	0.003	
Histological of response[a] at end of follow-up (week 72):			
Total no. of. patients[b]	177	179	181
Improved *n* (%)	85 (48)	68 (38)	72 (40)
95% CI (%)	40.5 to 55.6	30.9 to 45.5	32.6 to 47.3
No. of patients with paired biopsy samples[c]	143	143	125
No. of patients improved (%)	85 (59)	68 (48)	72 (58)
95% CI (%)	50.9 to 67.6	39.1 to 56.1	48.4 to 66.4
Ranked assessments of histological response[d]:			
Necroinflammatory activity:			
Total no. of patients	143	143	125
Improved *n* (%)	79 (55)	66 (46)	57 (46)
Worse *n* (%)	16 (11)	23 (16)	21 (17)
Fibrosis:			
Total no. of patients	143	143	125
Improved *n* (%)	21 (15)	18 (13)	22 (18)
Worse *n* (%)	11 (8)	15 (10)	6 (5)

continued

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.
[a] Histological response defined as a reduction from baseline of at least 2 points in the modified HAI. Scores for this index range from 0 to 24, with inflammation graded from 0 (none) to 6 (cirrhosis).
[b] Patients without paired biopsy samples were classified as having no response. $p = 0.144$ for the overall test of treatment effect.
[c] Patients without paired biopsy samples were excluded. $p = 0.101$ for overall test of treatment effect.
[d] 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 histological activity and either a biochemical or virological response at week 72, regardless of treatment group ($p < 0.001$). A histological response occurred in 151 of 292 patients with a biochemical response (52%) compared with 70 of 245 patients without a biochemical response (29%). A histological response was seen in 116 of 208 patients with a virological response (56%) as compared with 105 of 329 patients without a virological response (32%).

Adverse events, *n* (%)	**Group A (*n* = 177)**	**Group B (*n* = 179)**	**Group C (*n* = 181)**
Discontinuation:			
For safety reasons[a]	13 (7)	7 (4)	0
For other reasons[b]	2 (1)	3 (2)	4 (2)
Dose modification[c]:			
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[d]	9 (5)	12 (7)	5 (3)
Death	1 (1)[e]	0	0
≥ 1 reported AE[a]	155 (88)	155 (87)	86 (48)
Most common AE[f]:			
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:
[a] $p < 0.001$ for overall test of treatment effect.
[b] $p = 0.913$ for overall test of treatment effect.
[c] Some patients who required a dose modification had both an adverse event and a laboratory abnormality.
[d] A serious AE was one that presented a clinically significant hazard or resulted in a contraindication or side-effect.
[e] Thrombotic thrombocytopenic purpura developed in this patient.
[f] Patients may have had more than 1 AE. The AE listed are those reported by at least 5% of patients in Group A or B up to 8 weeks after therapy.

continued

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 pretreatment liver biopsy.

Additional results:
HBsAg loss (at week 72) occurred in 7 patients in Group A (5 Asian and 2 white) and in five Group B patients (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 and 3 Group B patients. No Group C patients 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 IFN tends to occur later than that observed with PEG-2a in this study.

At week 48, YMDD mutations were detected in 32 of 179 Group C patients (18%) and 1 of 173 Group B patients (1%, $p < 0.001$).

Methodological comments
- *Allocation to treatment groups* (method of randomisation and concealment of allocation): Randomisation was centralised and stratified according to geographic region and ALT 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? CIs given?): Efficacy analyses included all randomised patients who received at least one dose of study medication. Cochran–Mantel–Haenszel test, stratified according to geographic region and pretreatment ALT level, was used to compare differences in response rates between the treatment groups. Fisher'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% CIs 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 a 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: PEG-2a monotherapy group 12, LAM + PEG-2a group 17, LAM 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 6 months.
- Outcome measures: Appropriate outcome measures were used.
- Inter-centre variability: Not reported.
- Conflict of interests: Supported by Roche.
- No data provided for patient subgroups, 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 ITT analysis?	Partial
10. Were losses to follow-up completely described?	Adequate

Appendix 9

Data extraction – Perrillo *et al.*, 2004[33] (Study 465)

Extracted by: AT. Checked by: ST. Date: 24 January 2005.

Reference and design	Intervention	Participants	Outcome measures
Perrillo *et al.*,2004[33] Trial design: RCT with concurrent non-randomised study Number of centres: not stated Country: not stated Funding: GlaxoSmithKline; ADV provided by Gilead Sciences	*Group A1* *n* = 49[a] ongoing LAM Dose: 100 mg/day plus placebo [a] ITT excluded 1 patient owing to screening ALT level <1.3 times ULN and the absence of documented past HBsAg positivity *Group A2* *n* = 46 ongoing LAM Dose: 100 mg/day plus ADV Dose: 10 mg/day Duration: 52 weeks *Group B* *n* = 40 ADV (open label) Dose: 10 mg/day Duration: 52 weeks plus ongoing LAM Dose: 100 mg/day	HBeAg status: Group A positive, Group B mixed Total randomised: Group A *n* = 95, Group B *n* = 40 *Inclusion criteria:* HBsAg-positive adults receiving ongoing LAM therapy for ≥ 6 months for CHB HBV DNA concentration ≥ 106 copies/ml ALT >1.3 times ULN on at least 2 occasions in previous 6 months Group A patients had HBeAg-positive CHB with compensated liver disease Group B patients had signs of decompensated disease or recurrent hepatitis B after liver transplantation. Group B patients could be either HBeAg-positive or -negative *Exclusion criteria:* Coinfection with HCV, HDV or HIV Documented or suspected HCC, anaemia, leucopenia and granulocytopenia or thrombocytopenia A screening calculated creatine clearance <50 ml/minute or a serum creatine value >1.5 mg/dl Evidence of pancreatitis Patients 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 patients with undetectable serum HBV DNA Proportion of patients with YMDD mutant HBV DNA Additional end-points for Group B: proportion of patients with progression of clinical disease assessed at 2-point increase from baseline in CPT score or development of either spontaneous bacterial peritonitis, bleeding gastric/ oesophageal varices, HCC during treatment.

	A1 (*n* = 48)	**A2 (*n* = 46)**	**B with LT (*n* = 14)**	**B without LT (*n* = 26)**	**All B (*n* = 40)**
Median age (years) (range)	42 (25–68)	43 (24–67)	54.5 (22–72)	52 (33–73)	53 (22–73)
Median duration prior LAM, months (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-positive (%)[a]	42 (88)	40 (87)	9 (64)	18 (69)	27 (68)
No. HBe antibody positive	0	0	3 (21)	4 (15)	7 (18)
No. HBsAg-positive (%)[a]	48 (100)	44 (96)	13 (93)	26 (100)	39 (98)
Median HBV DNA level[b]	8.61 (4.2–10.1)	8.95 (6.6–10.1)	9.01 (7.2–10.1)	8.14 (5.4–9.4)	8.61 (5.4–10.1)

continued

Reference and design	Intervention	Participants	Outcome measures

	A1 (*n* = 48)	A2 (*n* = 46)	B with LT (*n* = 14)	B without LT (*n* = 26)	All B (*n* = 40)
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.
[b] $\log_{10}$ 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 (CPT, Child–Pugh–Turcotte, cirrhosis grading tool/system).

Length of follow-up: 52 weeks

Outcome	LAM plus placebo (*n* = 48)	LAM plus ADV (*n* = 46)	Difference
No. with HBV DNA level >105 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 PCR 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] $p \leq 0.01$ HBV DNA time series presented in paper but not data extracted.			
HBeAg loss	1/42 (2)	6/40 (15)	
Comments: Among those patients who were HBeAg-positive before treatment, 8% (3 of 40) receiving ADV and LAM underwent HBeAg seroconversion compared with 2% (1 of 42) receiving LAM and placebo at week 52. Loss of HBeAG occurred in 6 of 40 (15%) of patients receiving LAM and ADV and 1 of 42 (2%) of those receiving LAM and placebo. No patient lost HBsAg during the treatment period.			
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 (%)[b]	9	37	A1:A2 $p = 0.003$

continued

Comments: Percentiles also given in paper for changes from baseline.
[a] $p \leq 0.01$.
[b] 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 ($p = 0.002$)".

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:
[a] One patient received rescue medication and is not presented in this analysis.

Adverse events (AE)	**LAM plus placebo (n = 48*)**	**Lam plus ADV (n = 44*)**
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. 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	**Week 52**	**Baseline**	**Week 52**	**Baseline**	**Week 52**
No. with HBV DNA response at weeks 48 and 52 (%)	–	13/14 (93)	–	23/25 (92)	–	36/39 (92)
Median HBV DNA (log-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 normalisation (from Figure 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 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 normalisation of ALT levels at weeks 48 and 52.
One patient HBeAg seroconverted.

No. (%) with detectable YMDD mutant at baseline	13/13 (100)	24/25 (96)	37/38 (97)[a]
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:
[a] One patient had YMDD mutant detected at screening but not at baseline.

continued

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. Centralised 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? CIs given?): Primary efficacy analyses used ITT population, defined as all patients with confirmed CHB who were randomised 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 virological response (reduction in HBV DNA levels), assessed as the proportion of patients with either HBV DNA level ≤ 105 copies/ml or a >2 log 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 hypothesised HBV DNA response rates of 14% in the LAM plus placebo group and 44% in the LAM 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 LAM plus placebo completed the 52 weeks. One patient withdrew owing 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 LAM plus ADV completed treatment. One patient was withdrawn owing to a protocol violation, 1 withdrew consent and 2 were lost to follow-up. 95% (38 of 40) Group B patients completed treatment; 1 withdrew owing to adverse events and 1 owing 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 liver 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. ADV 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 ITT analysis?	Inadequate
10. Were losses to follow-up completely described?	Adequate

Appendix 10

Data extraction – Peters *et al.*, 2004[35] (Study 461)

Extracted by: AT. Checked by: ST. Date: 22 January 2005.

<table>
<tr><th>Reference and design</th><th>Intervention</th><th>Participants</th><th>Outcome measures</th></tr>
<tr>
<td>Peters et al., 2004[35]

Trial design: double-blind RCT

Number of centres: 20

Country: Australia, Canada, France, Germany, UK and USA

Funding: Not stated</td>
<td>Group A:
n = 19
LAM
Dose: 100 mg/day
Duration: 48 weeks
Plus placebo

Group B:
n = 19
ADV
Dose: 10 mg/day
Duration: 48 weeks
Plus placebo

Group C:
n = 20
ADV
Dose: 10 mg/day
Duration: 48 weeks

LAM
Dose: 100 mg/day
Duration: 48 weeks</td>
<td>HBeAg status: positive

Total randomised: 59

Inclusion criteria:
16–65 years old
HBsAg present for at least 6 months
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 LAM therapy for at least 6 months
Well-preserved liver function and no history of variceal bleeding, ascites or encephalopathy.

Exclusion criteria:
Serum phosphorus 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 or other immunomodulatory therapies within the 6 months preceding 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
Co-infection with HIV
Current alcohol or substance abuse
Pregnancy/lactation

Baseline measurements:
<table>
<tr><th></th><th>LAM (n = 19)</th><th>ADV (n = 19)</th><th>ADV+LAM (n = 20)</th></tr>
<tr><td>Age (years): median (range)</td><td>44.0 (33–69)</td><td>45.0 (26–64)</td><td>46.5 (28–66)</td></tr>
<tr><td>Male: n %</td><td>14 (74)</td><td>17 (89)</td><td>15 (75)</td></tr>
<tr><td>Race: n %</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>14 (74)</td><td>12 (63)</td><td>9 (45)</td></tr>
<tr><td>Asian</td><td>5 (26)</td><td>7 (37)</td><td>9 (45)</td></tr>
<tr><td>Black</td><td>0</td><td>0</td><td>1 (5)</td></tr>
<tr><td>Other</td><td>0</td><td>0</td><td>1 (5)</td></tr>
<tr><td>Prior LAM therapy (months): median (range)</td><td>24.0 (9–58)</td><td>37.0 (16–75)</td><td>29.5 (12–86)</td></tr>
</table>
</td>
<td>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 from baseline
% of patients with ALT normalisation
HBeAg loss
Seroconversion to anti-HBe
Loss of HBsAg.

Length of follow-up: 48 weeks</td>
</tr>
</table>

continued

Reference and design	Intervention	Participants	Outcome measures

	LAM (*n* = 19)	ADV (*n* = 19)	ADV + LAM (*n* = 20)
HBV DNA (log copies/ml): median (range)	8.2 (6.08–8.82)	8.42 (7.30–9.21)	7.94 (5.89–8.88)
HBeAg: (%)			
Positive	19 (100)	19 (100)	18 (90)
Negative	0	0	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)

Compliance: not reported.

Treatment history: all patients had received treatment with LAM for at least 6 months and had no prior use of ADV.

Genotype: genotypic analyses of HBV polymerase performed on all 58 patients had LAM resistance mutations by sequencing at baseline. All 4 major patterns of LAM resistance mutations were observed in these patients.

Outcome	LAM (*n* = 19)	ADV (*n* = 19)	ADV + LAM (*n* = 20)	Difference
DAVG16: Mean ± SD	–0.0 ± 0.34	–2.66[a] ± 0.80	–2.50[a] ± 0.54	[a] $p < 0.001$
DAVG48: Mean ± SD	–0.10 ± 0.39	–3.88[a] ± 1.05	–3.09[a] ± 0.67	[a] $p < 0.001$
Change in serum HBV DNA: mean ± SD (95% CI):				
Week 16	0.0 ± 0.28 (–0.14 to 0.13)	–3.11[a] ± 0.94 (–3.54 to –2.69)	–2.95[a] ± 0.64 (–3.23 to -2.66)	[a] $p < 0.001$
Week 48	–0.31 ± 0.93 (–0.74 to 0.12)	–4.00[a] ± 1.41 (–4.65 to –3.35)	–3.46[a] ±1.10 (–3.94 to –2.97)	[a] $p < 0.001$

Comments: DAVG16 (DAVG48) 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 copies/ml) divided by the number of days from baseline up to the last included value.

Outcome	LAM (*n* = 19)	ADV (*n* = 19)	ADV + LAM (*n* = 18)	Difference
HBeAg status:				
Negative at week 48 *n*/total (%)	0 (0)	3[a] (16)	3[b] (17)	[a] $p = 0.075$, [b] $p = 0.067$
Rate of seroconversion	0 (0)	2[a] (11)	1[b] (6)	[a] $p = 0.152$, [b] $p = 0.304$

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 (*n* = 19)	ADV (*n* = 19)	ADV + LAM (*n* = 20)	Difference
Change in serum ALT level (IU/l): Mean ± SD (95% CI)	± 30.8 (–4.2 to 14.2)	–87.7 ± 121.7 (–143.9 to –31.5)	–48.6 ± 82.0 (–84.5 to –12.6)	
Normalisation of serum ALT, *n*/total (%)	1/19 (5)	9[a]/19 (47)	10[b]/19 (53)	[a] $p = 0.004$, [b] $p = 0.001$

Comments: For normalisation of ALT analysis, 'total' includes only patients with an ALT level >ULN at baseline.

continued

Adverse events	LAM (*n* = 19)	ADV (*n* = 19)	ADV + LAM (*n* = 20)	Difference
Dose discontinuation for any adverse event *n* (%)	0 (0)	0 (0)	0 (0)	
Dose reduction for any adverse event *n* (%)	0 (0)	0 (0)	0 (0)	
No. (%) patients experiencing any adverse event	19 (100)	18 (95)	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)	
Sinusitis	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 patients 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 randomised centrally (Interactive Clinical Technologies, Yardley, PA, USA).
- *Blinding* (for patients, health workers and study personnel, and method): Haematology and biochemistry were analysed 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 6–12 months longer than other 2 groups.
- *Method of data analysis* (ITT, point estimates given? CIs given?): "Analysis included all randomised patients who received at least one dose of study medication" and one patient from 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 LAM) 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 post-baseline categorical response was missing at a given time were considered non-responders 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 normalisation 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 difference in DAVG16 between the LAM monotherapy group and each of the other groups. Sample size calculation was based on $\alpha = 0.025$ and an SD of 0.76. A drop-out 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 owing to non-compliance and one LAM patient discontinued at week 44 owing 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.

continued

- *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 subgroups, 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 10 mg 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 ITT analysis?	Inadequate
10. Were losses to follow-up completely described?	Adequate

Appendix 11

Data extraction – Lau *et al.*, 2005[40]

Extracted by: AT. Checked by: JS. Date: 5 July 2005.

<table>
<tr><th>Reference and design</th><th>Intervention</th><th>Participants</th><th>Outcome measures</th></tr>
<tr><td>Lau et al., 2005[40]

Trial design: Multicentre RCT, partially double blind

Number of centres: 67

Country: 16 countries in Asia, Australasia, Europe, North and South America

Funding: Sponsored by Roche</td><td>Group A:
$n = 271$
Drug 1: PEG
Dose: 180 μg once weekly
Duration: 48 weeks
Drug 2: placebo
Dose: once daily
Duration: 48 weeks

Group B:
$n = 271$
Drug 1: PEG
Dose: 180 μg once weekly
Duration: 48 weeks
Drug 2: LAM
Dose: 100 mg once daily
Duration: 48 weeks

Group C:
$n = 272$
Drug 1: LAM
Dose: 100 mg once daily
Duration: 48 weeks
Drug 2: none</td><td>HBeAg status: HBeAg positive

Total randomised: 814

Inclusion criteria:
Adults HBsAg positive for at least 6 months, negative for anti-HB antibodies and positive for HBeAg
HBV DNA level of >500,000 copies/ml
Serum ALT >1 but ≤10 × ULN
Liver biopsy findings within previous 12 months consistent with presence of CHB

Exclusion criteria:
Decompensated liver disease
Coexisting medical or psychiatric illness
Neutrophil count of <1500/ml
Platelet count <90,000/ml
Serum creatinine level >1.5 × ULN
History of drug/alcohol abuse within 1 year before entry
Co-infection with HCV, HDV or HIV
Treatment for CHB within previous 6 months (but previous treatment earlier than that permitted)

Baseline measurements:
<table>
<tr><th></th><th>PEG + placebo ($n = 271$)</th><th>PEG + LAM ($n = 271$)</th><th>LAM ($n = 272$)</th></tr>
<tr><td>Male: n (%)</td><td>214 (79)</td><td>208 (77)</td><td>215 (79)</td></tr>
<tr><td>Race: n (%)</td><td></td><td></td><td></td></tr>
<tr><td>White</td><td>24 (9)</td><td>23 (8)</td><td>32 (12)</td></tr>
<tr><td>Asian</td><td>237 (87)</td><td>236 (87)</td><td>232 (85)</td></tr>
<tr><td>Black</td><td>4 (1)</td><td>4 (1)</td><td>3 (1)</td></tr>
<tr><td>Other</td><td>6 (2)</td><td>8 (3)</td><td>5 (2)</td></tr>
<tr><td>Age: (years)</td><td></td><td></td><td></td></tr>
<tr><td>Mean ± SD</td><td>32.5 ± 9.6</td><td>31.7 ± 10.3</td><td>31.6 ± 9.7</td></tr>
<tr><td>Median</td><td>31</td><td>29</td><td>30</td></tr>
<tr><td>Range</td><td>18–77</td><td>18–66</td><td>17–65</td></tr>
<tr><td>ALT: (IU/l[a])</td><td></td><td></td><td></td></tr>
<tr><td>Mean ± SD</td><td>114.6 ± 114.3</td><td>114.9 ± 94.1</td><td>102.3 ± 78.4</td></tr>
<tr><td>Median</td><td>84.0</td><td>81.8</td><td>82.1</td></tr>
<tr><td>Range</td><td>11.4–1266.0</td><td>13.2–642.0</td><td>5.9–462.1</td></tr>
<tr><td>HBV DNA: (log copies/ml)</td><td></td><td></td><td></td></tr>
<tr><td>Mean ± SD</td><td>9.9 ± 2.1</td><td>10.1 ± 1.9</td><td>10.1 ± 2.0</td></tr>
<tr><td>Median</td><td>9.8</td><td>9.9</td><td>9.8</td></tr>
<tr><td>Range</td><td>4.4–16.1</td><td>3.1–17.9</td><td>3.0–16.0</td></tr>
<tr><td>Bridging fibrosis or cirrhosis n (%)</td><td>49 (18)</td><td>40 (15)</td><td>47 (17)</td></tr>
</table></td><td>Primary outcomes:
HBeAg seroconversion
HBV DNA <100,000 copies/ml

Secondary outcomes:
Combines response (HBeAg seroconversion, ALT normalisation and HBV DNA <100,000 copies/ml)
HBsAg seroconversion
Histological response
Adverse events

Length of follow-up:
24 weeks following 48 weeks of treatment</td></tr>
</table>

continued

Reference and design	Intervention	Participants	Outcome measures

	PEG + placebo (*n* = 271)	PEG + LAM (*n* = 271)	LAM (*n* = 272)
Previous use of IFN *n* (%)	30 (11)	32 (12)	32 (12)
Previous use of LAM *n* (%)	31 (11)	24 (9)	42 (15)
Genotype distn. *n* (%)			
A	23 (8)	18 (7)	15 (6)
B	76 (28)	82 (30)	73 (27)
C	162 (60)	156 (58)	162 (60)
D	9 (3)	11 (4)	17 (6)
E, F or H	0	3 (1)	4 (1)
Mixed	1 (<1)	1 (<1)	1(<1)

[a] ULN is 30 IU/litre.

Compliance: not stated.

Outcome	End of treatment, week 48			End of follow-up, week 72		
	PEG 180 µg + placebo (*n* = 271)	PEG 180 µg + LAM 100 mg (*n* = 271)	LAM 100 mg (*n* = 272)	PEG 180 µg + placebo (*n* = 271)	PEG 180 µg + LAM 100 mg (*n* = 271)	LAM 100 mg (*n* = 272)
HBeAg response						
HBeAg seroconversion[a]:						
Patients *n* (%)	72 (27)	64 (24)	55 (20)	87 (32)	74 (27)	52 (19)
95% CI	21.4 to 32.2	18.7 to 29.1	15.6 to 25.5	26.6 to 38.0	22.1 to 33.0	14.6 to 24.3
p-Value				<0.001	0.02	
Odds ratio (95% CI)[b]				2.0 (1.3 to 3.0)	1.6 (1.1 to 2.4)	
HBeAg loss:						
Patients *n* (%)	81 (30)	73 (27)	59 (22)	91 (34)	77 (28)	57 (21)
95% CI	24.5 to 35.7	21.7 to 32.6	16.9 to 27.1	28.0 to 39.5	23.1 to 34.2	16.3 to 26.3
p-Value				<0.001	0.04	
Comments:						
All *p*-values are from the Cochran–Mantel–Haenszel test for pairwise comparison of each PEG group with LAM monotherapy group at week 72.						
[a] $p = 0.003$ for the overall test of treatment effect and $p = 0.23$ for the comparison between PEG + placebo and PEG + LAM.						
[b] Odds ratios are given with 95% CI only for the 2 primary efficacy outcomes.						
Weekly data for seroconversion from baseline to week 72 are shown on Figure 1 in the paper. Not data extracted.						
Virological response						
HBV DNA <100,000 copies/ml[a]						
Patients *n* (%)	142 (52)	233 (86)	169 (62)	86 (32)	91 (34)	60 (22)
95% CI	46.3 to 58.5	81.3 to 89.9	56.1 to 67.9	26.2 to 37.6	28.0 to 39.5	17.3 to 27.5
p-Value				0.01	0.003	
Odds ratio (95% CI)[b]				1.6 (1.1 to 2.4)	1.8 (1.2 to 2.6)	
HBV DNA <400 copies/ml						
Patients *n* (%)	68 (25)	186 (69)	108 (40)	39 (14)	37 (14)	14 (5)
95% CI	20.0 to 30.7	62.7 to 74.1	33.8 to 45.8	10.4 to 19.1	9.8 to 18.3	2.8 to 8.5
p-Value				<0.001	<0.001	

continued

Outcome	End of treatment, week 48			End of follow-up, week 72		
	PEG 180 µg + placebo (*n* = 271)	**PEG 180 µg + LAM 100 mg (*n* = 271)**	**LAM 100 mg (*n* = 272)**	**PEG 180 µg + placebo (*n* = 271)**	**PEG 180 µg + LAM 100 mg (*n* = 271)**	**LAM 100 mg (*n* = 272)**
Change in HBV DNA						
Total no. of patients	248	249	249	248	254	241
Mean log copies/ml	–4.5	–7.2	–5.8	–2.4	–2.7	–1.9
95% CI (log copies/ml)	–4.1 to –4.9	–6.9 to –7.5	–5.4 to –6.1	–2.0 to –2.8	–2.2 to –3.1	–1.5 to –2.3
Comments: All *p*-values are from the Cochran–Mantel–Haenszel test for pairwise comparison of each PEG group with LAM monotherapy group at week 72. [a] $p = 0.007$ for the overall test of treatment effect and $p = 0.65$ for the comparison between PEG + placebo and PEG + LAM. [b] Odds ratios are given with 95% CI only for the two primary efficacy outcomes.						
Weekly data for HBV DNA from baseline to week 72 are shown on Figure 1 in the paper. Not data extracted.						
Biochemical response						
Normalisation of ALT:						
Patients *n* (%)	105 (39)	126 (46)	168 (62)	111 (41)	106 (39)	76 (28)
95% CI	32.9 to 44.8	40.4 to 52.6	55.7 to 67.6	35.0 to 47.1	33.3 to 45.2	22.7 to 33.7
p-Value				0.002	0.006	
Comments: All *p*-values are from the Cochran–Mantel–Haenszel test for pairwise comparison of each PEG group with LAM monotherapy group at week 72.						
Combined response						
HBeAg seroconversion, normalisation of ALT and HBV, DNA <100,000 copies/ml:						
Patients *n* (%)	27 (10)	42 (15)	50 (18)	62 (23)	56 (21)	28 (10)
95% CI	6.7 to 14.2	11.4 to 20.4	14.0 to 23.5	18.0 to 28.3	16.0 to 26.0	7.0 to 14.5
p-Value				<0.001	<0.001	
Comments: All *p*-values are from the Cochran–Mantel–Haenszel test for pairwise comparison of each PEG group with LAM monotherapy group at week 72.						
Histological response[a]						
All patients: no.[b]		Not reported		271	271	272
Improved: no. of patients (%)				102 (38)	112 (41)	93 (34)
95% CI				31.8 to 43.7	35.4 to 47.4	28.6 to 40.2
Patients with paired biopsy: Samples no.[c]				207	215	184
Improved: no. of patients (%)				102 (49)	112 (52)	93 (51)
95% CI				42.3 to 56.3	45.2 to 58.9	43.1 to 58.0
Comments: [a] Histological response was defined as a reduction of at least 2 points in the modified HAI score. Scores for this index can range from 0 to 24, with fibrosis graded from 0 (none) to 6 (cirrhosis) and inflammation graded from 0 to 18. [b] Patients without paired biopsy were classified as having no response. $p = 0.23$ for the overall test of treatment effect. [c] Patients without paired biopsy samples were excluded. $p = 0.79$ for the overall test of treatment effect. There was a significant association between improved histological activity and either HBeAg seroconversion, a virological response, or a biochemical response at week 72, regardless of the treatment group ($p < 0.001$). Among patients with paired biopsy samples, a histological response occurred in 133 of 179 patients (74%) who had HBeAg seroconversion as compared with 174 or 427 patients (41%) who did not have HBeAg seroconversion ($p < 0.001$ by the log-likelihood ratio test).						

continued

Effect of baseline factors and ALT during treatment on HBeAg seroconversion rates at week 72	**PEG 180 μg + placebo (*n* = 271)**	**PEG 180 μg + LAM 100 mg (*n* = 271)**	**LAM 100 mg (*n* = 272)**
No. of patients who HBeAg seroconverted/total no. patients (%):			
Overall study population	87/271 (32)	74/ 271 (27)	52/272 (19)
Patients with no previous anti-HBV therapy[a]	66/214 (31)	59/221 (27)	42/208 (20)
Patients with previous exposure to LAM:			
Exposed	10/31 (32)	6/24 (25)	7/42 (17)
Not exposed	77/240 (32)	68/247 (28)	45/230 (20)
Patients with previous exposure to IFN:			
Exposed	13/30 (43)	11/32 (34)	4/32 (12)
Not exposed	74/241 (31)	63/239 (26)	48/240 (20)
HBV genotype[b]			
A	12/23 (52)	4/18 (22)	3/15 (20)
B	23/76 (30)	24/82 (29)	17/73 (23)
C	50/162 (31)	43/156 (28)	29/162 (18)
D	2/9 (22)	2/11 (18)	3/17 (18)
Baseline HBV DNA levels (log copies/ml)			
≤ 9.07	37/70 (53)	20/56 (36)	24/78 (31)
>9.07–10.26	39/138 (28)	40/147 (27)	21/123 (17)
>10.26	11/63 (17)	14/68 (21)	7/71 (10)
Baseline ALT level (× ULN)[c]			
≤ 2	27/92 (29)	19/93 (20)	19/96 (20)
>2–5	36/121 (30)	30/111 (27)	20/129 (16)
>5	24/58 (41)	25/67 (37)	13/47 (28)
Maximum ALT level during treatment (× ULN)[c]			
≤ 5	39/149 (26)	35/150 (23)	33/177 (19)
>5–10	28/74 (38)	27/86 (31)	16/64 (25)
>10	20/48 (42)	12/35 (34)	3/31 (10)
Maximum ALT level during treatment (× baseline value)			
≤ 5	81/257 (32)	68/255 (27)	49/260 (19)
>5	6/14 (43)	6/16 (38)	3/12 (25)

Comments:
[a] This group includes patients who had previously been treated with LAM, IFN and PEG only.
[b] This group includes only patients infected with HBV genotype A, B, C or D.
[c] ULN denotes the upper limit of the normal range, which is 30 IU/l.

Adverse events, no (%)	**PEG 180 μg + placebo (*n* = 271)**	**PEG 180 μg + LAM 100 mg (*n* = 271)**	**LAM 100 mg (*n* = 272)**
Discontinuation:			
For safety reasons[a]	8 (3)	12 (4)	2 (1)
For other reasons[b]	9 (3)	6 (2)	12 (4)
Dose modification:[c]			
Total	124 (46)	127 (47)	0
Adverse event	20 (7)	23 (8)	0
Laboratory abnormality	99 (37)	102 (38)	0
Dose missed or dosage error	25 (9)	20 (7)	0
Other	2 (1)	2 (1)	0

continued

Adverse events:	**PEG 180 μg + placebo (*n* = 271)**	**PEG 180 μg + LAM 100 mg (*n* = 271)**	**LAM 100 mg (*n* = 272)**
≥ 1 reported serious adverse event (weeks 0–56)[d]	12 (4)	16 (6)	5 (2)
Deaths:			
Weeks 0–56	0	3 (1)[e]	0
Weeks 57–72	0	0	1 (< 1)[f]
≥ 1 reported adverse event (weeks 0–56)[g]	240 (89)	240 (89)	152 (56)
Most common adverse events (weeks 0–56)[h]:			
Pyrexia	133 (49)	13 (5)	12 (4)
Fatigue	108 (40)	148 (55)	37 (14)
Headache	76 (28)	101 (37)	27 (10)
Myalgia	70 (26)	81 (30)	8 (3)
Alopecia	55 (20)	77 (28)	6 (2)
Decreased appetite	40 (15)	78 (29)	5 (2)
Rash	27 (10)	34 (13)	10 (4)
Pruritus	26 (10)	22 (8)	5 (2)
Dizziness	25 (9)	26 (10)	11 (4)
Diarrhoea	25 (9)	32 (12)	9 (3)
Nausea	24 (9)	26 (10)	6 (2)
Injection-site reaction	24 (9)	27 (10)	0
Arthralgia	24 (9)	15 (6)	7 (3)
Upper respiratory tract infection	21 (8)	24 (9)	29 (11)
Insomnia	20 (7)	15 (6)	10 (4)
Rigors	19 (7)	23 (8)	0
Upper abdominal pain	19 (7)	27 (10)	20 (7)
Sore throat	15 (6)	14 (5)	19 (7)
Gingival bleeding	15 (6)	21 (8)	1 (< 1)
Cough	14 (5)	15 (6)	10 (4)
Dyspepsia	14 (5)	19 (7)	9 (3)
Depression	16 (6)	6 (2)	4 (1)

Comments: Values are based on all randomised patients who received ≥ 1 dose of study medication and had at least 1 safety assessment after baseline.

[a] $p = 0.03$ for the overall test of treatment effect. $p = 0.06$ for the comparison between PEG + placebo and LAM monotherapy, and $p = 0.01$ for the comparison between PEG + LAM and LAM monotherapy.

[b] $p = 0.36$ for the overall test of treatment effect.

[c] Some patients who required a dose modification had both an adverse event and a laboratory abnormality. Laboratory abnormalities include ALT elevation, neutropenia and thrombocytopenia. 'Other' includes circumstances related to patient compliance.

[d] A serious adverse event was one that presented a clinically significant hazard or resulted in a contraindication, side-effect or precaution. $p = 0.05$ for the overall test of treatment effect, $p = 0.09$ for the comparison between PEG + LAM and LAM monotherapy.

[e] All 3 deaths were accidental and were considered by the investigators to be unrelated to the study medication.

[f] Life-threatening hepatic encephalopathy developed in this patient, which was considered by the investigator to be related to discontinuation of lamivudine treatment.

[g] $p < 0.001$ for the overall test of treatment effect, $p < 0.001$ for the comparison between PEG + placebo and LAM monotherapy, and $p < 0.001$ for the comparison between PEG + LAM and LAM alone.

[h] Patients may have had more than one adverse event. The adverse events listed are those reported by at least 5% of patients in any treatment group.

Among the 3 groups, the incidence of adverse events was similar between Asian and non-Asian patients (79 and 82%, respectively).

continued

Additional results:

- HBsAg
  At week 72, HBsAg seroconversion was identified in 8 PEG monotherapy patients (3 Asian and 5 white, 5 with genotype A, one with genotype B, 4 with genotype C and 1 with genotype H). HBsAg seroconversion was not identified in any LAM monotherapy patients. The differences in HBsAg seroconversion between PEG monotherapy and LAM monotherapy, and between PEG + LAM and LAM monotherapy were significant ($p = 0.004$ for both comparisons with LAM monotherapy, by Fisher's exact test).
- Resistance
  At week 48, YMDD mutations were detected in 69 of 254 (27%) patients receiving LAM monotherapy and 9/256 (4%) of PEG + LAM patients ($p < 0.001$).

Methodological comments

- *Allocation to treatment groups:* Randomisation was centralised and stratified according to geographic region and ALT levels.
- *Blinding:* Trial described as partially double-blind. Details of placebo not specified. Biopsy samples were scored by an independent histopathologist who was unaware of the timing of the biopsy or the patient's treatment assignment. HBeAg and serum HBV DNA were measured at a central laboratory.
- *Comparability of treatment groups:* Baseline demographic and other characteristics were similar, but no *p*-values were reported. The trial authors report that there were no statistically significant differences.
- *Method of data analysis:* Efficacy analyses included all randomised patients who received at least 1 dose of study medication, according to the ITT principle. Patients with missing values at week 72 were classified as having no response.
- *Safety analyses:* Included all patients who underwent randomisation and received at least one dose of study medication and who underwent at least one safety assessment after the baseline assessment. The Cochran–Mantel–Haenszel test, stratified according to geographic region and pretreatment ALT, was used to compare differences in response rates between the treatment groups. Where this was significant, pairwise comparisons were performed. Fisher's exact test was used when appropriate. For each treatment group, response rates were computed with corresponding 95% CIs. No interim analyses were performed.
- *Sample size/power calculation:* A sample size of 231 per treatment group provided statistical power of at least 80% at the 0.0125 level of significance, with a 2-sided test, to detect a difference in HBeAg seroconversion rates of 20 vs 34%, or HBV DNA response rates of 30 vs 45%. The sample size was increased to 250 to allow for withdrawals. An overall significance level of 0.025 was chosen because of the two predetermined primary end-points and related regulatory reasons. For secondary efficacy measures, the level of significance was set at 0.05.
- *Attrition/drop-out:* 28 of the 271 patients randomly assigned to receive PEG monotherapy, 25 of the 271 assigned to receive PEG + LAM and 42 of the 272 assigned to LAM monotherapy either did not complete treatment or did not enter/complete the follow-up phase. This comprises 95 (12%) of the randomised patients.

General comments:

- *Generalisability:* Inclusion/exclusion criteria were fully defined.
- *Outcome measures:* Suitable outcome measures were used.
- *Inter-centre variability:* Not assessed.
- *Conflict of interests:* The study was designed by the sponsor (Roche). The sponsor held the data and conducted the statistical analyses. The principal authors had full access to the data and vouch for the veracity and completeness of the data and data analysis. The authors' links with the drug company are disclosed in the paper.

Quality criteria (CRD Report 4)

1. Was the assignment to the treatment groups really random?	Unknown
2. Was the treatment allocation concealed?	Unclear
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Unclear
7. Was the patient blinded?	Unclear
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were losses to follow-up completely described?	Partial

Appendix 12

Data extraction – Dando and Plosker systematic review[50]

Reviewer: AT. Date: 21 January 2005.

Reference and design	Methods
Dando and Plosker, 2003[50] *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 on 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 10 mg/day, and only trials with at least 20 patients were included. *Interventions:* ADV *Participants:* Patients with chronic hepatitis B who received ADV. *Outcome measures:* Outcome measures are not prespecified 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 non-comparative 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 CIs/SDs, *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 classical systematic review. The reviewers included details on pharmacokinetics, etc., in addition to a summary of efficacy.
- The 2 reviewers are employed by Adis International, New Zealand.

continued

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 10 mg/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 10 mg/day (*n* = 294) (%)**	**Placebo (*n* = 228) (%)**
Glycosuria ≥3+	1	3
Amylase >2 × ULN	4	4
Creatine kinase >4 × ULN	7	7
AST >5 × ULN	8	23
Haematuria ≥3+	11	10
ALT >5 × 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)[30]

Quality criteria for assessment of experimental studies

Criterion	Judgement[a]
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 ITT analysis?	
10. Were withdrawals and dropouts completely described?	

[a] E.g. adequate; inadequate; not reported; unclear.

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 pretreatment evaluations

Evaluation of a new patient with HBV

Item		Cost (£)
Outpatient appointment		
Time with nurse–30 minutes (grade H)		10.55
Time with doctor–20 minutes (consultant)		15.22
Overheads for clinic administration (pulling notes, etc.)		4.51
Staff cost for outpatient appointment		**30.28**
Tests and investigations		
Hepatitis c screen (HCV RNA), 3% of patients only	Virology	2.81
HCV antibody test (Hepatitis C IGM)		12.80
HBV	Virology	11.80
HBV viral load	Virology	77.30
Liver function tests (LFT)	Chemical pathology	4.12
α-Fetoprotein (all patients irrespective of whether cirrhotic) (AFP)	Chemical pathology	9.85
α-Antitrypsin (A1AT)	Chemical pathology	6.28
Thyroid-stimulating hormone (only for patients to be treated with interferon alfa?) (TSH)	Chemical pathology	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	Chemical pathology	7.47
Iron	Chemical pathology	4.87
Urea and electrolytes (U&E) (including renal profile and urea)	Chemical pathology	4.12
International normalised ratio (INR) – standard for reporting blood clotting tests	Haematology	2.70
Glucose	Chemical pathology	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		Cost (£)
Outpatient visit		
To review results from above tests and brief on treatment options:		
Time with nurse – 30 minutes (grade H)		10.55
Time with doctor – 20 minutes (consultant assumed)		15.22
Overheads for clinic administration (pulling notes, etc.)		4.51
Staff cost for outpatient appointment		**30.28**
Daycase for liver biopsy		
Additional tests undertaken prior to biopsy:		
Full blood count (FBC)	Haematology	2.49
INR	Haematology	2.70
Liver function test		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 minutes (grade D nurse assumed)		6.49
Ward time for recovery post-biopsy – 6 hours		20.28
Total		**388.06**

Decision-making about further treatment of follow-up

Item		Cost (£)
Outpatient visit		
Decision has been made to treat and further tests are carried out:		
Time with nurse – 30 minutes (grade H)		10.55
Time with doctor – 20 minutes (consultant assumed)		15.22
Overheads for clinic administration (pulling notes, etc.)		4.51
Staff cost for outpatient appointment		**30.28**
Final tests prior to treatment		
Time with nurse – 30 minutes (grade H)		10.55
Overheads for clinic administration (pulling notes, etc.)		4.51
Staff cost for outpatient appointment		**15.06**
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 X-ray		32.61
Total		**179.10**

Appendix 15

Costing protocols for monitoring patients during and post-treatment

Monitoring during treatment – IFN, 24-week course

Item		Cost (£)
Standard examination (during treatment with interferon) (weeks 1, 2, 3, 6, 8, 16, 20)		
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	Chemical pathology	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	Chemical pathology	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	Chemical pathology	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**

continued

Item		Cost (£)
FBC	Haematology	2.49
LFT	Chemical pathology	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		Cost (£)
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)	Chemical pathology	4.12
U & E		4.12
Blood clotting (for decompensation) (CS)	Haematology	3.80
α-Fetoprotein		9.85
Abdominal ultrasound		119.57
Total for detailed examination		**169.55**

Detailed annual examination
As for untreated patients.

Monitoring during treatment – PEG, 48-week course

Item		Cost (£)
Standard examination (during treatment with Interferon) (weeks 1, 2, 3, 6, 8, 16, 20, 28, 32, 36, 44)		
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	Chemical pathology	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	Chemical pathology	4.12
U & E		4.12
Blood clotting		3.80
INR		2.70
Total for each basic assessment		**32.28**

continued

Item		Cost (£)
Weeks 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	Chemical pathology	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	Chemical pathology	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		Cost (£)
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)	Chemical pathology	4.12
U & E		4.12
Blood clotting (for decompensation) (CS)	Haematology	3.80
α-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 – LAM–ADV, per year of treatment

Item		Cost (£)
Standard examination plus week 4		
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	Chemical pathology	4.12
U & E		4.12
Blood clotting		3.80
INR		2.70
Total for standard plus examination		**32.28**

Item		Cost (£)
Standard examination weeks 8, 18, 22, 30, 34 and 44		
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	Chemical pathology	4.12
U & E		4.12
Blood clotting		3.80
Total for standard examination		**29.58**

Detailed examination weeks 13 and 39

Item		Cost (£)
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	Chemical pathology	4.12
HBeAg		11.70
HBsAg		11.70
HBV DNA		77.30
U & Es	Chemical pathology	4.12
INR	Haematology	2.70
Blood clotting (for decompensation)	Chemical pathology	3.80
α-Fetoprotein		9.85
Total for detailed examination on treatment		**142.83**

Standard examination plus weeks 26 and 52

Item		Cost (£)
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	Chemical pathology	4.12
HBeAg		11.70
HBsAg		11.70
HBV DNA		77.30
U & Es	Chemical pathology	4.12
INR	Haematology	2.70
Blood clotting (for decompensation)	Chemical pathology	3.80
α-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		Cost (£)
Time with nurse 30 minutes (grade H)		10.55
Overheads for clinic administration		4.51
Staff cost for appointment		**15.05**
LFT	Chemical pathology	4.12
INR		2.70
FBC		2.49
Total for detailed examination on treatment		**24.36**

Detailed examination 6 months

Item		Cost (£)
Time with nurse 30 minutes (grade H) or 30 minutes with consultant		16.70
Overheads for clinic administration		4.51
Staff cost for appointment		**21.21**
LFT	Chemical pathology	4.12
INR		2.70
FBC		2.49
HBeAg		11.70
HBsAg		11.70
HBV DNA – 50% of patients		38.65
α-Fetoprotein		9.85
Abdominal ultrasound		119.57
Total for detailed examination on treatment		**221.99**

Detailed examination annually

Item		Cost (£)
Time 30 minutes with consultant		22.84
Overheads for clinic administration		4.51
Staff cost for appointment		**27.34**
LFT	Chemical pathology	4.12
INR		2.70
FBC		2.49
HBeAg		11.70
HBsAg		11.70
HBV DNA		77.30
α-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 48 *Costs and outcomes of sequential treatment strategies for patients with HBeAg-positive disease*

Strategy	Cost (£)	Life expectancy (years) (discounted at 1.5%)	Discounted QALYs	ICER
Best supportive care	7,402	34.29 (25.27)	20.08	
IFN	11,359	35.06 (25.78)	20.58	7,936
IFN followed by LAM	13,672	36.19 (26.52)	21.26	3,369
IFN followed by ADV	23,620	37.84 (27.54)	22.21	7,514
IFN followed by LAM with ADV salvage	22,905	38.00 (27.64)	22.29	9,034
PEG	14,704	35.37 (25.99)	20.78	16,166
PEG followed by LAM	16,911	36.48 (26.71)	21.45	17,162
PEG followed by ADV	26,361	38.22 (27.78)	22.36	18,167
PEG followed by LAM with ADV salvage	25,637	38.07 (27.70)	22.43	18,762

TABLE 49 *Costs and outcomes of sequential treatment strategies for patients with HBeAg negative disease*

Strategy	Cost (£)	Life expectancy (years) (discounted at 1.5%)	Discounted QALYs	ICER
Best supportive care	11,247	18.35 (15.32)	10.05	
IFN	15,524	19.99 (16.45)	11.14	3,922
IFN followed by LAM	18,628	21.17 (17.32)	11.89	4,101
IFN followed by ADV	36,361	22.79 (18.44)	12.83	12,298
IFN followed by LAM with ADV salvage	39,022	23.39 (18.85)	13.19	15,770
PEG	18,172	21.85 (17.72)	12.36	2,162
PEG followed by LAM	20,719	22.69 (18.34)	12.88	2,122
PEG followed by ADV	34,846	23.86 (19.16)	13.53	–2,172
PEG followed by LAM with ADV salvage	36,766	24.29 (19.45)	13.77	–3,856

Appendix 17

Additional tables used in economic analysis

TABLE 50 *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 seroconversion[a]	LAM/ADV	0.6931			Normal	μ = 0.6931; SD = 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

[a] Exponent of natural log of relative risk of HBeAg seroconversion is multiplied by the spontaneous HBeAg seroconversion rate (which is also sampled probabilistically) to get treatment response.

TABLE 51 *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

CC, compensated cirrhosis.

TABLE 52 *Transition probabilities for HBeAg-positive patients used in probabilistic analysis*

From	To	Mean (%)	Min. (%)	Max. (%)	Distribution	α	β
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
	Dead	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
	Dead	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
	Dead	39.000	30.000	50.000	Beta	140.4399	219.6624
HCC	Dead	56.000	45.000	90.000	Beta	41.2568	32.4160
LT	Dead	21.000	6.000	42.000	Beta	16.2762	61.2294
Post-LT	Dead	5.700	2.000	11.000	Beta	22.9017	378.8825

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant.

TABLE 53 *Transition probabilities for HBeAg-negative patients*

From	To	Mean (%)	Min. (%)	Max. (%)	Distribution	α	β
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
	Dead	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
	Dead	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
	Dead	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
	Dead	39.000	30.000	50.000	Beta	140.4399	219.6624
HCC	Dead	56.000	45.000	90.000	Beta	41.2568	32.4160
LT	Dead	21.000	6.000	42.000	Beta	16.2762	61.2294
Post-LT	Dead	5.700	2.000	11.000	Beta	22.9017	378.8825

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant.

TABLE 54 *Utility decrements to age-specific health state utilities: values used in probabilistic analysis*

	Mean	Min.	Max.	Distribution	α	β
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 55 *Health state cost distributions*[a]

	Mean (£)	Standard Error (£)[b]	Distribution	α	β
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
CC	1,138.00	21.56	Gamma	2786.9370	0.4083
DC	9,120.00	240.25	Gamma	1440.9964	6.3290
HCC	8,127.00	427.05	Gamma	362.1622	22.4402
LT	27,330.00	352.43	Gamma	6013.4892	4.5448
	9,458.00	311.28	Gamma	923.1796	10.2450
Post-LT	1,385.00	43.37	Gamma	1019.6660	1.3583

CC, compensated cirrhosis; DC, decompensated cirrhosis; LT, liver transplant.
[a] Costs of transplant and first-year care are estimated separately. Liver transplant cost is the sum of the two values.
[b] Standard error for HBeAg seroconverted and CHB costs assumed to be 20% of mean value.

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We look forward to hearing from you.

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