Tenofovir (Viread®)

for the treatment of chronic hepatitis B

SINGLE TECHNOLOGY APPRAISAL

Submission to the National Institute for Health and Clinical Excellence

December 2008

Amended version in response to comments from the Evidence Review Group.

Text in red and the post-submission addendum section have been amended since the original submission.

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List of abbreviations

AASLD	American Association for the Study of Liver Diseases
ADV	Adefovir
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AWMSG	All Wales Medicines Strategy Group
B-hCG	Beta human chorionic gonadotropin
b.d.	Twice daily
BMI	Body mass index
BSC	Best supportive care
CHB	Chronic hepatitis B
CI	Confidence interval
CPK	Creatine phosphokinase
CPT	Child-Pugh-Turcotte
CrI	Credible interval
CSR	Clinical study report
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
EMEA	European Medicines Agency
ETV	Entecavir
FDA	Food and Drug Administration
FTC	Emtricitabine
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
HRQL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IVRS	Interactive voice response system
KOL	Key opinion leader
LAM	Lamivudine
LAM-R	Lamivudine-resistant
LdT	Telbivudine
LLQ	Lower limit of quantification
LTE	Long-term evaluation
MTC	Mixed treatment comparison
NA	Nucleos(t)ide analogue
NHS	National health service
NICE	National Institute for Health and Clinical Excellence
o.d.	Once daily
OR	Odds ratio
PCR	Polymerase chain reaction
PCT	Primary care trust

PSS	Personal social services
QALY	Quality-adjusted life year
RAT	Randomised and treated
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Seroconverted/seroconversion
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single technology appraisal
TDF	Tenofovir
Tenofovir DF	Tenofovir disoproxil fumarate
U&E	Urea and electrolytes
ULN	Upper limit of normal
VAS	Visual analogue scale
VS	Viral suppression

Glossary

Antiviral	For the purposes of this report, this term is used to describe all nucleoside and nucleotide medications that are used to treat CHB.
Alanine aminotransferase	An enzyme that is measured to see if the liver is damaged or diseased
Antigen	A substance that prompts the generation of antibodies and can trigger an immune system response
Anti-HBe	Antibody to the HBeAg antigen
Anti-HBs	Antibody to the HBsAg antigen
Ascites	An accumulation of serous fluid in the peritoneal cavity, often due to liver dysfunction
Chronic hepatitis B	Infection with hepatitis B for greater than six months
Cirrhosis	A serious liver condition characterised by replacement of liver tissue with fibrous scar tissue and regenerative nodules leading to progressive loss of liver function
Compensated cirrhosis	The liver is still able to cope with or compensate for the damage and residual function is preserved
Complete/simple dominance	Complete/simple dominance means that the 'dominant' treatment is both more effective and less costly than its comparator.
Cost-effectiveness frontier	The cost-effectiveness frontier joins the treatments that may be cost-effective, i.e. those that are not dominated by any other treatment by either complete or extended dominance. Treatments that lie above or to the left of the frontier are dominated by those that lie on the frontier and are therefore not cost-effective regardless of how much society is willing to pay for a QALY if the agents on the frontier are also available.
Decompensated cirrhosis	A state where the liver can no longer compensate for the damaged (scarred) tissue
Extended dominance	Extended dominance means that one treatment is both more cost-effective and more effective than the 'dominated' treatment.
Fibrosis	Development or formation of excess fibrous connective tissue in an organ or tissue, most often a consequence of inflammation or injury
HBeAg negative disease	Chronic hepatitis B infection characterised by the absence of hepatitis B e antigen, but with the presence of liver disease often due to a mutation of the hepatitis B virus
HBeAg positive disease	Chronic hepatitis B infection characterised by the presence of hepatitis B e antigen and liver disease
HBeAg seroconversion	Loss of HBeAg and development of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative
Hepatic flare	Characterised by a short-lived rise in ALT levels caused by the destruction of infected hepatocytes by the immune system. Flares often indicate that the body is trying to clear the infection
Hepatitis B e antigen (HBeAg)	The non-structural viral protein exported from infected cells in non-viral proteins while hepatitis B is actively replicating
Hepatitis B	Antibodies derived from blood that provide passive

immunoglobulin (HBIG)	protection against hepatitis B (as opposed to active vaccination)
Hepatitis B s antigen (HBsAg)	The structural viral proteins contained within the lipid envelope surrounding the nucleocapsid
HBV mutant	A variant that develops under specific selection pressure and that has been shown to confer a specific phenotype
Hepatocellular carcinoma	A malignant tumour of the liver
Nucleoside analogue	Any of a group of antiviral drugs, such as lamivudine, that interfere with the activity of the viral enzyme reverse transcriptase and are used in the treatment of HIV or chronic hepatitis B
Nucleotide analogue	Any of a group of antiviral drugs, such as adefovir, that interfere with the activity of the viral enzyme reverse transcriptase and are used in the treatment of HIV or chronic hepatitis B
Odds ratio (OR)	Measure of how many times bigger (or smaller) the risk of an event is with treatment rather than without (or in one subgroup of patients relative to another). Calculated by dividing the odds within one group by the odds within another group. This gives a measure that approximates the relative risk in situations where the absolute risk of an event is very small.
Precore mutant	A mutant strain of HBV that does not produce the hepatitis B e antigen
QALY	A QALY is a 'quality-adjusted life year', which is a measure of both the quantity and quality of life. For example, if a treatment extends life expectancy by a year but at only 50% of full health then the QALY gain is 0.5 years (1 x 0.5). The advantage of measuring the effect of an intervention using QALYs is that you can compare across different indications as well as evaluate different therapy options within a particular disease area.
Viraemia	The presence of the virus in the blood stream
Viral load	The amount of virus present in a person’s blood stream
YMDD mutation	The change in the hepatitis B genome that confers resistance to the drug lamivudine

Section A

1. Description of technology under assessment

1.1. Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device

Viread (tenofovir disoproxil fumarate)

Therapeutic class: Nucleoside and nucleotide reverse transcriptase inhibitors

1.2. Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Received approval from the European Commission for the treatment of CHB on 23rd April 2008.

1.3. What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use

Hepatitis B infection: Viread is indicated for the treatment of CHB in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

This indication is based on histological, virological, biochemical and serological responses mainly in adult nucleoside naïve patients with HBeAg positive and HBeAg negative CHB with compensated liver function.

In addition to the hepatitis B indication, tenofovir is also indicated for use in HIV-1: Viread is indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected adults over 18 years of age.

1.4. To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Viread has been available for use by the NHS since April 2008 in UK patients with CHB. Viread has also been available for the treatment of HIV since 2002.

1.5. Does the technology have regulatory approval outside the UK? If so, please provide details.

Viread has been approved for the treatment of CHB by both the EMEA and the FDA. Viread for HBV has received marketing authorisations in the EU, US, Australia, Turkey, Canada and New Zealand.

1.6. Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Viread has received approval by both the SMC and AWMSG for the treatment of CHB. However, no other UK health technology assessments are underway.

1.7. For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Film-coated tablet.

Each film-coated tablet contains 245 mg of tenofovir disoproxil (as fumarate), equivalent to 300 mg of tenofovir disoproxil fumarate, or 136 mg of tenofovir.

One pack size is available in the UK: 1 x 30 tablet bottle. A second pack size (3 x 30 tablet bottles is licensed in the UK, but not marketed.

1.8. What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Adults: The recommended dose for the treatment of CHB is 245 mg (one tablet) once daily taken orally with food. Dose reductions may be required in patients with renal impairment.

Treatment with tenofovir disoproxil fumarate may be discontinued if there is HBsAg loss or HBsAg seroconversion, otherwise the optimal duration of treatment is unknown.

In HBeAg-positive patients without cirrhosis, treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or there is loss of efficacy. Serum ALT and HBV DNA levels should be followed regularly after treatment discontinuation to detect any late virological relapse.

In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than two years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

1.9. What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

Price: UK NHS price for tenofovir is £255 per bottle of 30 film coated tablets.

This is less costly than telbivudine, entecavir and adefovir (1).

1.10. What is the setting for the use of the technology?

Viread therapy should be initiated by a physician experienced in the treatment of CHB. However, continuation of therapy under shared-care arrangements with a general practitioner is recommended for other nucleos(t)ides. Since tenofovir is taken orally, treatment will be self-administered by patients at home.

1.11. For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. Patients with renal impairment may require additional monitoring.

Tenofovir has demonstrated efficacy when used as monotherapy (1-3) and no other therapies need to be routinely administered at the same time as tenofovir. The SPC for tenofovir does not explicitly recommend the use of tenofovir in combination with other nucleos(t)ides in HBV monoinfected patients, but similarly does not state that tenofovir is not licensed for use in combination therapy, except to state that it should not be used in combination with adefovir, didanosine, nephrotoxic agents or any medicinal products containing tenofovir (Appendix 1). Furthermore, evidence shows that there are no significant pharmacokinetic interactions between tenofovir and lamivudine (Appendix 1). Expert interviews (Section 7.2.7.5) suggest that tenofovir plus lamivudine is used to treat CHB in UK clinical practice. Consequently, this report focuses on use of tenofovir as monotherapy, although trials using tenofovir in combination with other nucleos(t)ides are presented and use of tenofovir in combination with other antiviral drugs is evaluated in the economic evaluation.

2. Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Intervention(s)	Tenofovir disoproxil fumarate alone or in combination with other therapies	Tenofovir disoproxil fumarate alone. Secondary analyses of combination therapy regimens which may be considered clinically appropriate have been included for completeness.
Population(s)	Adults with active CHB (evidence of viral replication and active liver inflammation) and compensated liver disease. HBeAg-positive and HBeAg-negative disease will be considered separately.	Adults with active CHB (evidence of viral replication and active liver inflammation) and compensated liver disease. HBeAg-positive and HBeAg-negative disease will be considered separately.
Standard comparator(s)	• Interferon alfa-2a • Interferon alfa-2b • Peginterferon alfa-2a • Lamivudine • Adefovir dipivoxil • Entecavir	• Lamivudine • Adefovir dipivoxil • Entecavir Secondary analyses of combination therapy regimens comprising the above agents which may be considered clinically appropriate have been included for completeness. However, neither interferon alfa-2a/2b nor peginterferon alfa-2a will be considered in the analysis since they are generally given as an initial treatment to a selected group of patients.
Outcomes	The outcome measures to be considered include: • HBeAg seroconversion rate • HBsAg seroconversion rate • Virological response (HBV DNA) • Histological improvement (inflammation and fibrosis) • Biochemical response (e.g. ALT levels) • Time to treatment failure • Survival • Adverse effects of treatment • Health-related quality of life	
Economic Analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY).	The cost effectiveness of treatments will be expressed in terms of incremental cost per QALY gained.

	Final scope issued by NICE	Decision problem addressed in the submission
	The time horizon for the economic evaluation should reflect the chronic nature of hepatitis B.	A lifetime time horizon will be taken to reflect the chronic nature of CHB.
	The economic evaluation should incorporate key assumptions that were accepted by the appraisal committee in TA96 and TA153	The economic evaluation will incorporate key assumptions stated and endorsed in the guidance documents for TA96 and TA153 unless there is evidence that best practice has changed since guidance was published.
	Costs will be considered from a National Health Service (NHS) and Personal Social Services (PSS) perspective.	Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.	The economic evaluation will consider only licensed treatment options used in accordance with their licensed indications, although patients will be assumed to continue therapy after hepatic decompensation, since expert interviews suggest that this comprises current UK practice. However, the assumptions about stopping rules. Although the analysis focuses on tenofovir monotherapy, use of antiviral combination therapy will also be considered (Section 1.11).
	If evidence allows, the appraisal will seek to identify sub-groups (e.g. people with treatment resistant disease) of individuals for whom the technology is particularly clinically and cost- effective.	Subgroup analyses will be conducted on patients with compensated cirrhosis and non-cirrhotic patients and on patients who are lamivudine-resistant at baseline. If evidence allows, the appraisal will seek to identify other subgroups of individuals for whom the technology is particularly clinically and/or cost-effective.
	If the evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy.	If the evidence allows, the appraisal will consider sequential use of antiviral drugs and combination therapy. However, the focus is on the efficacy and cost-effectiveness of first-line use of tenofovir monotherapy due to the licensing issues discussed in Section 1.11.
	In line with the Technology Appraisal 96, this STA will not specifically consider people with CHB known to be co-infected with hepatitis C, hepatitis D or HIV.	In line with TA96, this STA will not specifically consider people with CHB known to be co-infected with hepatitis C, hepatitis D or HIV.

	Final scope issued by NICE	Decision problem addressed in the submission
Special considerations, including issues related to equity or equality		Equity considerations and implications of the analysis will be discussed in the report. However, QALYs will be given the same weight in the economic evaluation regardless of the other characteristics of the individuals receiving the health benefit.

Section B

3. Executive summary

Background

Hepatitis B is a viral infection of the liver that causes both acute and chronic hepatitis. Acute infection is largely asymptomatic and is cleared by 95% of adults. Chronic hepatitis B (CHB) is defined as persistence of hepatitis B surface antigen (HBsAg) for more than six months (2). Patients who develop CHB have a 100-fold higher risk of complications such as cirrhosis, liver failure, hepatocelluar carcinoma (HCC) and death (3). Latest estimates suggest that about 326,000 people in the UK have CHB (4), with 7,700 new cases of CHB arising each year, mostly through immigration (5). Current prevalence and incidence may be an underestimate of the problem since many patients are not diagnosed and these figures do not take into account the impact of recent migration into the country.

The main goals of treatment of CHB are the sustained suppression of hepatitis B virus (HBV) replication and prevention of end-stage liver disease. Markers of successful therapy include hepatitis B e antigen (HBeAg) seroconversion, decreased or undetectable levels of HBV DNA, and lack of disease progression. HBsAg loss/seroconversion is the ultimate goal of therapy, although this is rarely achieved. Current treatment options for CHB include interferon therapy (peginterferon-alpha 2a and interferon alpha 2a/2b) and the nucleos(t)ide analogues lamivudine, adefovir, entecavir and tenofovir. Interferons are often poorly tolerated (1, 6, 7) and significant clinical endpoints are far more likely to be achieved in carefully selected patients (HBeAg positive, low viral load, alanine aminotransferase (ALT) >3 x upper limit of normal (ULN) and ideally genotype A or B) (8). Nucleos(t)ide analogues act directly to inhibit viral replication and are well-tolerated. Currently available nucleos(t)ides vary in cost, potency (i.e. the extent to which they lower HBV DNA), and the risk of resistance. Drug resistance to lamivudine monotherapy is extremely common: around 67–75% of patients develop lamivudine resistance after four years of continuous treatment (9, 10), while virologic resistance to adefovir monotherapy occurs in up to 14% of patients after four years of therapy (11). Although studies have demonstrated that entecavir has a low risk of resistance and is more potent than lamivudine (12-14), it is considerably more expensive than other treatment options, including tenofovir (15).

There is still an unmet need in the treatment of CHB; agents that can achieve rapid viral suppression with a low rate of resistance, whilst remaining safe, well-tolerated

and easy to administer are required. This submission demonstrates the superior efficacy, favourable resistance profile and cost-effectiveness of tenofovir in patients with CHB.

Tenofovir disoproxil fumarate (Viread®) is a nucleotide reverse transcriptase inhibitor with potency against HBV (16-22) including lamivudine-resistant viral strains (23-25). In the UK, tenofovir was licensed for use in CHB in 2008, although it has been used to treat HIV since 2002. Tenofovir is indicated for the treatment of CHB in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and/or fibrosis. Tenofovir is supplied as 245 mg film-coated tablets (equivalent to 300mg tenofovir disoproxil fumarate) in 30-tablet bottles and the recommended dose for treatment of CHB is 245 mg (one tablet) once daily with food. The optimal duration of treatment is unknown, although in HBeAg-positive patients without cirrhosis, it is recommended that treatment should be administered for at least 6-12 months after HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection) is confirmed or until HBs seroconversion or loss of efficacy (Appendix 1). In HBeAg-negative patients without cirrhosis, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy (Appendix 1). In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

The European Association for the Study of the Liver (EASL) has recently released practice guidelines that recommend tenofovir should be used as a preferred first-line monotherapy for the treatment of chronic hepatitis B (8).

Clinical effectiveness

Head to head randomised controlled trials (RCTs) have shown that tenofovir is significantly superior to adefovir in treatment-naïve patients (19-22).

In HBeAg-negative patients:

- Significantly more tenofovir treated patients (71%) than adefovir treated patients (49%) achieved the primary efficacy endpoint (HBV DNA levels <400 copies/mL and histologic improvement) after 48 weeks of treatment ($p<0.001$) (17, 20).
- Significantly more subjects receiving tenofovir than adefovir experienced suppression of HBV DNA levels below a number of different thresholds at 48 weeks:
    - <400 copies/mL: 94% for tenofovir; 64% for adefovir ($p<0.001$)
    - <300 copies/mL: 92% for tenofovir; 59% for adefovir ($p<0.001$)
    - <169 copies/mL: 91% for tenofovir; 56% for adefovir ($p<0.001$)

In HBeAg-positive patients:

- Significantly more tenofovir treated patients (67%) than adefovir treated patients (12%) achieved the primary efficacy endpoint after 48 weeks of treatment ($p<0.001$) (19, 26).
- Significantly more subjects receiving tenofovir than adefovir experienced suppression of HBV DNA levels below a number of different thresholds at 48 weeks:
    - <400 copies/mL: 80% for tenofovir; 13% for adefovir ($p<0.001$)
    - <300 copies/mL: 74% for tenofovir; 12% for adefovir ($p<0.001$)
    - <169 copies/mL: 69% for tenofovir; 9% for adefovir ($p<0.001$)

- Significantly more tenofovir-treated (3.2%; 5/158) than adefovir-treated (0%; 0/82) subjects achieved HBsAg loss at Week 48 (p=0.018) (19, 26).

Tenofovir was shown to provide continued viral suppression after 96 weeks of long term follow up. At 2 years 89% of HBeAg positive and 99% of HBeAg negative patients on treatment have achieved viral suppression (i.e. HBV DNA < 400 cps/mL). (17, 18).

A randomised phase II RCT has demonstrated that tenofovir is also effective in patients who did not experience viral suppression with the closely-related nucleotide analogue, adefovir (16). Notably, this trial found tenofovir to be effective in patients who had adefovir resistance mutations at baseline and those infected with lamivudine-resistant HBV (16).

Non-randomised trials suggest that tenofovir is safe and effective when used in combination with other antiviral medications such as emtricitabine or lamivudine (27). Studies also suggest that tenofovir is an extremely effective treatment in lamivudine resistant patients (24, 25, 27-29) and in lamivudine resistant patients who have failed adefovir (30, 31). There is evidence of continued efficacy and safety with no cases of virologic resistance in up to five years of continuous treatment (24, 25, 27-29, 31).

Due to an absence of head to head trials against all of the nucleos(t)ides licensed for CHB, a large systematic review and mixed treatment comparison meta-analysis were conducted to evaluate the relative efficacy of adefovir, entecavir, lamivudine, telbivudine, tenofovir or combinations of these medications in antiviral-naive patients with CHB (32) (Appendix 4). This meta-analysis comprises the key clinical evidence demonstrating the efficacy of tenofovir compared with lamivudine or entecavir and provided the key efficacy inputs used in the economic evaluation.

The meta-analysis demonstrated that tenofovir had the highest probability of achieving HBV DNA levels undetectable by PCR after one year of therapy for HBeAg-positive nucleos(t)ide-naive patients. The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other treatments considered in the analysis at the 0.05 level, including entecavir and telbivudine. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide considered in this analysis in terms of suppression of HBV DNA.

Safety of tenofovir

An assessment of tenofovir safety is based on head to head clinical trial data (16, 26, 33). Tenofovir is well tolerated and continues to demonstrate a desirable safety profile at two years (17, 18). RCTs found no significant difference in the overall incidence of adverse events between tenofovir and adefovir (26, 33) or between tenofovir and tenofovir/emtricitabine (16). The most common adverse events across the studies included headache, nasopharyngitis, backpain, nausea and fatigue. These results in patients with CHB are consistent with those observed in HIV, where there are currently 2 million patient-years of safety data (34).

Resistance profile of tenofovir

Tenofovir displays a favourable resistance profile: no cases of virologic HBV resistance have been identified to date over six years of clinical experience in HIV/HBV co-infected patients or up to 2 years of continuous use in controlled clinical trials in HBV monoinfection (19, 23-25, 29, 35) (Section 6.10.1.5).

Cost-effectiveness

A model-based economic evaluation was conducted to evaluate the cost-effectiveness of tenofovir compared with other nucleoside and nucleotide therapies licensed and used in the UK from the perspective of the NHS and personal and social services. Interferons were not considered to be appropriate comparators in this submission as they are suitable only as an initial treatment for a carefully-selected subgroup of patients (Section 4.1).

The most appropriate comparators used in the analysis therefore comprised the nucleos(t)ides adefovir, lamivudine and entecavir and the most commonly-used or most plausible combinations of these drugs (lamivudine plus adefovir, lamivudine plus tenofovir and adefovir plus entecavir[a]). Tenofovir is less costly than adefovir, entecavir or any combination therapy regimen based on drug acquisition cost alone: tenofovir costs £8.50/day, compared with £10.50/day for adefovir and £12.60/day for entecavir (1). Sequences of up to three of these treatments were modelled in order to identify the most cost-effective positioning for each drug. The analysis calculated the costs and benefits of all 211 logically-plausible treatment strategies.

A Markov model was used in the economic evaluation in order to combine evidence from a wide range of sources and allow for the dynamic way in which CHB progresses over a lifetime. A cost-utility analysis, in which health outcomes were quantified in quality-adjusted life-years (QALYs), was conducted in accordance with the NICE reference case.

The model considered a cohort of HBeAg-positive and HBeAg-negative patients with HBV mono-infection and compensated liver disease and included 18 disease states representing CHB progression. Costs for severe disease states and utilities for all states were based on published studies (36-38), while additional cost data were based on expert opinion. Transition probabilities and relative risks were based on the meta-analysis, supplemented where necessary by individual RCTs, non-randomised studies, natural history studies or expert opinion.

The main assumptions comprised:

- Patients were assumed to continue treatment after the development of decompensated cirrhosis, based on expert opinion.
- Tenofovir-treated patients were assumed to receive renal monitoring every four weeks in Year 1, which is not currently routine clinical practice.
- The transition probabilities and resistance rates for lamivudine-resistant patients were applied to patients who were resistant to adefovir, tenofovir and/or entecavir as well as those resistant to lamivudine.
- Most transition probabilities were assumed to be constant over time.
- Although no cases of virologic resistance to tenofovir have yet been identified, the model used resistance rates based on the assumption that the next person to be treated in clinical trials would develop resistance.
- The efficacy of newer combinations was based on relative risks calculated from trials on adefovir+lamivudine.
- The benefits of treatment in severe disease states and the probability of regaining detectable HBV DNA that were observed in studies evaluating adefovir, lamivuidine or telbivudine were applied to all treatments included in the analysis.

[a] Although this combination is not commonly used in UK clinical practice, it was included in the analysis as it represents the most plausible entecavir combination that does not include concomitant use of tenofovir. In particular, it would not be appropriate to use entecavir in combination with lamivudine due to cross-resistance (14).

All assumptions used in the analysis are discussed in detail in Sections 7.2.6.1, 7.2.7.6 and 7.3.4.3. All key assumptions were validated by clinicians and in the majority of cases, conservative assumptions were used that bias the analysis against tenofovir. Furthermore, extensive sensitivity analyses demonstrated that none of these assumptions had any impact on the conclusions.

The base case analysis demonstrates that first-line use of tenofovir is the most cost-effective antiviral strategy for managing both HBeAg-negative and HBeAg-positive CHB if the NHS is willing to pay between £20,000 and £30,000 per QALY gained.

- In HBeAg-positive patients, first-line tenofovir cost £9,940/QALY compared with the next most effective treatment on the frontier (lamivudine then tenofovir).
- In HBeAg-negative patients, first-line tenofovir cost £9,811/QALY compared with the next most effective treatment on the frontier (BSC)
- Subsequently, first-line use of tenofovir would be cost-effective at any ceiling ratios above £9,811/QALY.

First-line use of tenofovir is less costly and generates more QALYs than first-line use of entecavir, adefovir or combination therapy. It is also more cost-effective to use tenofovir first line than to wait until after lamivudine resistance has developed.

Although the choice of second or third-line treatment has minimal impact on total costs or benefits over a lifetime, second-line use of lamivudine or lamivudine plus tenofovir in any patients who may develop tenofovir resistance is likely to be most cost-effective.

Probabilistic sensitivity analysis demonstrated that we can be 60% confident that first-line tenofovir is the most cost-effective antiviral strategy for HBeAg-positive patients at a £20,000/QALY threshold (increasing to 71% if society is willing to pay £30,000/QALY gained). Similarly, there was found to be a 58% probability that first-line tenofovir is the most cost-effective antiviral strategy for HBeAg-negative patients based on a £20,000/QALY ceiling ratio (69% at a £30,000/QALY threshold).

Deterministic sensitivity analyses demonstrated that the results are extremely robust, but highlighted five parameters that could affect the conclusions (Section 7.3.3.2).

Budget impact

The total net budget impact associated with using tenofovir first-line in patients who would otherwise have received other nucleos(t)ides is £744,899 over the next five years, if 50% of newly diagnosed patients receive tenofovir. The total cost of using tenofovir second-line in 50% of the 296 patients developing resistance to currently-available nucleos(t)ides each year is £908,607 over the next five years. If tenofovir is used in 50% of patients who would otherwise have received other nucleos(t)ides, the total anticipated budget impact is £1,653,506 over the next five years. These budget impact calculations exclude the savings that would arise through slowing disease progression and assume that the market share of the more costly nucleos(t)ides would remain stable; subsequently, the true budget impact associated with tenofovir is likely to be substantially lower.

Conclusions

- Tenofovir has been shown to be highly effective in HBeAg-positive and negative patients over two years (19, 20).
- No cases of virologic resistance to tenofovir have yet been identified.
- Tenofovir has a demonstrated safety profile within clinical trials lasting up to two years (19, 20) and in 2 million patient-years of experience in patients with HIV (34).
- Pivotal studies are ongoing and will follow patients over eight years of therapy.
- A mixed treatment comparison meta-analysis demonstrates that tenofovir is significantly superior to all licensed nucleos(t)ides in terms of viral suppression (32).
- The available evidence demonstrates that tenofovir is efficacious in all patients covered by its licensed indication, including both lamivudine-resistant patients (23-25, 27-29, 39), treatment-naïve patients (19, 20) and those who have failed adefovir (16).
- Tenofovir has a lower drug acquisition cost than entecavir, adefovir, telbivudine or any nucleos(t)ide combination licensed for CHB (1).
- First-line use of tenofovir is the most cost-effective strategy for managing CHB.
- Tenofovir also comprises the most cost-effective strategy for patients who have already developed lamivudine resistance.
- Subgroup and sensitivity analyses demonstrate that these results are robust and apply to all of the main patient subgroups.

4. Context

4.1. Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Chronic hepatitis B (CHB) affects over 350 million people worldwide, while over 1 million die annually of hepatitis B virus (HBV)-related chronic liver disease (40, 41). Latest estimates suggest that about 326,000 people in the UK have CHB (4), with 7,700 new cases of CHB arising each year, mostly through immigration (5). If inadequately treated, CHB will lead to liver cirrhosis, the potential for hepatic carcinoma and a risk of disease related death. At later stages of the disease, a liver transplant may be considered an appropriate option. As the disease progresses, the cost of treatment increases and the patient's health decreases.

Current treatment options in the UK include nucleosides (entecavir, lamivudine and telbivudine) and nucleotide analogues (adefovir and tenofovir), as well as interferon therapy (peginterferon-alpha-2a and interferon-alpha-2a/b). The aim of therapy is to reduce HBV DNA and to prevent disease progression.

Interferons are often poorly tolerated (1, 6, 7) and significant clinical endpoints are far more likely to be achived in carefully selected patients (HBeAg positive, low viral load, ALT >3 x ULN and ideally genotype A or B) (8). Approximately 30% of patients who are suitable for treatment with peginterferon-alpha-2a achieve hepatitis B e antigen (HBeAg) seroconversion and/or viral suppression after 48 weeks of therapy (42); the remaining patients are likely to require nucleos(t)ide treatment to achieve sustained viral suppression. It is for this reason that interferons have not been

considered an appropriate comparator for tenofovir in this submission; i.e. patients who are not eligible or for whom interferons have been unsuccessful, would be treated with nucleos(t)ides, of which tenofovir represents one option and the other nucleos(t)ides represent appropriate comparator treatments.

Although nucleos(t)ides are well-tolerated, lamivudine resistance arises rapidly, with up to 70% of patients becoming resistant after four years of continuous therapy (10). However, newer nucleos(t)ides, such as tenofovir and entecavir, are associated with substantially lower resistance rates (11, 14, 39, 43), while also displaying greater efficacy than lamivudine or adefovir (13, 19, 20, 32, 43-46).

Tenofovir-treated patients have a significantly higher probability of achieving undetectable HBV DNA at one year compared with those receiving other nucleos(t)ides licensed in the UK (32, 45). Tenofovir also displays a favourable resistance profile: no cases of virologic HBV resistance have been identified to date over six years of clinical experience in HIV/HBV co-infected patients or up to 96 weeks of continuous use in controlled clinical trials on CHB (19-22) (Section 6.10). These factors make tenofovir an advantageous treatment option for patients with CHB. Furthermore, the European Association for the Study of the Liver (EASL) has recently released practice guidelines that recommend tenofovir should be used as a preferred first-line monotherapy for the treatment of chronic hepatitis B (8).

4.2. What was the rationale for the development of the new technology?

It was necessary to develop new nucleos(t)ide treatment options with improved potency in reducing HBV DNA in addition to reduced risk of treatment resistance versus currently available options.

4.3. What is the principal mechanism of action of the technology?

Tenofovir disoproxil fumarate is the fumarate salt of the prodrug tenofovir disoproxil. Tenofovir disoproxil is absorbed and converted to the active substance tenofovir, which is a nucleoside monophosphate (nucleotide) analogue. Tenofovir is then converted to the active metabolite, tenofovir diphosphate, an obligate chain terminator, by constitutively expressed cellular enzymes. Tenofovir diphosphate inhibits HIV-1 reverse transcriptase and the HBV polymerase by direct binding competition with the natural deoxyribonucleotide substrate and, after incorporation into DNA, by DNA chain termination.

4.4. What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Until the mixed treatment comparison detailed in this submission (32, 45), it was unclear which nucleos(t)ide monotherapy, combination and/or sequence was preferential in terms of potency in reducing HBV DNA. This is because there were no head to head trials comparing the various alternatives. The meta-analysis established that tenofovir-treated patients have a significantly higher probability of achieving undetectable HBV DNA at one year compared with those receiving other nucleos(t)ides licensed in the UK (32, 45).

The Markov model (32, 45) described in this submission established that first-line use of tenofovir is the most cost-effective treatment strategy for patients with CHB who are indicated for nucleos(t)ide therapy at a £20,000-£30,000/QALY threshold

(Section 7). Tenofovir was also found to be the most cost-effective treatment for patients who have already developed resistance to lamivudine (Section 7).

This information, combined with the favourable resistance profile and the fact that these benefits are provided at a lower cost versus comparator treatments (Table 34, Section 7.2.9.6) suggests that tenofovir should be the first-line treatment of choice for patients who are nucleos(t)ide naïve and for patients who have already developed resistance to lamivudine.

4.5. Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

In current clinical practice, the main issues are:

- Older antiviral drugs (particularly lamivudine) have suboptimal viral suppression (32) and are associated with early emergence of viral resistance (9, 10). Although an increasing number of clinicians now use tenofovir or tenofovir plus lamivudine first-line, lamivudine followed by a switch to adefovir (or lamivudine+adefovir combination therapy) remains one of the most commonly used treatment strategies in the UK (Section 7.2.7.5). There are however a number of issues relating to this current treatment pathway. Resistance to lamivudine is estimated to occur in up to 70% of cases after four years of continuous therapy (9, 10). Development of lamivudine resistance increases the risk of disease progression and acute hepatic flare if left untreated. In addition it could also restrict future treatment options due to the potential development of cross-resistance to telbivudine and reduced susceptibility to entecavir (14, 47, 48). The need to prevent resistance in treatment-naïve patients has been recognised in the AASLD and NICE guidelines (49, 50).

- There is uncertainty around the relative efficacy of the newer nucleos(t)ides (tenofovir, entecavir and telbivudine), although the meta-analysis described in Section 6.6 demonstrates that tenofovir is the most effective.

- There is uncertainty around the benefits of combination therapy and a shortage of RCTs evaluating use of two or more nucleos(t)ides in combination.

- Clinicians vary in the tests conducted at routine consultations. Although most clinicians advocate quarterly monitoring with viral load quantification and other tests and generally add in adefovir when lamivudine resistance develops, expert interviews did highlight some variations in the frequency of monitoring and the duration of treatment after HBeAg or HBsAg seroconversion (Appendix 10).

- Although a number of studies have evaluated newer antiviral drugs in lamivudine-resistant patients, there is currently little evidence on the most effective treatments in patients resistant to other antivirals and clinicians vary in their choice of second-line treatments (Section 7.2.7.5).

- Many patients with CHB remain undiagnosed and therefore do not receive treatment until they have already developed severe liver disease (51).

4.6. Provide details of any relevant guidelines or protocols.

The UK National Guideline on the Management of the Viral Hepatitides A, B and C (2005) recommends that patients with CHB should be considered for therapy with lamivudine, adefovir, or interferon-alpha (52). However, since these guidelines were published, new therapies (such as entecavir and tenofovir) have become available.

The SMC has approved adefovir for treatment of CHB in lamivudine-resistant 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 (53). Subsequent NICE guidance (50), recommended adefovir dipivoxil for a similar patient group, but also allowed for its use in lamivudine-naïve patients who are at particular risk of resistance or rapid disease progression (5). The NICE guidance also permitted use of adefovir in combination with lamivudine in the same circumstances.

Entecavir has been appraised by the SMC and is accepted for use within NHS Scotland for the treatment of CHB in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum ALT levels and histological evidence of active inflammation and or fibrosis (54). Telbivudine has not yet been appraised by the SMC.

Entecavir and telbivudine have been appraised by NICE. Entecavir is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated (55). Telbivudine is not recommended for the treatment of CHB (56).

Pegylated interferon-alfa-2a is accepted for use within NHS Scotland for the treatment of HBeAg-positive or HBeAg-negative CHB in adult patients with compensated liver disease and evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis (57). Subsequent NICE guidance, has recommended peginterferon-alfa-2a as a possible first-line treatment for adults with either HBeAg-positive or HBeAg-negative CHB (50).

The European Association for the Study of the Liver (EASL) has recently released practice guidelines that recommend tenofovir should be used as a preferred first-line monotherapy for the treatment of chronic hepatitis B (8).

5. Equity and equality

5.1. Identification of equity and equalities issues

At present, there are large disparities in care provision across the UK. Expert interviews suggested that there are substantial variations in clinical practice between clinics. A survey of 41 specialists from 33 NHS trusts conducted in 2004 suggested that the proportion of patients with CHB who were receiving treatment varied from 10% to 80% between centres (51). Although access to nucleos(t)ide treatment is likely to have improved following the 2004 NICE and SMC guidance, expert interviews suggested that some patients are not referred to specialist centres, while others remain undiagnosed. Expert interviews also suggested that tenofovir is now commonly used in England and Wales. This NICE appraisal raises a further equity issue, as the AWMSG and SMC have recommended that tenofovir should be used in Wales and Scotland in accordance with its licensed indications, whereas PCTs in England are still waiting for this recommendation.

Variations in other aspects of disease management, such as frequency of monitoring, suggest that treatment at some centres may be inefficient and that the quality of care differs between hospitals. Clear evidence-based protocols might reduce such variations and enable more efficient and more equitable treatment of patients in this disease area.

Chronic hepatitis B is more common among ethnic minorities, people living in deprived areas and those of lower social class (58) and around 96% of new cases of CHB in England and Wales involve people who have emigrated into this country (59). Many of these people do not speak English and may be less likely to seek treatment.

Although there is currently limited evidence on the impact of tenofovir on the risk of infecting other people with HBV, transmission has not been documented in patients with viral load below 4,000 copies/mL (60), most European countries permit health professionals with viral load below 1,000-10,000 copies/mL to perform exposure-prone procedures (60) and lamivudine has been shown to reduce the risk of vertical transmission from mother to child (61, 62). Since tenofovir allows at least 74% of people to achieve HBV DNA <300 copies/mL (19, 20), it is therefore likely that treatment will also reduce the risk of transmission, in addition to the benefits to the patient treated.

How has the analysis addressed these issues?

In clinical practice there is uncertainty about which is the most effective of the newer agents and also about the order of giving entecavir and tenofovir. This creates disparity of practice. The evidence in this submission examines many different treatment variations and provides a clear pathway based on clinical and cost-effectiveness that, if adhered to, should reduce treatment disparity for CHB.

Additional equity issues raised by the results of the economic evaluation are discussed in Section 7.3.4.5.

6. Clinical evidence

6.1. Identification of studies

A systematic review was conducted to identify all papers relating to the use of tenofovir, entecavir, telbivudine,[b] lamivudine and/or adefovir dipivoxil in the treatment of CHB. The main inclusion criteria are summarised below and full details are given in Appendix 2.

Subjects

- Entire study population chronically infected with HBV, or reported results separately for a subgroup of patients with CHB. The presence of comorbidities or co-infection with HCV or other viruses did not limit inclusion.
- Studies specifically recruiting children (<18 years) were excluded.

Intervention

- Evaluated ≥1 of the following treatments: 300 mg/day tenofovir; 10 mg/day adefovir; 0.5 mg/day or 1 mg/day entecavir; 600 mg/day telbivudine; 100 mg/day or 150 mg/day lamivudine; or any combination of the above treatments.

Study type and size

- Studies evaluating tenofovir in HBV mono-infection or populations in which <50% of patients were co-infected with HIV were included if they were: RCTs; systematic reviews or meta-analyses; non-randomised studies with >50 patients; or non-randomised studies with a control group or crossover from one nucleos(t)ide to another.
- Studies evaluating entecavir, lamivudine, adefovir or telbivudine and those evaluating tenofovir in populations in which ≥50% of patients were co-infected with HIV were included if they were: RCTs; systematic reviews or meta-analyses; non-randomised studies in which ≥50 patients were followed up for ≥2 years; or pooled analyses on resistance.

Date of publication

- No limit on date of publication, although searches for studies on adefovir and lamivudine were limited to those published in July 2004 onwards as earlier studies were identified in previous systematic reviews (63, 64).

Language of publication

- Inclusion was not limited to published trials. Language limited inclusion only if no English translation was available from the British Library.

Searches on entecavir, telbivudine and tenofovir were not subject to any limits by date. Searches were conducted from 1st July 2004 onwards for adefovir and lamivudine as previous systematic reviews using similar inclusion criteria have been conducted for these agents up until this point. (63-65).

A total of 1,272 publications were identified for in inclusion in the systematic review (57 of which were identified by hand[c]), 170 of which met the inclusion criteria (Figure

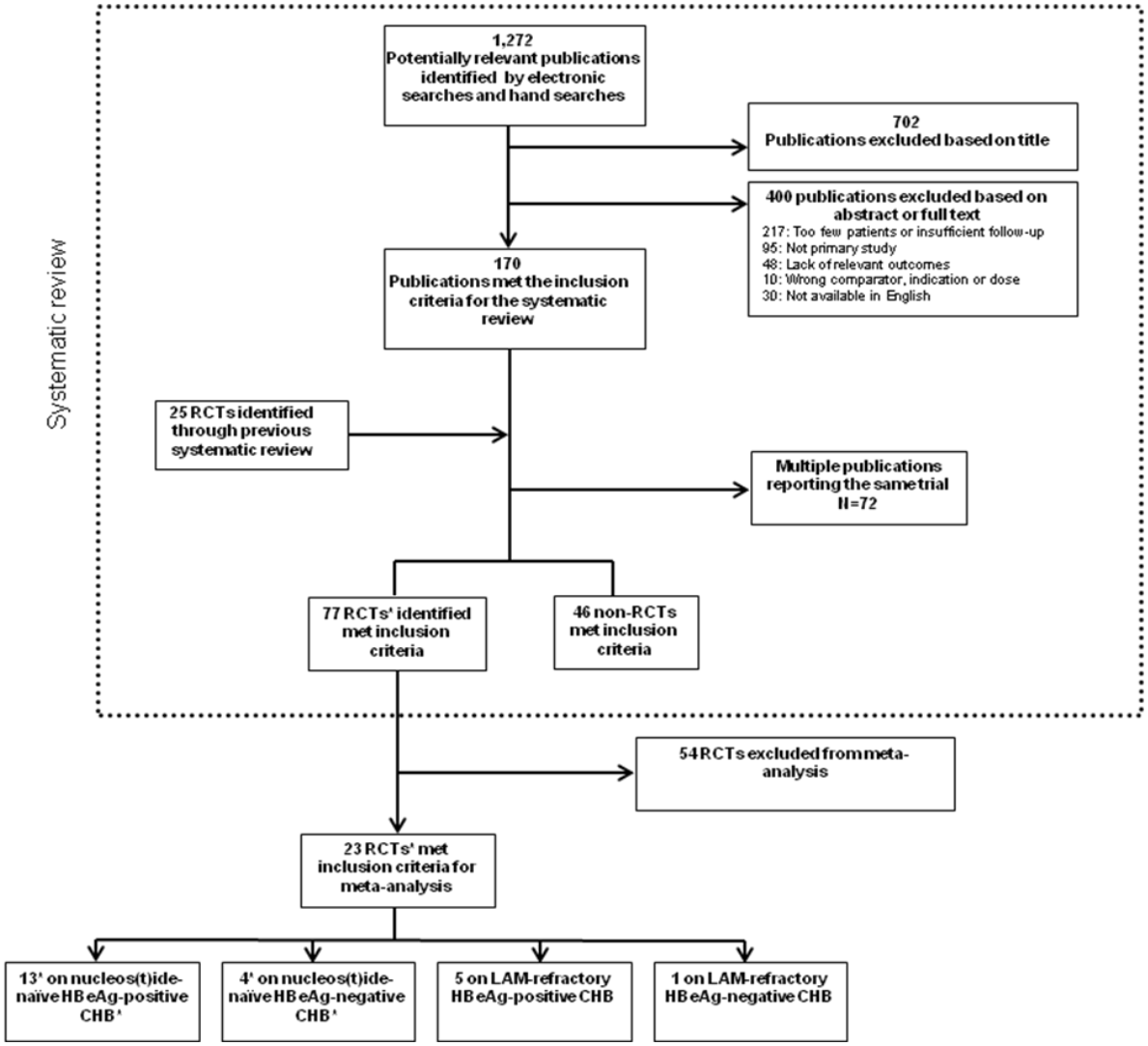
[b] Telbivudine was included as a comparator in the systematic review and meta-analysis as the techniques of mixed treatment comparison meta-analysis allow evidence from telbivudine trials to inform the comparison between tenofovir and treatments that are used more widely in clinical practice. Interferon and peginterferon were excluded from the analysis as they are not direct alternatives to tenofovir in clinical practice because taking account of the various dosing schedules and forms of interferon would substantially complicate the analysis and as studies evaluating interferons frequently include 24–52 weeks of treatment and 24 weeks of follow up with no therapy.

[c] The main literature searches were conducted by carrying out a systematic search of electronic databases. In addition, a number of other references were identified from the reference lists of reviews identified in literature searches, from contact with Gilead and clinicians and from lists of abstracts being presented at AASLD 2007.

1). Of these, there were 52[d] RCTs; 46 non-randomised studies; and 22 follow-up studies of RCTs counted elsewhere. The RCTs comprised 7 studies on tenofovir; 14 studies on entecavir; 4[c] studies on telbivudine; 7 studies that compared adefovir with lamivudine or placebo; and 20 studies comparing lamivudine with placebo or non-nucleos(t)ide treatment. Together with results from the earlier systematic review (eight on adefovir and 17 on lamivudine), there were a total of 15 studies for adefovir and 37 for lamivudine.

To date, no completed RCT has directly compared tenofovir with any treatment other than adefovir, although trials comparing tenofovir monotherapy with tenofovir plus emtricitabine (67) and/or entecavir monotherapy are underway (68) (Section 6.2.5). Subsequently, indirect comparisons are necessary in order to compare the efficacy of tenofovir with that of entecavir, lamivudine and telbivudine. A mixed treatment comparison has been performed as part of this submission (32); this will be described in section 6.6. The meta-analysis was presented as a poster at the European Association for the Study of the Liver conference in April 2008 (32).

Figure 1[†]: Flow diagram showing study identification for the systematic review



[d] The GLOBE study (66) was included as two trials: one on HBeAg-positive patients and one on HBeAg-negative patients. [†] In response to comments from the Evidence Review Group, this figure is an amended version of the original. * The GLOBE study (66) was included as two trials: one on HBeAg-positive patients and one on HBeAg-negative patients.

6.2. Study selection

6.2.1. Complete list of tenofovir RCTs

A complete list of RCTs comparing tenofovir with other therapies in the relevant patient groups is shown in Table 1.

Table 1: Complete list of randomised controlled trials comparing tenofovir with other therapies

Trial no.	Study design	Treatment arms	Patient population	Reference
Study 0102	Phase III, randomised, double-blind, active comparator	Tenofovir 300 mg o.d.; Adefovir 10 mg o.d.	Treatment naive HBeAg-negative	**(20, 33)**
Study 0103	Phase III, randomised, double-blind, active comparator	Tenofovir 300 mg o.d.; Adefovir 10 mg o.d.	Treatment naive HBeAg-positive	**(19, 26)**
Study 0106	Phase II, randomised, double-blind	Tenofovir 300 mg o.d.; Emtricitabine/tenofovir 200 mg/300 mg combination tablets	HBeAg-positive and HBeAg-negative currently treated with adefovir dipivoxil 10 mg o.d. and having persistent viral replication	**(69)**
Study 0108	Phase II, double-blind	Tenofovir 300 mg o.d.; Emtricitabine 200 mg + tenofovir 300 mg; Entecavir 0.5 mg or 1 mg o.d.	Adult subjects with CHB who have developed decompensated liver disease	**(68)**
Study 0121[†]	Phase IIIb, randomised, double-blind, double-dummy	Tenofovir 300 mg o.d.; Emtricitabine/tenofovir 200 mg/300 mg combination tablets	HBeAg-positive and HBeAg-negative with lamivudine resistance	**(70)**
ACTG 5127	Randomised, double-blind, placebo-controlled	Tenofovir 300 mg o.d.; Adefovir 10 mg o.d.	HIV/HBV co-infected patients	**(71)**
Study 903	Phase III, randomised, double-blind	Tenofovir 300 mg o.d. + lamivudine 150 mg b.d.; Lamivudine 150 mg b.d.	HIV/HBV co-infected patients, antiretroviral therapy-naive	**(72)**
Study 907	Phase III, randomised, double-blind	Tenofovir 300 mg o.d.; Placebo	HIV/HBV co-infected patients, antiretroviral therapy-experienced	**(23)**

[†] This study has been included in this table for completeness, it is an ongoing trial and was not identified as part of the systematic review. **Abbreviations**; b.d., twice daily; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; o.d., once daily

6.2.2. Inclusion and exclusion criteria for tenofovir RCTs

Trials including co-infected patients (ACTG, study 903 and study 907) were identified but not included in the base case analysis of the mixed treatment comparison or the model. However, a sensitivity analysis to the mixed treatment comparison was conducted which included these trials and this sensitivity analysis was used to supply data on lamivudine-resistant patients for the model due to a paucity of data pertaining to this patient group. Studies 0108 and 0121 are current ongoing studies.

6.2.3. List of relevant tenofovir RCTs

The relevant tenofovir RCTs are shown in Table 2. The methodologies and results of these trials are presented in sections 6.3 and 6.4.

Table 2: Relevant RCTs evaluating the safety and efficacy of tenofovir in the management of CHB

Trial no.	Title	Drug dosages	Comparator	Population	Design	Duration	Objectives
Study 0102 (20, 33)	A randomised, double-blind, controlled evaluation of tenofovir versus adefovir dipivoxil for the treatment of presumed pre-core mutant chronic hepatitis B	Tenofovir 300 mg o.d.; Adefovir 10 mg o.d.	Adefovir	Treatment naive HBeAg-negative	Phase III, randomised, double-blind, active comparator	48 weeks followed by open label tenofovir 300 mg o.d. through week 384	Efficacy/safety of tenofovir for the treatment of presumed pre-core mutant CHB
Study 0103 (19, 26)	A randomised, double-blind, controlled evaluation of tenofovir versus adefovir dipivoxil for the treatment of HBeAg positive chronic hepatitis B	Tenofovir 300 mg o.d.; Adefovir 10 mg o.d.	Adefovir	Treatment naive HBeAg-positive	Phase III, randomised, double-blind, active comparator	48 weeks followed by open label tenofovir 300 mg o.d. through week 384	Efficacy/safety of tenofovir for the treatment of HBeAg-positive CHB
Study 0106 (69)	A Phase II, randomised, double-blind study exploring the efficacy, safety and tolerability of tenofovir disoproxil fumarate monotherapy versus emtricitabine plus tenofovir fixed-dose combination therapy in subjects currently being treated with adefovir dipivoxil for chronic hepatitis B and having persistent viral replication	Tenofovir 300 mg o.d.; Emtricitabine/tenofovir 200 mg/300 mg combination tablets	Emtricitabine /tenofovir combination therapy	HBeAg-positive and HBeAg-negative currently treated with adefovir dipivoxil 10 mg o.d. and having persistent viral replication	Phase II, randomised, double-blind	48 weeks double-blind. Subjects with HBV DNA ≥ 400 copies/mL at week 24 or later may switch to open-label emtricitabine/tenofovir through week 168	Efficacy, safety and tolerability of tenofovir

Co-infected studies excluded as detailed in previous section.
Abbreviations; o.d., once daily; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen

6.2.4. List of relevant tenofovir non-randomised controlled trials

The relevant tenofovir non-RCTs are shown in Table 3. The methodologies and results of these trials are presented in section 6.8.

Table 3: List of relevant non-RCT evidence

Trial	Title of study	Study type	Treatment arm	Patient population	Max follow up	Justification for inclusion
Van Bommel et al 2007 (25)	First multicenter evaluation of the efficacy of tenofovir in nucleos(t)ide analog experienced patients with HBV monoinfection	Retrospective multi-centre analysis	TDF 300 mg o.d.	Lamivudine treated CHB with/without prior adefovir therapy	63 mths	Includes five years of follow-up and resistance surveillance in lamivudine resistant patients
Van Bommel et al 2006 (24)	No evidence for tenofovir resistance in patients with lamivudine-resistant HBV infection during long-term treatment for up to 5 years	Retrospective	TDF 300 mg o.d.	chronic lamivudine-resistant HBV infection and different co-morbidities. 24 patients were HIV/HBV co infected and 47 HBV mono infected	61 mths	Includes five years of follow-up and resistance surveillance in lamivudine resistant patients
Im et al 2005 (27)	Comparison of tenofovir versus adefovir based combination therapy in subjects with chronic hepatitis B	Retrospective database study	TDF + FTC TDF + lamivudine ADV + FTC ADV + lamivudine	CHB patients receiving combination nucleos(t)ide analog therapy for minimum of 6 months (20/30 HBeAg-positive)	31 months	Directly compares adefovir plus lamivudine with tenofovir plus lamivudine and Truvada
Hann et al 2006 (28)	Tenofovir (TDF) has stronger antiviral effect than adefovir dipivoxil (ADV) against lamivudine (LAM) resistant hepatitis B virus (HBV)	Retrospective	TDF TDF + lamivudine ADV ADV + lamivudine	LAM-resistant HBV	24 mths	Directly compares adefovir plus lamivudine with tenofovir plus lamivudine in addition to comparing adefovir and tenofovir monotherapy
Van Bommel et al 2004 (29)	Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection	Open-label	TDF 300 mg o.d. ADV 10 mg o.d.	Lamivudine-resistant CHB	130 wks	Directly compares adefovir with tenofovir in lamivudine resistant patients

Van Bommel et al 2006 (30, 31)[e]	Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy	Retrospective	TDF 300 mg o.d.	Lamivudine-resistant CHB with persistent viral replication after 15 months of ADV monotherapy	28 mths	Evaluates tenofovir in patients who are resistant to lamivudine and have failed to respond to adefovir

Abbreviations; ADV, adefovir; CHB, chronic hepatitis B; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HIV; human immunodeficiency virus; LAM, lamivudine; mths, months; o.d., once daily; TDF, tenofovir; wks, weeks

[e] These studies are counted as one study as their description of the patient populations suggests that the full paper (31) includes 100% of the patients in the abstract (30).

6.2.5. Ongoing tenofovir studies

A list of ongoing tenofovir studies is shown in Table 4.

Table 4: List of ongoing tenofovir studies

Study name/ number	Study objectives	Study design	Study interventions	Primary/ relevant outcome measured	Main inclusion criteria	Anticipated date of completion
Study 0102	See Table 2	Long-term follow-up of RCT	After the 48-week double-blind phase of the trial, all patients were switched to open-label tenofovir. Any patients with HBV DNA ≥400 copies/mL at week 72 were permitted to switch to tenofovir plus emtricitabine at the discretion of the investigator.	See Table 10	See Table 6	2011
Study 0103	See Table 2	Long-term follow-up of RCT		See Table 10	See Table 6	2011
Study 0106 (69)	See Table 2	Long term follow-up of RCT	Oral tenofovir 300 mg o.d. + emtricitabine/tenofovir placebo tablet Oral emtricitabine 200 mg/tenofovir 300 mg o.d. + tenofovir placebo tablet	See Table 10	See Table 6	2010
Study 0108 (68)	Primary: Evaluate and compare safety and tolerability of tenofovir; emtricitabine + tenofovir; and entecavir for treatment of subjects with CHB and decompensated liver disease Secondary: Provide a preliminary assessment of efficacy of tenofovir; emtricitabine + tenofovir; and entecavir for treatment of subjects with CHB and decompensated liver disease a) determine the probability of remaining free from HBV recurrence post-transplantation; b) determine the incidence and patterns of	Randomised, double-blind, multicentre	Tenofovir 300 mg + emtricitabine/tenofovir placebo + entecavir placebo o.d. Emtricitabine 200 mg /tenofovir 300 mg + tenofovir placebo + entecavir placebo o.d. Entecavir 0.5 mg or 1 mg + tenofovir placebo + emtricitabine/tenofovir placebo o.d.	Co-primary endpoints in this exploratory study will include: Proportion of subjects experiencing tolerability failure. Tolerability failure is defined as permanent discontinuation of study drug due to a treatment-emergent AE. Any patient that temporarily discontinues study drug due to an AE but does not restart study drug will be considered a tolerability failure. Proportion of subjects with a confirmed increase in serum creatinine of ≥ 0.5 mg/dL from baseline or a confirmed serum phosphorus < 2.0 mg/dL.	Adult subjects with CHB who have decompensated liver disease; plasma HBV DNA ≥10^3 copies/mL; CPT score of 7–12; ALT<10× ULN; no evidence of HCC; HCV, HIV, and HDV negative; no prior use of tenofovir or entecavir; <12 months prior adefovir	2011

Study name/ number	Study objectives	Study design	Study interventions	Primary/ relevant outcome measured	Main inclusion criteria	Anticipated date of completion
	drug resistance mutations in HBV DNA polymerase					
Study 0121 (70)	Primary: To compare the antiviral efficacy against HBV of tenofovir versus emtricitabine + tenofovir combination treatment in subjects with lamivudine resistance. Secondary: To evaluate the safety/tolerability of tenofovir versus emtricitabine + tenofovir in lamivudine resistant subjects; to evaluate biochemical and serological responses; to compare changes in the resistance profile of each treatment arm; to evaluate the steady-state pharmacokinetics of tenofovir in subjects with lamivudine resistance.	Randomised, double-blind, double dummy, 240 week study	Oral tenofovir 300 mg o.d. + emtricitabine/tenofovir placebo tablet Oral emtricitabine 200 mg/tenofovir 300 mg o.d. + tenofovir placebo tablet	The primary efficacy endpoint is HBV DNA <400 copies/mL at Week 48 (and every 48 weeks thereafter).	Adults currently receiving lamivudine for CHB, HBeAg-positive or –negative, and are naïve to tenofovir. Subjects must have HBV DNA > 4 $\log_{10}$ copies/mL at screening; confirmation of HBV reverse transcriptase mutation known to confer resistance to lamivudine; CL_{CR} ≥ 50mL/min; ALT <10 x ULN; no evidence of HCC; HCV, HIV and HDV negative. Previous treatment with interferon ended >6 months prior to screening	2014

Abbreviations; AE, adverse event; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CPT, Child-Pugh-Turcotte; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HDV, hepatitis D virus; o.d., once daily; RCT, randomised controlled trial; ULN, upper limit of normal;

6.3. Summary of methodology of relevant tenofovir RCTs

The methodology of the relevant tenofovir RCTs is summarised in tabular form in the following sections.

6.3.1. Methods

Table 5: Tenofovir RCT design

RCT	Interventions	Duration	Degree and method of blinding	Randomisation
Study 0102 **Study 0103** As trials 0102 and 0103 had virtually identical methodologies they have been combined here, with any differences between the studies highlighted.	T DF 300 mg o.d. versus ADV 10 mg o.d. All patients treated as outpatients.	The duration of the double-blind treatment period was 48 weeks. The overall study duration is 384 weeks. At Week 48 eligible subjects were switched to open-label TDF 300 mg o.d., and continued on open-label TDF through Week 240. Subjects with confirmed HBV DNA ≥ 400 copies/mL from Week 72 onward are eligible to switch to open-label FTC 200 mg/TDF 300 mg o.d.	The study was double-blind for the first 48 weeks. Subjects electing to continue open-label treatment with TDF after Week 48, as well as investigators, were to remain blinded to their original treatment assignment throughout the study. A double-dummy placebo approach was used to maintain the double blind. All subjects received both active randomised study drug and placebo tablets to maintain subject blinding.	Study 0102 Subjects were randomised in a 2:1 ratio to either TDF 300 mg o.d. or ADV 10 mg o.d. for 48 weeks, and randomisation was stratified on the basis of prior lamivudine or FTC exposure at screening and geographic location. Study 0103 Subjects were randomised in a 2:1 ratio to either TDF 300 mg o.d. or ADV 10 mg o.d. for 48 weeks, and randomisation was stratified on the basis of screening ALT value and geographic region.
Study 0106	TDF 300 mg o.d. monotherapy versus fixed-dose combination of FTC 200 mg o.d./TDF 300 mg o.d. Subjects were instructed to take two tablets of study medication daily (one from each bottle; i.e., one active tablet and one placebo tablet), without regard to the timing or content of meals.	Study duration is 168 weeks. Subjects with confirmed (within 4 weeks) plasma HBV DNA ≥ 400 copies/mL during double blind treatment at Week 24 or any time thereafter have the option of receiving 12 weeks of open-label FTC/TDF, which may be continued through the end of the 168-week treatment period if there is a virologic response (HBV DNA <400 copies/mL). Alternatively, subjects with confirmed HBV DNA ≥ 400 copies/mL at or any time after Week 24 of double blind treatment can discontinue the study and initiate commercially available HBV therapy rather than initiate open-label FTC/TDF.	Double dummy matching placebos were used to preserve the double-blind. The placebo tablets were visually indistinguishable from the product they were designed to resemble (TDF or FTC/TDF combination tablets). All subjects received both active randomised study drug and placebo tablets to maintain subject blinding.	Subjects were randomised 1:1 to switch from ADV to either TDF 300 mg o.d. monotherapy or the fixed-dose combination of FTC 200 mg o.d./TDF 300 mg o.d.; randomisation was stratified by history of lamivudine experience (< 12 weeks vs. ≥ 12 weeks of lamivudine therapy) and HBeAg status at screening.

Abbreviations; ADV, adefovir; ALT, alanine aminotransferase; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; o.d., once daily; TDF, tenofovir

6.3.2. Participants

6.3.2.1. Inclusion and exclusion criteria

Table 6: Details of the inclusion and exclusion criteria for the relevant tenofovir RCTs

	Inclusion Criteria	Exclusion Criteria

Studies 0102 and 0103 (26, 33)
 	
As trials 0102 and 0103 had virtually identical methodologies they have been combined here, with any differences between the studies highlighted.
	• Chronic HBV infection (positive serum HBsAg for at least 6 months)
	• Aged 18–69 years;
	• Raised ALT levels
	  o Trial 0102: ALT greater than the upper limit of normal (ULN)
	  o Trial 0103: ALT >2 x ULN
	• ALT no more than 10× ULN
	• HBV DNA >10^5 copies/mL at screening for 0102 and >10^6 copies/mL for 0103
	• Creatinine clearance ≥ 70 mL/min haemoglobin ≥ 8 g/dL
	• Neutrophils ≥ 1000/mm^3
	• Knodell necroinflammatory score ≥ 3 and Knodell fibrosis score <4 (up to 120 subjects with cirrhosis (Knodell fibrosis score of 4) were eligible)
	• Negative serum beta human chorionic gonadotropin (β-hCG)
	• Nucleoside naïve
	  o up to 120 subjects with >12 weeks of prior lamivudine or emtricitabine experience were eligible to enter study 0102
	• Willing and able to provide written informed consent
	• Had a liver biopsy performed within 6 months of screening and had readable biopsy slides or agreed to have a biopsy performed prior to baseline
	
	Subjects in study 0102 were required to have active HBeAg− chronic HBV infection, with HBeAg− and anti-HBe+ at screening (33), while those in study 0103 were required to have active HBeAg+ chronic HBV infection (26).
		• Pregnant or lactating women;
		• Women who believed they may wish to become pregnant during the course of the study;
		• Males and females of reproductive potential who were unwilling to use an effective method of contraception during the study; for males, condoms were to be used, and for females a barrier contraception method was to be used;
		• Decompensated liver disease, defined as conjugated bilirubin >1.5 × ULN, prothrombin time (PT) >1.5 × ULN, platelets <75,000/mm^3, serum albumin <3.0 g/dL, or prior history of clinical hepatic decompensation;
		• Prior therapy with any nucleoside, nucleotide, or interferon within 6 months of the pretreatment biopsy;
		• Evidence of HCC;
		• Coinfection with hepatitis C virus (HCV), HIV, or hepatitis D virus (HDV);
		• Significant renal, cardiovascular, pulmonary, or neurological disease;
		• History of solid organ or bone marrow transplantation;
		• Currently receiving therapy with immunomodulators, investigational agents, nephrotoxic agents, or agents capable of modifying renal excretion;
		• Current proximal tubulopathy;
		• Known hypersensitivity to the study drugs, metabolites, or formulation excipients.

	Inclusion Criteria	Exclusion Criteria
Study 0106	• Chronic HBV infection (positive serum HBsAg for at least 6 months) • Age 18- 69 years • Active chronic HBV infection with all the following: o Currently treated with adefovir dipivoxil 10 mg o.d. (for ≥ 24 weeks but ≤ 96 weeks) o HBeAg+ or HBeAg– at screening o Plasma HBV DNA ≥ 1000 copies/mL at screening o ALT < 10 × ULN o Creatinine clearance ≥ 70 mL/min by the following formula: $\frac{(140-\text{age [years]})\ (\text{body weight [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$ o Hemoglobin ≥ 8 g/dL o Neutrophils ≥ 1000 /mm^3 • Nucleoside naïve or lamivudine experienced (≥ 12 weeks of therapy) • Negative serum beta human chorionic gonadotropin (β-hCG) • Compliant with adefovir dipivoxil • Willing and able to provide written informed consent	• Pregnant women and women who were breastfeeding or who believed they may wish to become pregnant during the course of the study • Male or females of reproductive potential who were unwilling to use an effective method of contraception while enrolled in the study; for males, condoms were to be used and for females, a barrier contraception method was to be used • Decompensated liver disease defined as conjugated bilirubin > 1.5 × ULN, prothrombin time (PT) > 1.5 × ULN, platelets < 75,000/mm^3, serum albumin < 3.0 g/dL, or prior history of clinical hepatic decompensation (e.g., ascites, jaundice, encephalopathy, variceal hemorrhage) • Prior use of tenofovir or entecavir • Received treatment with interferon or pegylated interferon within 6 months of the screening visit • Evidence of HCC; for example, α-fetoprotein > 50 ng/mL, or by any other standard-of-care measure • Coinfection with HCV (based on serology), HIV, or HDV • Significant renal, cardiovascular, pulmonary, or neurological disease • Received solid organ or bone marrow transplantation • Currently receiving therapy with immunomodulators (e.g., corticosteroids, etc.), investigational agents, nephrotoxic agents, or agents capable of modifying renal excretion • Proximal tubulopathy • Known hypersensitivity to tenofovir or emtricitabine/tenofovir , tenofovir or emtricitabine or their phosphorylated forms, or study drug product formulation excipients

6.3.2.2. Patient characteristics at baseline

Patient characteristics at baseline for the relevant tenofovir RCTs are given in Tables 7, 8 and 9.

Table 7: Patient characteristics at baseline (RAT analysis set): Study 0102

Characteristic	Tenofovir (N=250)	Adefovir (N=125)	Overall (N=375)	P-value
Age (years)				
Mean (SD)	44 (10.6)	43 (10.0)	44 (10.4)	0.304
Race				
White	161 (64.4%)	81 (64.8%)	242 (64.5%)	
Asian	63 (25.2%)	30 (24.0%)	93 (24.8%)	
Other	11 (4.4%)	8 (6.4%)	19 (5.1%)	
Black	8 (3.2%)	4 (3.2%)	12 (3.2%)	
Pacific Islander	7 (2.8%)	2 (1.6%)	9 (2.4%)	
Sex				
Male	193 (77.2%)	97 (77.6%)	290 (77.3%)	0.931
BMI (kg/m^2)				
N	247	124	371	
Mean (SD)	25.7 (4.34)	26.3 (3.95)	25.9 (4.21)	0.102
Geographic region				0.888
Europe	158 (63.2%)	76 (60.8%)	234 (62.4%)	
North America	53 (21.2%)	29 (23.2%)	82 (21.9%)	
Australia/New Zealand	39 (15.6%)	20 (16.0%)	59 *15.7%)	
HBV DNA (Log_{10} copies/mL)				
Mean (SD)	6.86 (1.308)	6.98 (1.266)	6.90 (1.294)	0.527
Baseline ALT above ULN?				
No	14 (5.6%)	7 (5.6%)	21 (5.6%)	1.000
Baseline ALT strata				
≤ 2x ULN	96 (38.4%)	39 (31.2%)	135 (36.0%)	0.171
Previous lamivudine/emtricitabine experience (>12 weeks)				
No	207 (82.8%)	102 (81.6%)	309 (82.4%)	0.774
Previous interferon experience				
No	208 (83.2%)	102 (81.6%)	310 (82.7%)	0.700
HBV genotype				0.588
A	28 (11.5%)	14 (11.2%)	42 (11.4%)	
B	22 (9.1%)	17 (13.6%)	39 (10.6%)	
C	29 (11.9%)	12 (9.6%)	41 (11.1%)	
D	156 (64.2%)	79 (63.2%)	235 (63.9%)	
E	5 (2.1)	2 (1.6)	7 (1.9)	
F	1 (0.4%)	0 (0.0%)	1 (0.3%)	
G	0 (0.0%)	1 (0.8%)	1 (0.3%)	
H	2 (0.8%)	0 (0.0%)	2 (0.5%)	
Missing/unevaluable	7	0	7	

Abbreviations; ALT, alanine aminotransferase; HBV, hepatitis B virus; RAT, randomised and treated; SD, standard deviation; ULN, upper limit of normal

Table 8: Patient characteristics at baseline (RAT analysis set): Study 0103

Characteristic	Tenofovir (N=250)	Adefovir (N=125)	Overall (N=375)	P-value
Age (years)				
Mean (SD)	44 (10.6)	43 (10.0)	44 (10.4)	0.304
Race				
White	161 (64.4%)	81 (64.8%)	242 (64.5%)	
Asian	63 (25.2%)	30 (24.0%)	93 (24.8%)	
Other	11 (4.4%)	8 (6.4%)	19 (5.1%)	
Black	8 (3.2%)	4 (3.2%)	12 (3.2%)	
Pacific Islander	7 (2.8%)	2 (1.6%)	9 (2.4%)	
Sex				
Male	193 (77.2%)	97 (77.6%)	290 (77.3%)	0.931
BMI (kg/m^2)				
N	247	124	371	
Mean (SD)	25.7 (4.34)	26.3 (3.95)	25.9 (4.21)	0.102
Geographic region				0.888
Europe	158 (63.2%)	76 (60.8%)	234 (62.4%)	
North America	53 (21.2%)	29 (23.2%)	82 (21.9%)	
Australia/New Zealand	39 (15.6%)	20 (16.0%)	59 *15.7%)	
HBV DNA (Log_{10} copies/mL)				
Mean (SD)	6.86 (1.308)	6.98 (1.266)	6.90 (1.294)	0.527
Baseline ALT above ULN?				
No	14 (5.6%)	7 (5.6%)	21 (5.6%)	1.000
Baseline ALT strata				
≤2x ULN	96 (38.4%)	39 (31.2%)	135 (36.0%)	0.171
Previous lamivudine/emtricitabine experience (>12 weeks)				
No	207 (82.8%)	102 (81.6%)	309 (82.4%)	0.774
Previous interferon experience				
No	208 (83.2%)	102 (81.6%)	310 (82.7%)	0.700
HBV genotype				0.588
A	28 (11.5%)	14 (11.2%)	42 (11.4%)	
B	22 (9.1%)	17 (13.6%)	39 (10.6%)	
C	29 (11.9%)	12 (9.6%)	41 (11.1%)	
D	156 (64.2%)	79 (63.2%)	235 (63.9%)	
E	5 (2.1)	2 (1.6)	7 (1.9)	
F	1 (0.4%)	0 (0.0%)	1 (0.3%)	
G	0 (0.0%)	1 (0.8%)	1 (0.3%)	
H	2 (0.8%)	0 (0.0%)	2 (0.5%)	
Missing/unevaluable	7	0	7	

Abbreviations; ALT, alanine aminotransferase; HBV, hepatitis B virus; RAT, randomised and treated; SD, standard deviation; ULN, upper limit of normal

Table 9: Patient characteristics at baseline (RAT analysis set): Study 0106

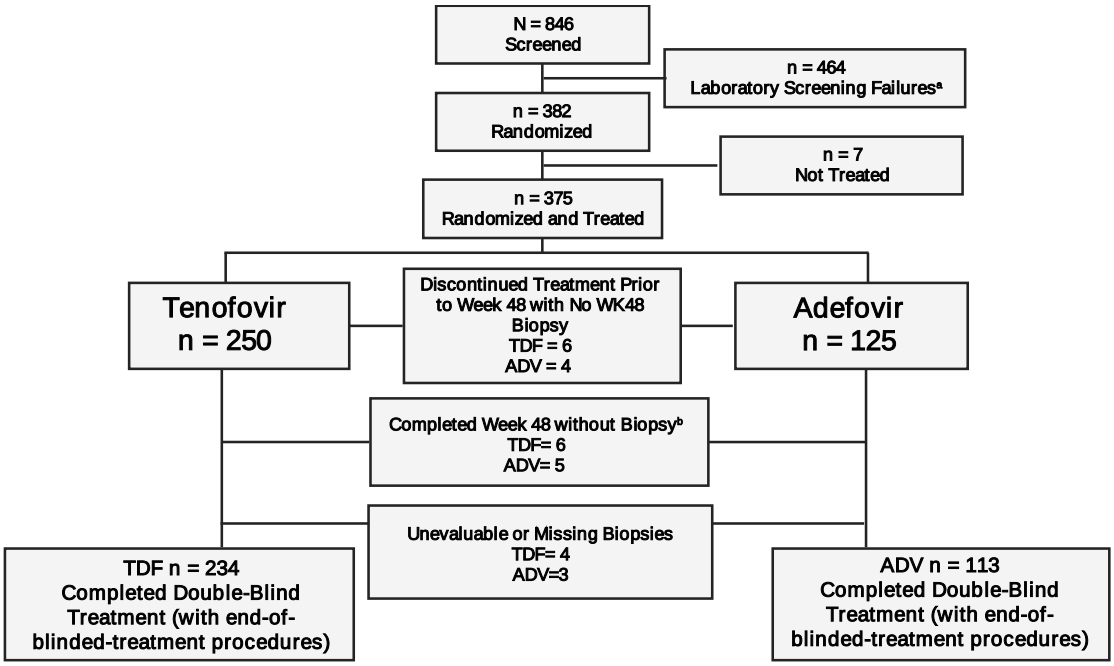
Characteristic	TDF (N=53)	FTC/TDF (N=52)	Overall (N=105)	P-value
Age (years)				
Mean (SD)	40 (11.4)	39 (10.4)	39 (10.9)	0.331
Race				
White	23 (43.4%)	21 (40.4%)	44 (41.9%)	
Asian	26 (49.1%)	18 (34.6%)	44 (41.9%)	
Other	2 (3.8%)	5 (9.6%)	7 (6.7%)	
Black and African American	2 (3.8%)	8 (15.4%)	10 (9.5%)	
Sex				
Male	38 (71.7%)	42 (80.8%)	80 (76.2%)	0.214
BMI (kg/m^2)				
N	49	52	101	
Mean (SD)	25.9 (5.95)	24.9 (3.45)	25.4 (4.83)	0.696
HBV DNA (Log_{10} copies/mL)				
Mean (SD)	6.06 (1.430)	5.87 (1.779)	5.97 (1.607)	0.208
Baseline ALT above ULN?				
No	26 (49.1%)	26 (50.0%)	52 (49.5%)	0.862
Baseline ALT as multiple of ULN				
Mean (SD)	1.45 (1.429)	1.94 (3.008)	1.69 (2.349)	0.630
Baseline HBeAg				
Negative	15 (28.3%)	13 (25.0%)	28 (26.7%)	
Positive	38 (71.7%)	39 (75.0%)	77 (73.3%)	
Previous lamivudine experience				
No	23 (43.4%)	21 (40.4%)	44 (41.9%)	
Previous interferon experience				
No	43 (81.1%)	38 (73.1%)	81 (77.1%)	0.314
Duration of previous Adefovir treatment (days)				
N	52	52	104	
Mean (SD)	431.2 (178.57)	413.4 (183.39)	422.3 (180.34)	0.305
HBV genotype				
A	11 (20.8%)	9 (17.3%)	20 (19.0%)	0.815
B	6 (11.3%)	4 (7.7%)	10 (9.5%)	
C	15 (28.3%)	11 (21.2%)	26 (24.8%)	
D	18 (34.0%)	21 (40.4%)	39 (37.1%)	
E	2 (3.8%)	6 (11.5%)	8 (7.6%)	
Missing/unevaluable	1 (1.9%)	1 (1.9%)	2 (1.9%)	

Abbreviations; ALT, alanine aminotransferase; HBeAg; hepatitis B e antigen; HBV, hepatitis B virus; RAT, randomised and treated; SD, standard deviation; ULN, upper limit of normal

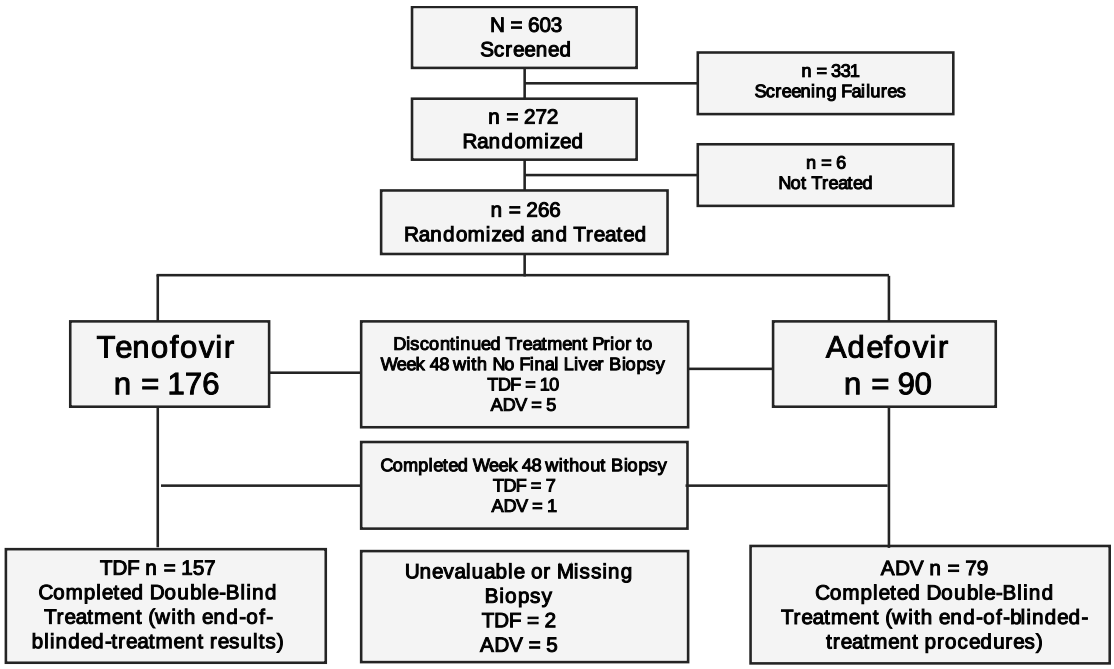
6.3.3. Patient numbers

Consort flow charts for each study are shown below. The disposition of study subjects is also given in tabulated form in Appendix 3.

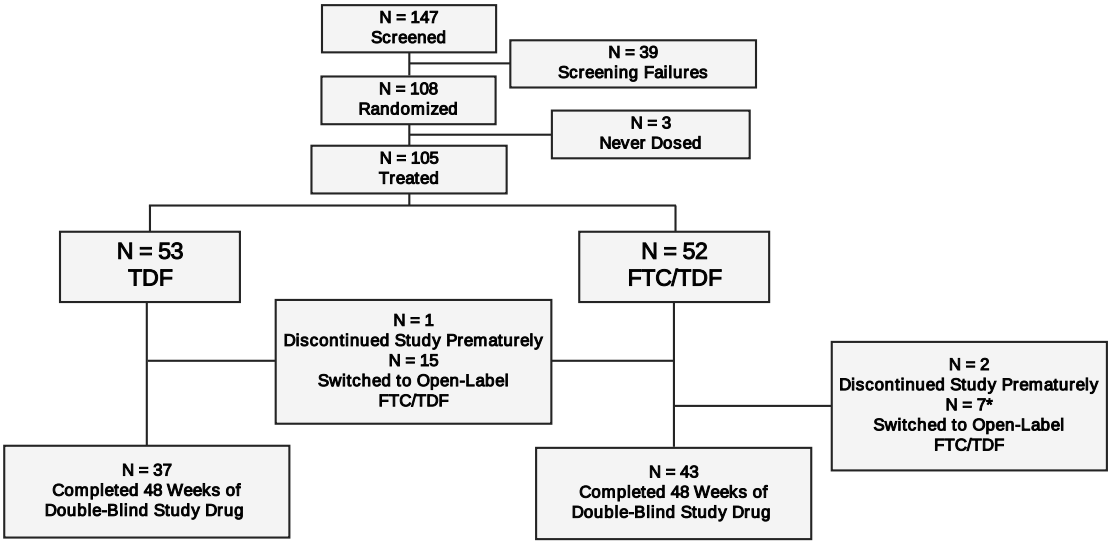
6.3.3.1. Study GS-US-174-0102



6.3.3.2. Study GS-US-174-0103



6.3.3.3. Study GS-US-174-0106



6.3.4. Outcomes

Details of the outcomes investigated in the relevant tenofovir RCTs and the measures used to investigate the outcomes are shown in Table 10.

Table 10: Details of the outcomes investigated in the relevant tenofovir RCTs

RCT	Primary outcomes and measures	Secondary outcomes and measures	Validity of outcome and measures
Studies 0102 and 0103 (26, 33) As trials 0102 and 0103 had virtually identical methodologies they have been combined here, with any differences between the studies highlighted.	The primary efficacy parameter was the proportion of subjects who achieved a composite virological and histologic response at Week 48 (19, 20). Complete response was defined as suppression of HBV DNA below 400 copies/mL and at least a two-point reduction in the Knodell necroinflammatory score and no worsening in the Knodell fibrosis score (19, 20). Plasma HBV DNA was measured using the Roche HPS/COBAS TaqMan HBV 48 assay, which has a LLQ of 29 U/mL (equivalent to169 copies/mL). Knodell necroinflammatory score was computed by summing the periportal necrosis, portal inflammation, and lobular necrosis scores.	*HBV DNA* • Change from baseline in $\log_{10}$ plasma HBV DNA levels • Proportions of subject with HBV DNA values <400 copies/mL, 300 copies/mL and 169 copies/mL • proportion of subjects with HBV DNA values: <1,000 copies/mL, <10,000 copies/mL, <100,000 copies/mL, and <1,000,000 copies/mL *Virology* • Genotypic changes from baseline at conserved sites of HBV polymerase for subjects with persistent viraemia or who experienced virologic breakthrough at Week 48. *Histology* • Ranked assessment (worsening, no change, and improved) of necroinflammation and fibrosis at Week 48 versus baseline. • Overall histologic response and histologic improvement in Knodell and Ishak necroinflammation and fibrosis scores *Alanine aminotransferase* • Change from baseline in ALT levels *Serology* • In study 0103, the proportion of RAT subjects with HBeAg loss (i.e. who were HBeAg+ at baseline and HBeAg− by Week 48) or seroconversion to anti-HBe (i.e. who were HBeAg+ and anti-HBe− at baseline but HBeAg− and anti-HBe+ by Week 48) was summarised (26).	The primary aims of CHB treatment with oral antivirals are to achieve sustained suppression of the virus and prevent serious liver disease while avoiding resistance to therapy. The 2-point reduction in Knodell necroinflammatory score with no worsening of fibrosis is commonly used as an endpoint. The 2006 EMEA CHMP guidance notes for analysis of large patient groups states that this change is acceptable as an endpoint. Study secondary endpoints which are clinically valid and currently recommended by external agencies include single and composite measures from HBeAg seroconversion, number HBV viral load "undetectable", viral load (HBV DNA measured by PCR) and ALT normalisation endpoints. The correlation between HBV viral load and disease progression is well documented (73)
Study 0106	The primary efficacy endpoint was the percentage of subjects with HBV DNA < 169 and < 400 copies/mL at Week 48.	• Change from baseline in $\log_{10}$ plasma HBV DNA levels • Change from baseline in ALT levels	The primary aims of CHB treatment with oral antivirals are to achieve sustained suppression of the virus and prevent serious liver disease while avoiding

RCT	Primary outcomes and measures	Secondary outcomes and measures	Validity of outcome and measures
		• Proportion of subjects with plasma HBV DNA < 169 copies/mL by study visit • Proportion of subjects with plasma HBV DNA < 400 copies/mL by study visit • Proportion of subjects with normal ALT and normalised ALT (i.e., of subjects with elevated ALT at baseline) by study visit • HBeAg loss (defined as having negative serum HBeAg for subjects with positive serum HBeAg at baseline) and seroconversion (defined as having negative serum HBeAg and positive serum antibody to HBeAg [anti-HBe] for subjects with positive serum HBeAg at baseline) by study visit • HBsAg loss (defined as having negative serum HBsAg for subjects with positive serum HBsAg at baseline) and seroconversion (defined as having negative serum HBsAg and positive serum antibody to HBsAg [anti-HBs] for subjects with positive serum HBsAg at baseline) by study visit • Genotypic changes from baseline at conserved-site locations within the HBV polymerase for subjects who were viraemic (HBV DNA≥ 400 copies/mL) at Week 48 or early discontinuation; with confirmed virologic breakthrough; or with virologic failure after at least 12 weeks of open-label emtricitabine/tenofovir	resistance to therapy. The 2-point reduction in Knodell necroinflammatory score with no worsening of fibrosis is commonly used as an endpoint. The 2006 EMEA CHMP guidance notes for analysis of large patient groups states that this change is acceptable as an endpoint. Study secondary endpoints which are clinically valid and currently recommended by external agencies include single and composite measures from HBeAg seroconversion, number HBV viral load “undetectable”, viral load (HBV DNA measured by PCR) and ALT normalisation endpoints. The correlation between HBV viral load and disease progression is well documented (73)

Abbreviations; ALT, alanine aminotransferase; HBeAg; hepatitis B e antigen; HBsAg; hepatits B surface antigen; HBV, hepatitis B virus; LLQ, lower limit of quantification; ULN, upper limit of normal

6.3.5. Statistical analysis and definition of study groups

Table 11: Summary of the statistical analysis and definition of study groups for the relevant tenofovir RCTs

	Hypotheses, objectives	Statistical analysis	Data management, patient withdrawals	Sample size, power calculation	Subgroup analyses
Study 0102 **Study 0103** As trials 0102 and 0103 had virtually identical method-ologies they have been combined here, with any differences between the studies highlighted.	**Study 0102** Null hypothesis; The tenofovir treatment was inferior to the adefovir treatment (the difference in proportions was less than 0.100). Alternative hypothesis; The tenofovir treatment was not inferior to the adefovir treatment. **Study 0103** Null hypothesis; the tenofovir treatment was inferior to the adefovir (the difference in proportions was less than −0.080). Alternative hypothesis; the tenofovir treatment was not inferior to	All analyses were based on the randomised-and-treated (RAT) analysis set, which included all subjects who were randomised and received at least one dose of study medication (26, 33). A two-sided 95% confidence interval (CI), stratified by baseline ALT (baseline ALT ≤ 2 × ULN or > 2 × ULN (33) or baseline ALT ≤4x ULN or >4x ULN (26)) was used to evaluate the difference in the proportion of complete responders between treatment groups. The CI was not stratified for the randomisation strata (geographic region or prior lamivudine or emtricitabine experience) (26, 33). The difference was calculated as tenofovir 300 mg o.d. minus adefovir 10 mg o.d. for each stratum (26, 33). As a sensitivity analysis, the primary endpoint was analysed for the histologically evaluable RAT analysis set (26, 33). Adjustments for multiple comparisons were not required as there was a single primary endpoint to be compared between two treatment groups. No interim statistical analyses were performed prior to the Week 48 analysis (26, 33).	If a subject had an end-of-double-blind-treatment biopsy, the last HBV DNA result that was on or after Week 40 and prior to switching to open-label therapy was paired with the post-baseline biopsy. A subject was considered a failure if the end of double-blind treatment biopsy was missing or there was no end of double-blind HBV DNA result (26, 33). A secondary sensitivity analysis of the primary efficacy endpoint was conducted using the histologically evaluable RAT analysis set (excluding subjects with a baseline necroinflammatory score less than two, who could not have histologic improvement as defined above). For the sensitivity analysis, a subject was considered a non-responder for the primary endpoint if the end of double-blind treatment biopsy was missing or if there was no HBV DNA value available at or	**Study 0102** The planned sample size was 300 randomised subjects (200 tenofovir and 100 adefovir), which would have 95% power to reject the null hypothesis in favour of the alternative hypothesis (33). This assumed the expected difference in proportions between treatment groups was 0.11, and the proportion with complete response in the adefovir group was 0.281 (74), which was adjusted for an assumed 20% discontinuation rate in this trial (33). In addition, a two-group chi-square test with a 0.050 two-sided significance level would have 87% power to detect a difference of 0.19 (observed difference in response within Study GS-98-437 between adefovir dipivoxil 10 mg and 30 mg (75)) between tenofovir and adefovir, assuming a proportion with complete response of 0.28 in the adefovir group and sample sizes of 200 and 100, respectively (33). **Study 0103** The planned sample size was 240 randomised subjects (26). A sample size of 160 subjects in the tenofovir group and 80 subjects in the adefovir group, would have 95% power to reject the null hypothesis in favour of the alternative hypothesis. This assumed the expected difference in proportions between treatment groups was 0.13, and the	No subgroup analyses were planned for studies 0102 and 0103. However, several post hoc subgroup analyses have been conducted, such as comparing LAM-resistant and naïve patients (77) and comparing patients with and without compensated cirrhosis (78).

	Hypotheses, objectives	Statistical analysis	Data management, patient withdrawals	Sample size, power calculation	Subgroup analyses
	the adefovir treatment.		beyond Week 40 (26, 33).	proportion with complete response in the adefovir group was 0.176 (calculated using the observed rate for the adefovir 10 mg group in Study GS-98-437 (76). The rate of 0.176 was adjusted for a 20% discontinuation rate (26). In addition, a two-group chi-square test with a 0.050 two-sided significance level would have at least 85% power to detect a difference of 0.19 (observed difference in response within Study GS-98-437 (76)) between tenofovir and adefovir, assuming a proportion with complete response of 0.176 in the adefovir group and sample sizes 160 and 80, respectively (26).	
0106	The primary objective was to characterise the antiviral activity of tenofovir 300 mg o.d. versus emtricitabine 200 mg/tenofovir 300 mg o.d. in subjects currently being treated with adefovir dipivoxil for CHB who have persistent viral replication	All analyses used the RAT analysis set. All available data through Week 48 were included. The difference in the proportion of subjects with complete viral suppression at Week 48 (emtricitabine/tenofovir – tenofovir) was evaluated using the Cochran-Mantel-Haenszel test (stratified by baseline HBeAg status and prior lamivudine use). In the primary analysis of all categorical efficacy endpoints, subjects who switched to open-label emtricitabine/tenofovir were analysed according to the original randomised treatment group, and subjects who discontinued the study early were counted as failures (e.g., HBV DNA ≥ threshold). A secondary analysis of the primary endpoint was performed when considering the subjects who discontinued the study early or switched to open-label emtricitabine/tenofovir as failures (16). Adjustment for multiple comparisons was not required for this study because there was a single primary endpoint to be compared between two treatment groups	When data were missing for an endpoint at baseline (defined as the first date study drug was dispensed), the last nonmissing data collected prior to this date were used as a baseline measurement (16). Subjects who withdrew from the study prior to Week 48 were considered failures for all antiviral efficacy endpoints at all time points following withdrawal (16).	The planned sample size was 90 subjects (45 subjects per arm), which would provide at least 76% power to detect a 30% difference between the two treatment arms in the percentage of subjects with plasma HBV DNA < 169 copies/mL at Week 48 (16).	Efficacy endpoints were evaluated within lamivudine- and adefovir-resistant subgroups as well as overall.

6.3.6. Critical appraisal of relevant tenofovir RCTs

A critical appraisal of the relevant tenofovir RCTs is given in Table 12.

Table 12: Critical appraisal of relevant tenofovir RCTs

	GS-US-174-0102	**GS-US-174-0103**	**GS-US-174-0106**
How was allocation concealed?	Double-blind	Double-blind	Double-blind
What randomisation technique was used?	Randomisation was stratified based on prior therapy with lamivudine or emtricitabine exceeding 12 weeks (yes/no), and by region (North America, Europe, Australia/New Zealand). A centralised randomisation procedure was used in which numbered bottles were assigned to subjects via an interactive voice response system (IVRS) according to the randomisation code.	Randomisation was stratified by screening ALT level (≤ 4 and > 4 × ULN) and by region (North America, Europe, and Australia/New Zealand). A centralised randomisation procedure was used in which numbered bottles were assigned to subjects via an IVRS according to the randomisation code.	Randomisation was stratified by history of lamivudine experience ($<$ 12 weeks of therapy or $\geq$ 12 weeks of therapy) and HBeAg status at screening. A centralised randomisation procedure with a block size of four was used whereby numbered bottles were assigned to subjects via an IVRS.
Was a justification of the sample size provided?	Yes	Yes	Yes
Was follow-up adequate?	Yes	Yes	Yes
Were the individuals undertaking the outcomes assessment aware of allocation?	No	No	No
Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.	Parallel	Parallel	Parallel
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where	RCT was multinational with participating centres from the US (15 sites), Germany (10 sites), Australia (8 sites), France (8 sites), Poland (6 sites), Canada (5 sites), Bulgaria (4 sites), Czech Republic (4	RCT was multinational with participating centres from the US (20 sites), Germany (13 sites), Australia (10 sites), France (7 sites), Poland (7 sites), Canada (5 sites), Turkey (5 sites), Bulgaria (4 sites),	RCT was multinational with participating centres from the US (10 sites), Germany (10 sites), France (7 sites), Spain (1 site)

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was the RCT conducted, and is clinical practice likely to differ from UK practice?	sites), Greece (4 sites), Turkey (4 sites), New Zealand (3 sites), Spain (3 sites), Italy (2 sites), the United Kingdom (2 sites), and the Netherlands (1 site).	Czech Republic (4 sites), New Zealand (4 sites), Spain (4 sites), the United Kingdom (3 sites), Greece (2 sites), Italy (1 site), and the Netherlands (1 site).	
How do the included RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Comparable to patients in the UK who have HBeAg-negative CHB. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.	Comparable to patients in the UK who have HBeAg-positive CHB. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.	Comparable to patients in the UK who have HBeAg-positive or HBeAg-negative CHB and are currently treated with adefovir dipivoxil and having persistent viral replication. However, this comprises a relatively small subgroup of patients at present. Given that UK patients often originate from countries outside of the UK the multinational design of the study provides a representative population.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	The doses of tenofovir and adefovir dipivoxil were according to the SPC.	The doses of tenofovir and adefovir dipivoxil were according to the SPC.	The doses of tenofovir and emtricitabine/tenofovir were according to the SPC.
Were the study groups comparable?	Yes	Yes	Yes
Were the statistical analyses used appropriate?	Yes	Yes	Yes
Was an intention-to-treat analysis undertaken?	Yes	Yes	Yes
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	No	No	No

6.4. Results of the relevant tenofovir comparative RCTs

Key results from tenofovir comparative RCTs

Tenofovir demonstrates robust efficacy in HBeAg-negative patients at 2 years

- Treatment with tenofovir was significantly superior to adefovir for the primary efficacy endpoint ($p<0.001$).
- At 48 weeks significantly more patients in the tenofovir group than the adefovir group had HBV DNA <400 copies/mL; 94% vs 64% ($p<0.001$).
- Viral suppression was achieved by 99% of patients on tenofovir therapy at 96 weeks (on-treatment data), and HBV DNA declined rapidly in those subjects who switched to tenofovir after 48 weeks of adefovir.

Tenofovir demonstrates robust efficacy in HBeAg-positive patients at 2 years

- In terms of the primary endpoint, tenofovir was significantly superior to adefovir ($p<0.001$).
- At 48 weeks significantly more patients in the tenofovir group than the adefovir group had HBV DNA <400 copies/mL; 80% vs 13% ($p<0.001$).
- Viral suppression was achieved by 89% of patients on tenofovir therapy at 96 weeks (on-treatment data), and HBV DNA levels declined rapidly in those subjects who switched to tenofovir after 48 weeks of adefovir.

Tenofovir continues to demonstrate 0% genotypic resistance at 2 years

- Despite widespread use of tenofovir, no clinically-significant cases of virologic resistance have yet been identified.

Tenofovir continues to demonstrate a desirable safety profile at 2 years

- The results in patients with CHB are consistent with those observed in HIV, where there are currently 2 million patient years of safety data (34).

Tenofovir demonstrates efficacy in lamivudine-resistant patients

- The available evidence supports the use of tenofovir in all patients covered by its licensed indication; treatment experienced patients, including those previously treated with lamivudine, as well as treatment-naive patients.

6.4.1. Study GS-US-174-0102

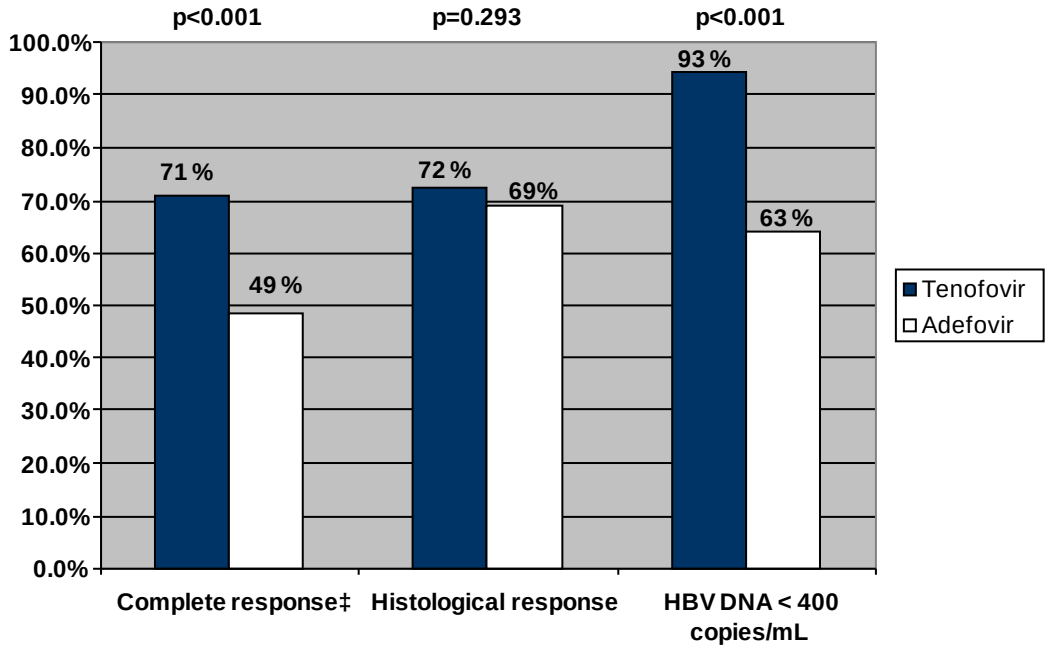
Trial summary

- An ongoing, randomised phase III study comparing the safety and efficacy of tenofovir 300 mg versus adefovir 10 mg for treatment of HBeAg-negative CHB.
- Treatment with tenofovir was significantly superior to adefovir (p<0.001) for the primary efficacy endpoint.
- Significantly more patients in the tenofovir than adefovir group experienced suppression of HBV DNA below a number of different thresholds at 48 weeks:
  - <400 copies/mL: 94% for tenofovir; 64% for adefovir (p<0.001)
  - <300 copies/mL: 92% for tenofovir; 59% for adefovir (p<0.001)
  - <169 copies/mL: 91% for tenofovir; 56% for adefovir (p<0.001)
- There was no significant difference in histologic response between the treatment arms.

6.4.1.1. Results of the primary analysis of the primary outcome

At Week 48, significantly more tenofovir-treated subjects than adefovir-treated subjects experienced complete response (p<0.001;Table 13, Figure 2) (20). Significantly more subjects in the tenofovir than adefovir group had HBV DNA values below 400 copies/mL at Week 48 (p<0.001) (33). Histologic response was similar between groups (20).

Figure 2: **Primary efficacy outcomes at Week 48 for Study 0102**



‡Complete response is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL.
These figures are taken from the AASLD 2007 presentation (20).

Table 13: Primary efficacy response outcomes and components at Week 48 for Study 0102 (RAT analysis set) (33)

Response category (n, %)	Tenofovir N=250	Adefovir N=125	Difference estimate (95% CI)[†]	P-value
Complete response[‡]				
Yes	177 (70.8)	61 (48.8)	23.5% (13.2, 33.8)	<0.001
No	73 (29.2)	64 (51.2)		
Histologic response[§]				
Yes	181 (72.4)	86 (68.8)	5.2% (-4.5, 14.9)	0.293
No	69 (27.6)	39 (31.2)		
HBV DNA <400 copies/mL				
Yes	236 (94.4)	80 (64.0)	30.3% (21.6, 39.1)	<0.001
No	8 (3.2)	41 (32.8)		
Missing	6 (2.4)	4 (3.2)		

[†]Difference and CI are adjusted for baseline ALT stratum.
[‡]Complete response is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL.
[§] Histological response/improvement was defined as a ≥2-point reduction in Knodell necroinflammatory score without worsening in fibrosis.

6.4.1.2. Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes

HBV DNA
Significantly more subjects in the tenofovir group (236/250 [94.4%]) than the adefovir group (80/125 [64.0%]) had HBV DNA <400 copies/mL (difference: 30.3%, 95% CI: 21.6, 39.1; p<0.001) (33). The majority of subjects (>50%) receiving tenofovir had HBV DNA results below 400 copies/mL by Week 12, whereas the majority of those treated with adefovir did not fall below 400 copies/mL until at least Week 28 (33).

The proportion of subjects with HBV DNA below 300 copies/mL was significantly higher in the tenofovir group (230/250 [92.0%]) than adefovir (74/125 [59.2%]) (p<0.001) (20, 33). The proportion of subjects with HBV DNA below 169 copies/mL yielded similar results (tenofovir, 228 [91.2%]; adefovir, 70 [56.0%]; (p<0.001) (20, 33).

The percentage of subjects with HBV DNA levels <1,000, <10,000, <100,000, and <1,000,000 copies/mL at the end of blinded treatment was significantly greater with tenofovir than adefovir (p≤0.048, difference ≥5.7%) when subjects with missing values within the Week 48 visit window were considered non-responders. The mean (SD) reduction from baseline in plasma HBV DNA at Week 48 was also significantly greater in the tenofovir group (−4.57 $\log_{10}$ copies/mL [1.347]) than the adefovir group (−4.07 $\log_{10}$ copies/mL [SD 1.331]) (p<0.001) (33).

Histology
The proportion of subjects with improvement in necroinflammation (tenofovir, 194/250 [77.6%] vs adefovir 93/125 [74.4%]; difference estimate, 5.1% [95% CI: -3.9, 14.1]; p=0.268) and the proportion with worsening in fibrosis (tenofovir, 16/250 [6.4%] vs adefovir 11/125 [8.8%]; difference estimate, -0.2% [95% CI: -5.4, 5.1]; p=0.955) at the end of blinded treatment were not significantly different between groups (33).

The mean change from baseline in the Knodell necroinflammatory score was similar for both tenofovir (-3.5 [SD 2.50]) and adefovir (-3.4 [SD 2.36]; p=0.693; difference estimate, -0.11 [95% CI: -0.65, 0.43]; p=0.693]). Similar results were seen with the

Knodell fibrosis score (tenofovir, -0.1 [SD 0.86] vs adefovir, -0.1 [SD 0.88]; difference estimate, -0.03 [-0.23, 0.17]; p=0.750). These results are consistent with those achieved with the Ishak system (necroinflammatory score: tenofovir, -2.6 [SD 1.93] vs adefovir, -2.6 [SD 1.90], difference estimate, -0.01 [95% CI: -0.44, 0.42], p=0.964; fibrosis score: tenofovir, -0.2 [SD 0.92] vs adefovir, -0.2 [SD 1.07], difference estimate, 0.01 [95% CI: -0.22, 0.24], p=0.947) (33).

Alanine aminotransferase response
At Week 48, the majority of subjects had normalised (180/236 [76%], tenofovir; 91/118 [77%], adefovir) (33) and normal ALT (193/250 [77%], tenofovir; 97/125 [78%], adefovir) (20, 33).

Mean (SD) baseline ALT was higher in the adefovir group (163.6 U/L [146.02]) than the tenofovir group (127.5 U/L [101.21]); consequently, greater changes from baseline in ALT were observed in the adefovir group, as the proportion of subjects with normalised ALT was not significantly different between groups. At Week 48, mean change from baseline in ALT was −95.0 U/L (102.31) in the tenofovir group and −124.4 U/L (137.23) in the adefovir group (p=0.040) (33).

Serology
No subjects in either treatment group experienced HBsAg loss or seroconverted to anti-HBs by Week 48 (33).

6.4.1.3. Resistance data

Of the 50 serum isolates from viraemic subjects, only eight (3.2%) were in the tenofovir group compared with 42 (33.6%) receiving adefovir. Seven viraemic subjects in the adefovir group (compared with none receiving tenofovir) developed changes at conserved site residues within the HBV polymerase after 48 weeks of treatment (33). No subject developed a substitution in the HBV polymerase/reverse transcriptase associated with resistance to tenofovir (39). Phenotypic analysis of serum HBV isolated from subjects with virologic breakthrough demonstrated full sensitivity to tenofovir *in vitro*.

6.4.1.4. Conclusions for study 0102

Significantly more subjects receiving tenofovir than adefovir:

- Experienced a complete response (p<0.001); therefore, the primary outcome was successfully met.
- Had reductions in HBV DNA levels below 400, 300, and 169 copies/mL (p<0.001).

There were greater mean changes in ALT levels in the adefovir group than tenofovir due to higher mean baseline levels in these subjects. There were no significant differences in histology between the two groups.

There was 0% resistance to tenofovir after 48 weeks of treatment.

6.4.1.5. Results from Weeks 48-96

At Week 48, subjects who completed 48 weeks of double-blind treatment and underwent the required Week 48 liver biopsy were given the option to continue (or initiate) treatment with open-label tenofovir up to Week 384, while remaining blinded to their original randomised treatment assignment. Subjects with HBV DNA ≥ 400 copies/mL at Week 72 or later were eligible to be switched to open-label

emtricitabine 200 mg/tenofovir 300 mg o.d. combination treatment for the remainder of the study. The open-label extension phase of the study is ongoing.

Three hundred forty-seven subjects entered the open-label tenofovir treatment period (235 subjects originally randomised to tenofovir and 112 subjects originally randomised to adefovir dipivoxil). Two hundred twenty-five (95.7%) subjects in the TDF-TDF group and 110 (98.2%) subjects in the ADV-TDF group completed the study through Week 96.

Key results include:

- Viral suppression was maintained with continued tenofovir treatment.
- HBV DNA rapidly declined in those subjects who switched from adefovir to tenofovir at Week 48.
    - The proportion of subjects with HBV DNA < 400 copies/mL increased from 64.2% at Week 48 to 87.8% at Week 64.
- Three subjects (all in the TDF–TDF group) were switched to open-label emtricitabine/tenofovir (Truvada) during the open-label period due to confirmed viraemia. One of these 3 subjects had achieved complete viral suppression by Week 96.
- At Week 96, a similar proportion of subjects in the TDF–TDF group (90.6%) and in the ADV–TDF group (89.3%) had an HBV DNA value < 400 copies/mL (LTE analysis[f], including patients who switched to tenofovir/emtricitabine).
- Viral suppression was achieved by 99% of patients in the TDF-TDF group at 96 weeks (on-treatment data).
- At Week 72, prior to any subjects having switched to emtricitabine/tenofovir, 91% of subjects in the TDF–TDF group and 87.8% in the ADV–TDF group had HBV DNA < 400 copies/mL (LTE analysis).
- 100% subjects originally randomised to adefovir achieved a virologic response to tenofovir by Week 96 whether they had been an adefovir dipivoxil responder or adefovir dipivoxil non-responder at Week 48 (based on on-treatment data).
- No amino acid substitutions at conserved sites within the HBV DNA polymerase were detected among viraemic subjects receiving continuous

[f] Long-term evaluation (LTE) analysis; subjects discontinuing the study early with HBV DNA ≥ 400 copies/mL or an ongoing AE at the last on-study visit were considered failures. Any subject with HBsAg loss who discontinued the study for any reason with HBV DNA < 400 copies/mL at the last on-study visit had the last HBV DNA value carried forward and was included in the analysis as a success. For the LTE analysis of ALT, the same algorithm was applied, substituting abnormal ALT for HBV DNA ≥ 400 copies/mL and normal ALT for HBV DNA < 400 copies/mL in the criteria for failure and success. For the LTE analysis of HBsAg loss and seroconversion, the same algorithm was applied, substituting positive HBsAg and negative anti-HBs for HBV DNA ≥ 400 copies/mL, and substituting negative HBsAg and positive anti-HBs for HBV DNA < 400 copies/mL in the criteria for failure and success. In the LTE analyses, subjects who switched from open-label tenofovir DF monotherapy to emtricitabine/tenofovir at or beyond Week 72 due to viraemia were not considered failures if they achieved the endpoint of interest thereafter. On-treatment data analysis; subjects with missing data were excluded at each applicable time point for the analysis of HBV DNA, ALT, and HBsAg loss/seroconversion.

treatment with tenofovir through Week 96. Since all subjects who switched from adefovir dipivoxil to tenofovir had HBV DNA values below 400 copies/mL at their last time point on tenofovir, no subject was genotyped. Therefore, no conserved-site changes were detected.

- In this HBeAg-negative population, 96 weeks of continued or 48 weeks of deferred treatment with tenofovir did not produce HBsAg loss or seroconversion.

- Tenofovir was well tolerated during both treatment periods.

6.4.2. Study GS-US-174-0103

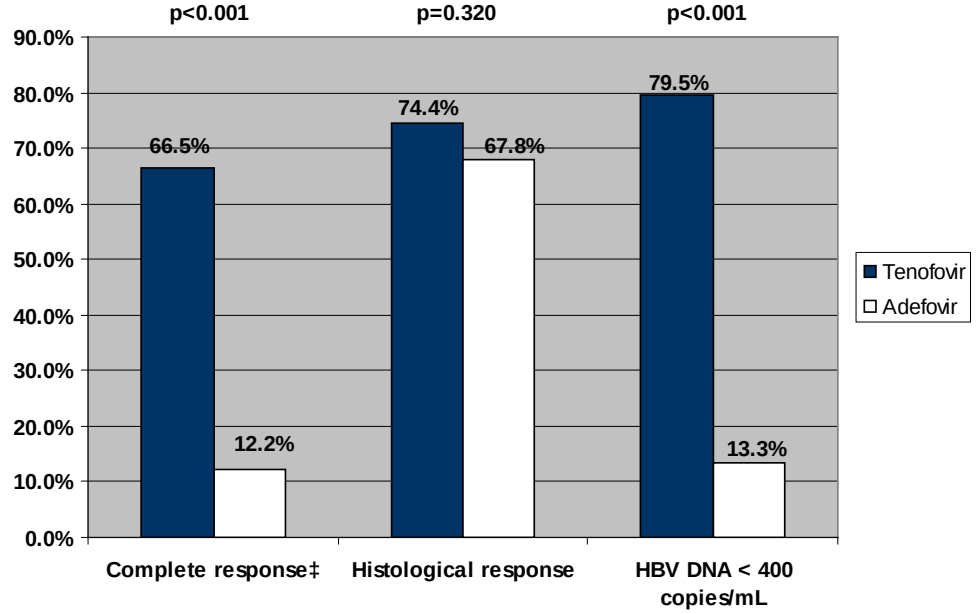
Trial summary

- An ongoing, randomised phase III study comparing the safety and efficacy of tenofovir 300 mg versus adefovir 10 mg for treatment of HBeAg-positive CHB.
- In terms of the primary endpoint, tenofovir was significantly superior to adefovir (p<0.001).
- Significantly more patients receiving tenofovir than adefovir experienced suppression of HBV DNA below a number of different thresholds at 48 weeks:
  - <400 copies/mL: 80% for tenofovir; 13% of adefovir (p<0.001)
  - <300 copies/mL: 74% for tenofovir; 12% for adefovir (p<0.001)
  - <169 copies/mL: 69% for tenofovir; 9% for adefovir (p<0.001)
- There was no significant difference between groups in terms of histologic response at Week 48; however, significantly more patients in the tenofovir group than adefovir group had normal (p=0.018) or normalised (p=0.032) ALT.
- Similar proportions of patients in both treatment arms had HBeAg loss or seroconversion; however, significantly more patients receiving tenofovir than adefovir had HBsAg loss (p=0.018).

6.4.2.1. Results of the primary analysis of the primary outcome

At Week 48, significantly more tenofovir-treated subjects than adefovir-treated subjects achieved complete response (p<0.001) (Table 14, Figure 3) (19). Significantly more subjects in the tenofovir than adefovir group had HBV DNA values below 400 copies/mL (p<0.001) when subjects with missing data from Week 40 or beyond were considered non-responders (26). Histologic response was similar between groups (19).

Figure 3: Primary efficacy outcomes at Week 48 in Study 0103



‡Complete response is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL

Table 14: Primary efficacy response outcomes and components at Week 48 of Study 0103 (RAT analysis set) (26).

Response category (n, %)	Tenofovir N=176	Adefovir N=90	Difference estimate (95% CI)[†]	P-value
Complete response[‡]				
Yes	117 (66.5%)	11 (12.2%)	54.1% (44.6, 63.6)	<0.001
No	59 (33.5%)	79 (87.8%)		
Histologic response[§]				
Yes	131 (74.4%)	61 (67.8%)	5.8% (-5.6, 17.2)	0.320
No	45 (25.6%)	29 (32.2%)		
HBV DNA <400 copies/mL				
Yes	140 (79.5%)	12 (13.3%)	65.9% (56.8, 75.0)	<0.001
No	29 (16.5%)	74 (82.2%)		
Missing	7 (4.0%)	4 (4.4%)		

[†]Difference and CI are adjusted for baseline ALT stratum.
[‡]Complete response is a composite endpoint defined as histologic response and HBV DNA below 400 copies/mL.
[§] Histological response/improvement was defined as a ≥2-point reduction in Knodell necroinflammatory score without worsening in fibrosis.

6.4.2.2. Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes

HBV DNA

Significantly more subjects receiving tenofovir (140/176 subjects, 79.5%) than adefovir (12/90 subjects, 13.3%) had HBV DNA <400 copies/mL at Week 48 (p<0.001). More than 50% (103/176) of subjects treated with tenofovir had HBV DNA below 400 copies/mL after 28 weeks of treatment, while the majority of those treated with adefovir never fell below 400 copies/mL during the 48-week period.

Over half of subjects in the tenofovir group had HBV DNA below 300 copies/mL by Week 28 (95/176) compared with 2/90 for the adefovir group. At Week 48, significantly more subjects had HBV DNA <300 copies/mL in the tenofovir group (130/176, 74%) versus the adefovir group (11/90, 12%) (p<0.001) (19, 26).

Over 50% (97/176) of subjects in the tenofovir group had HBV DNA results below 169 copies/mL by Week 32, compared with only 3% (3/90) of subjects receiving adefovir. At Week 48, significantly more subjects had HBV DNA below 169 copies/mL in the tenofovir (121/176 [69%]) than adefovir (8/90 [9%]) groups (p<0.001) (19, 26).

The mean (SD) reduction from baseline in plasma HBV DNA at Week 48 was significantly greater with tenofovir (−6.17 $\log_{10}$ copies/mL [1.067]) than adefovir (−3.93 $\log_{10}$ copies/mL [1.738]) (p<0.001) (26).

The percentage of subjects with HBV DNA levels <1,000, <10,000, <100,000, and <1,000,000 copies/mL was also significantly greater in the tenofovir group than the adefovir group (p<0.001, difference ≥ 22.9%) when subjects with missing values were considered non-responders (26).

Histology
Based on Knodell scores, the proportion of subjects with improvement in necroinflammation (tenofovir, 137/176 [77.8%] vs adefovir, 64/90 [71.1%]; difference estimate, 6.2% [95% CI: -4.8, 17.3]) and the proportion with worsening in fibrosis (tenofovir, 3/176 [1.7%] vs adefovir, 3/90 [3.3%]; difference estimate, -1.9% [95% CI: -5.9, 2.1]) at Week 48 were similar (26).

At Week 48, mean change from baseline values for the Knodell necroinflammatory (tenofovir, -3.6 [SD 2.30] vs adefovir, -3.2 [SD 2.35]; difference estimate, -0.34 [95% CI: -0.98, 0.30]) and fibrosis (tenofovir, -0.1 [SD 0.61] vs adefovir, -0.2 [SD 0.79]; difference estimate, 0.04 [95% CI: -0.16, 0.24]) scores were similar in each group. There was no significant difference in the mean (SD) Knodell necroinflammatory score (5.2 [1.96], adefovir; 4.7 [2.02], tenofovir) (26).

Similar results were achieved with the mean change in Ishak necroinflammatory (tenofovir, -2.7 [SD 1.70] vs adefovir, -2.6 [SD 1.94]; difference estimate, -0.01 [95% CI: -0.51, 0.48]) and fibrosis (tenofovir, -0.2 [SD 0.69] vs adefovir, -0.1 [SD 0.85]; difference estimate, -0.07 [95% CI: -0.28, 0.15]) scores (26).

Alanine aminotransferase response
At Week 48, a significantly greater proportion of subjects receiving tenofovir than adefovir had normalised (115/176, tenofovir vs 49/90, adefovir; difference estimate, 13.6% [95% CI: 1.1, 26.1]; p=0.032) (26) or normal (122/176, tenofovir vs 49/90, adefovir; difference estimate, 14.9% [95% CI: 2.5, 27.2]; p=0.018) ALT levels (19, 26).

Serology
Similar proportions of evaluable subjects in the tenofovir and adefovir groups had HBeAg loss at Week 48 (34/153 [22%], tenofovir; 14/80 [18%], adefovir) (26), and similar proportions of subjects in both treatment groups achieved HBeAg seroconversion (32/153 [21%] and 14/80 [18%], respectively) (19).

Significantly more tenofovir-treated (5/158 [3%]) than adefovir-treated subjects (0/82) achieved HBsAg loss at Week 48 (p=0.018) (19) and 2/158 subjects in the tenofovir group (vs 0/82 in the adefovir group) achieved HBsAg seroconversion at Week 48 (26).

6.4.2.3. Resistance data

Among the serum isolates from viraemic subjects, 31 (17.6%) were from the tenofovir group, while 75 (83.3%) received adefovir. Genotypic testing of HBV polymerase demonstrated that at 48 weeks, 2 viraemic subjects receiving tenofovir, and 8 viraemic subjects receiving adefovir had conserved-site changes (26). No subject developed a substitution in the HBV polymerase/reverse transcriptase associated with resistance to tenofovir (39). Phenotypic analysis of serum HBV isolated from subjects with virologic breakthrough demonstrated full sensitivity to tenofovir *in vitro*.

6.4.2.4. Conclusions of study 0103

- Significantly more subjects receiving tenofovir than adefovir:
    - Experienced a complete response (p<0.001); therefore, the primary outcome was successfully met.
    - Had reductions in HBV DNA levels below 400, 300, and 169 copies/mL (p<0.001).
    - Had normalised (p=0.032) or normal (p=0.018) ALT levels.

- Had HBsAg loss (p=0.018).

- There were no significant differences in histology between the two groups, and similar proportions of patients had HBeAg loss or seroconversion.
- There was no evidence of resistance to tenofovir after 48 weeks of treatment.

6.4.2.5. Results from Weeks 48-96

At week 48, subjects who completed 48 weeks of double-blind treatment and underwent the required Week 48 liver biopsy were given the option to continue (or initiate) treatment with open-label tenofovir up to Week 384, while remaining blinded to their original randomised treatment assignment. Subjects with HBV DNA ≥ 400 copies/mL at Week 72 or later were eligible to be switched to open-label emtricitabine 200 mg/tenofovir 300 mg o.d. combination treatment for the remainder of the study. The open-label extension phase of the study is ongoing.

A total of 238 subjects, 154 subjects originally randomised to tenofovir and 84 subjects originally randomised to adefovir dipivoxil, entered the open-label tenofovir treatment period. Of these, 145 subjects (94.2%) in the TDF–TDF group and 83 (98.8%) in the ADV–TDF group completed the study through Week 96.

Two analyses were conducted, a LTE analysis and an on-treatment data analysis as described for study 0102 (Section 6.4.1.5).

- Viral suppression was maintained with continued tenofovir treatment.

- HBV DNA rapidly declined in those subjects who switched from adefovir to tenofovir at Week 48.

    - The proportion of subjects with HBV DNA < 400 copies/mL increased from 13.3% at Week 48 to 70.8% at Week 64.

- Sixteen subjects in the TDF–TDF group and 13 subjects in the ADV-TDF group switched to open-label emtricitabine/tenofovir during the open-label period due to confirmed viraemia. Twenty-three of these subjects never achieved viral suppression < 400 copies/mL at any time during the study up to Week 96.

- At Week 96, a similar proportion of subjects in the TDF–TDF group (77.6%) and in the ADV–TDF group (77.9%) had an HBV DNA value < 400 copies/mL (LTE analysis, including patients who switched to tenofovir+emtricitabine).

- Viral suppression was achieved by 89% of patients in the TDF-TDF group at 96 weeks (on-treatment data).

- At Week 72, prior to any subjects having switched to emtricitabine/tenofovir, 78.5% of subjects in the TDF–TDF group and 75.9% in the ADV–TDF group had HBV DNA < 400 copies/mL (LTE analysis).

- Following the switch to tenofovir, 71.8% of adefovir non-responders achieved HBV DNA < 400 copies/mL at Week 64 and 82.1% at Week 96.

- 100% of the 12 adefovir responders continued to respond after switching to tenofovir.

- Biochemical response was maintained with continued tenofovir therapy, and switching from adefovir dipivoxil to tenofovir had a positive effect on biochemical response in ADV–TDF subjects by Week 96, when the percentage of subjects with normal ALT increased from 55.7% at Week 48 to 74.4% at Week 96 (LTE analysis), and was similar to the percentage in the group receiving continued tenofovir monotherapy.

- The percentage of subjects achieving HBeAg loss or HBeAg seroconversion (HBeAg loss plus positive anti-HBe result) increased notably in those switching from adefovir dipivoxil to open-label tenofovir at Week 48 (11% increase by Week 96), and increased slightly in the group receiving continued tenofovir therapy.

- The development of conserved site changes in HBV DNA polymerase was infrequent and did not correspond with virologic breakthrough among subjects treated with up to 96 weeks of tenofovir monotherapy.

- Tenofovir was well tolerated during both treatment periods.

6.4.3. Subgroup analyses on both GS-US-174-0102 and GS-US-174-0103

Cirrhotic patients

A total of 123 patients with cirrhosis were recruited to studies 0102 or 0103, of whom 81 received tenofovir and 42 received adefovir and 59% (72/123) of whom were HBeAg-negative (78). The results for cirrhotic patients were similar to those for the total trial population[g]: 85% of cirrhotic patients receiving tenofovir had HBV DNA <400 copies/mL, compared with 48% of those receiving adefovir ($p<0.001$). Furthermore, 79% of tenofovir-treated cirrhotics had histological response, while 69% had normal ALT. These data demonstrate that tenofovir is equally effective in cirrhotic and non-cirrhotic patients.

Lamivudine-experienced patients

Seventy patients within trials 0102 and 0103 had previously received more than 12 weeks' treatment with lamivudine, of whom 87% (61/70) were HBeAg-negative (77). Tenofovir was found to be as effective in this population as in the total trial populations: 88% of lamivudine-experienced patients and 86% of lamivudine-naïve patients had HBV DNA <400 copies/mL at Week 48, while 78% of lamivudine-experienced patients and 74% of lamivudine-naïve patients had normal ALT. Tenofovir produced a superior antiviral response compared with adefovir in both populations.

[g] In studies 0102 and 0103 376/426 (88.3%) subjects receiving tenofovir had HBV DNA <400 copies/mL at Week 48.

6.4.4. GS-US-174-0106

Trial summary

- An ongoing, randomised phase II study comparing the efficacy, safety and tolerability of tenofovir 300 mg versus emtricitabine plus tenofovir combination therapy for treatment of subjects receiving adefovir dipivoxil for CHB with persistent viral replication
- There were no significant differences between treatment groups in any of the efficacy endpoints examined
- Tenofovir monotherapy and emtricitabine/tenofovir combination therapy were effective in this treatment-experienced population, including 10 subjects with adefovir resistance mutations at baseline and 16 subjects with lamivudine resistance mutations at baseline
- No subject developed conserved-site changes, including those with adefovir or lamivudine resistance mutations detected at baseline.

6.4.4.1. Results of the primary analysis of the primary outcome

At week 48 the percentage of subjects with HBV DNA <169 copies/mL was similar in the two treatment groups using either method of analysis (non-completer = failure analysis or non-completer/switch = failure analysis) (Table 15).

Table 15: Number and Percentage of Subjects with HBV DNA below 169 and 400 copies/mL (RAT Analysis Set)

Subjects with HBV DNA <169 and <400 copies/mL[†], n (%)	Tenofovir (N=53)	Emtricitabine /tenofovir (N=52)	Overall (N=105)	P-value[‡]
Non-completer = failure analysis				
HBV DNA < 169 copies/mL				
Baseline	0 (0.0%)	1 (1.9%)[§]	1 (1.0%)[§]	
Week 24	29 (54.7%)	31 (59.6%)	60 (57.1%)	0.504
Week 48	40/ (75.5%)	36 (69.2%)	76 (72.4%)	0.544
HBV DNA < 400 copies/mL				
Baseline	0 (0.0%)	1 (1.9%)[§]	1 (1.0%)[§]	
Week 24	35 (66.0%)	36 (69.2%)	71 (67.6%)	0.672
Week 48	43 (81.1%)	42 (80.8%)	85 (81.0%)	0.988
Non-completer/switch = failure analysis				
Baseline	0 (0.0%)	1 (1.9%)[§]	1 (1.0%)[§]	
Week 24	29 (54.7%)	31 (59.6%)	60 (57.1%)	0.504
Week 48	34 (64.2%)	36 (69.2%)	70 (66.7%)	0.557
HBV DNA < 400 copies/mL				
Baseline	0 (0.0%)	1 (1.9%)[§]	1 (1.0%)[§]	
Week 24	35 (66.0%)	36 (69.2%)	71 (67.6%)	0.672
Week 48	35 (66.0%)	40 (76.9%)	75 (71.4%)	0.234

[†] Taqman assay LLQ = 169 copies/mL; values < LLQ were set to 168 copies/mL for quantitative analyses.

[‡] P-values were from a Cochran-Mantel-Haenszel test, controlling for baseline HBeAg status and prior lamivudine use.

[§] One subject had an HBV DNA level of 31,661 copies/mL at screening, but HBV DNA was < 169 copies/mL at the baseline visit 30 days later and at all assessments through Week 48.

6.4.4.2. Results of relevant secondary analyses of the primary outcome and analyses of relevant secondary outcomes

HBV DNA
The number and percentage of subjects with HBV DNA < 169 copies/mL and those with HBV DNA < 400 copies/mL were similar over time in the tenofovir and emtricitabine/tenofovir groups, when switch subjects were included in the analysis (NC = F analysis), and were also similar when switch subjects were considered failures.

The mean (SD) reduction from baseline in plasma HBV DNA over 48 weeks of treatment was similar in the two treatment groups; at Week 48, the mean (SD) change was −3.58 (1.290) $\log_{10}$ copies/mL in the tenofovir group and −3.34 (1.753) $\log_{10}$ copies/mL in the emtricitabine/tenofovir group.

ALT
Approximately half of the subjects in either treatment group had normal ALT values (i.e., ≤ ULN) at baseline (49% and 50% for the tenofovir and emtricitabine/tenofovir groups, respectively). At Week 48, the percentage of subjects with normal ALT increased to 67% and 73%, respectively. There was no significant difference between groups.

Subjects were considered to have normalised ALT if the baseline ALT value was > ULN and decreased to ≤ ULN during the study. The percentage of subjects with normalised ALT tended to be higher in the emtricitabine/tenofovir group than in the tenofovir group, but the differences were not statistically significant. At Week 48, 41% of subjects in the tenofovir group and 62% of subjects in the emtricitabine/tenofovir group had normalised ALT.

The mean (SD) change from baseline in serum ALT at Week 48 was greater in the emtricitabine/tenofovir group (−42.9 [147.03] U/L) than in the tenofovir group (−21.6 [54.53] U/L), but the difference was not statistically significant (p = 0.694).

Serology
Similar proportions of subjects in the tenofovir group and in the emtricitabine/tenofovir group had HBeAg loss at Week 48 (8% in each group), and similar proportions of subjects in both treatment groups achieved HBeAg seroconversion (5% and 8%, respectively), defined as HBeAg loss and a positive result for anti-HBe.

One subject (in the tenofovir group) achieved HBsAg loss at Week 36 and seroconversion to anti-HBs at Week 48. The subject remained on double-blind tenofovir treatment through Week 48.

6.4.4.3. Resistance analyses

Eighteen viraemic subjects (17% of the total RAT population) were evaluated for genotypic changes from baseline, including one who discontinued the study at Week 36, six who were viraemic at Week 48 after viral breakthrough, and 11 who were viraemic at Week 48 without viral breakthrough during the study.

Conserved-site changes from the baseline HBV polymerase sequence were detected in 6 subjects at Week 48; all had previously switched to open-label emtricitabine/tenofovir treatment and none had virologic breakthrough. Each change was observed in only a single subject and the changes observed in four of the six subjects are not known to be associated with antiviral resistance. A lamivudine

resistance mutation was detected in one subject and in one subject an adefovir resistance mutation that was determined to have been present at baseline at a low level. The significance of the conserved-site changes is under exploration by phenotypic analysis of recombinant virus derived from these subjects. No subject with adefovir dipivoxil- or lamivudine-associated resistance mutations detected at baseline or with virologic breakthrough during tenofovir monotherapy developed conserved-site changes at Week 48.

6.4.4.4. Efficacy analysis of subgroups

Lamivudine-Resistant Subjects
Thirteen subjects had lamivudine-resistant HBV at baseline. Seven of these 13 subjects were randomised to blinded therapy with tenofovir group and 6 to emtricitabine/tenofovir. No substantive differences were observed between the lamivudine-resistant subgroup (13 subjects) and the non-resistant subgroup (92 subjects). The percentage of subjects with HBV DNA < 169 copies/mL was similar in the two subgroups. At Week 48, 77% of lamivudine-resistant subjects and 72% of non-resistant subjects had HBV DNA < 169 copies/mL (NC = F analysis).

The percentage of subjects with normal and normalised ALT was similar among lamivudine-resistant and non-resistant subjects at Week 48 (69% and 70% with normal ALT, and 56% and 50% with normalised ALT, respectively [NC = F analysis]).

Adefovir-Resistant Subjects
10 subjects had adefovir-resistant HBV at baseline, including 8 subjects in the tenofovir group and 2 subjects in the emtricitabine/tenofovir group. The percentages of subjects with HBV DNA < 169 and < 400 copies/mL were similar between the two subgroups. At Week 48, 70% of adefovir-resistant subjects and 73% of non-resistant subjects had HBV DNA < 169 copies/mL (NC = F analysis).

Except at baseline, when 30% of adefovir-resistant and 52% of non-resistant subjects had normal ALT, the percentage of subjects with normal ALT was similar in the two subgroups (78% and 69% in adefovir-resistant and non-resistant subjects, respectively, at Week 48).

6.5. Meta-analysis

Mixed treatment comparison meta-analyses were conducted and are presented in Section 6.6.

6.6. Indirect/mixed treatment comparisons

A meta-analysis was conducted to evaluate the relative efficacy of adefovir, entecavir, lamivudine, telbivudine, tenofovir or combinations of these medications in antiviral-naïve patients with CHB.

The analysis was conducted using mixed treatment comparison (MTC) meta-analytical techniques, which consider all of the evidence on the relative efficacy of each treatment simultaneously to produce estimates of the efficacy of each treatment relative to all others considered in the analysis.

Study identification

A systematic review was conducted to obtain all the relevant evidence for tenofovir versus comparators. The inclusion criteria and search strategy used to identify relevant studies to be included in the systematic review are described in Appendix 2 and Section 6.1.

The meta-analysis was conducted on studies meeting additional, more stringent inclusion criteria in addition to those for the broader systematic review to ensure that only comparable studies were combined statistically. In particular, the meta-analysis was restricted to RCTs that met the below criteria:

- <50% of patients were co-infected with HIV.
- The trial evaluated one or more of the below treatments:
  - 300 mg/day tenofovir
  - 10 mg/day adefovir
  - 0.5 or 1 mg/day entecavir
  - 600 mg/day telbivudine
  - 100 or 150 mg/day lamivudine
  - any combination of the above nucleos(t)ides.
- The trial reported one of the below outcomes after 40-72 weeks of therapy:
  - Percentage/number of patients with HBV DNA levels below a threshold of 1,000 copies/mL or less
  - Percentage/number of patients with HBeAg seroconversion or loss

- Studies and study arms evaluating interferons, unlicensed treatments/doses or sequential use of several treatments within the same 12-month period were excluded from the analysis.
- Studies on patient populations falling into one of the below subgroups:
  - HBeAg-positive nucleos(t)ide naïve patients:
    - ≥66.7% of the population was HBeAg-positive at baseline or if results were reported separately for HBeAg-positive subgroup.
    - <33% of patients were resistant/refractory to lamivudine or one of the nucleos(t)ides considered in the analysis.
  - HBeAg-negative nucleos(t)ide naïve patients:
    - ≥66.7% of the population was HBeAg-negative at baseline or if results were reported separately for HBeAg-positive subgroup.

        - <33% of patients were resistant/refractory to lamivudine or one of the nucleos(t)ides considered in the analysis.
    - HBeAg-positive lamivudine-refractory patients:
        - ≥66.7% of the population was HBeAg-positive at baseline or if results were reported separately for HBeAg-positive subgroup.
        - ≥66.7% of patients were resistant/refractory to lamivudine or one of the nucleos(t)ides considered in the analysis.
    - HBeAg-negative lamivudine-refractory patients:
        - ≥66.7% of the population was HBeAg-negative at baseline or if results were reported separately for HBeAg-positive subgroup.
        - ≥66.7% of patients were resistant/refractory to lamivudine or one of the nucleos(t)ides considered in the analysis.

Full details of the criteria used to identify comparable evidence appropriate for meta-analysis are described in Appendix 4.

The methodology, data inputs and full results of these meta-analyses can be seen in Appendix 4. The results of the meta-analysis on HBeAg-positive patients was the subject of an poster presentation at the European Association for the Study of the Liver (EASL) (32).

6.6.1. Methods of the meta-analysis

Summary of methods
Meta-analyses were conducted on two outcomes: the probability of HBeAg seroconversion and the probability of achieving HBV DNA <300 copies/mL[h]. Statistical transformations were used to estimate these parameters from data on closely related outcome measures. Data on the number of patients undergoing HBeAg loss were converted into estimates of the number undergoing HBeAg seroconversion by assuming that 92% of patients losing HBeAg will also undergo HBeAg seroconversion within the same year, based on data extracted from the three largest trials reporting both measures (26, 79, 80). The proportion of patients with HBV DNA <300 copies/mL was estimated from data on other thresholds by fitting curves to data from the 0102 and 0103 tenofovir trials (26, 33) to identify the method that best estimated the proportion of patients below any given HBV DNA threshold from data at another threshold. A logarithmic function was found to fit the data best. The algorithm was validated against data from an entecavir trial (79) and was used to estimate the proportion of patients with HBV DNA <300 copies/mL for trials where other thresholds were used.

The techniques of Bayesian mixed treatment comparison meta-analysis (81, 82) were used to analyse the data collected in the systematic review and assess the relative efficacy of the different treatments. These techniques allow for the relative treatment effect seen in each trial (measured as odds ratios) and consider all evidence, whether direct (odds ratios measured in a head-to-head RCT) or indirect (odds ratios calculated from a series of pair-wise comparisons that connect the two

[h] The meta-analysis used the outcome measure of the proportion of patients with HBV DNA < 300 copies/mL rather than any other threshold since this outcome measure was reported in a larger number of the studies meeting the inclusion critiera for the meta-analysis than any other threshold HBV DNA value. It was not possible to use the threshold that formed the primary analysis in the pivotal trials on tenofovir (400 copies/mL) since it was reported less commonly in studies on other drugs and use of this threshold would have meant that a higher proportion of the data in the meta-analysis would have had to be imputed, instead of being based on on-treatment data.

treatments). Such methods have been endorsed by NICE (83) and have been used in various NICE appraisals and publications (84-86).

Analyses were conducted in WinBUGS Version 14 using code for fixed and random effects mixed treatment comparison analyses that allows for trials with up to three treatment arms. The two outcome measures (HBeAg seroconversion and HBV DNA) were analysed separately. All analyses were conducted using random-effects models unless the between-studies standard deviation (tau) was close to zero.

A number of sensitivity analyses were conducted to assess the robustness of the analysis, including using both fixed and random effects models, allowing for covariates (baseline viral load and the proportion of patients who were HBeAg-positive at baseline), changing priors and adding/removing trials from the analysis.

Additional statistical details

Gaussian non-informative priors were used for all treatment effects and baseline odds of response. However, sensitivity analyses demonstrated that the width of 95% credible intervals (95% CrI) was sensitive to the prior for the between-studies SD, although the analysis produced similar estimates of the mean of the posterior distribution of the probability of response for each treatment regardless of the priors used. In order to allow for a realistic degree of heterogeneity between studies, an informative half-normal prior was used for the between-studies SD, which was based on that calculated from a re-analysis of the data from a previous systematic review on interferon-alpha (7) using a standard Bayesian random effects meta-analysis; data on HBeAg seroconversion and undetectable HBV DNA were analysed separately to produce priors specific to each outcome measure.

For each of the main analyses, a burn in of between 500,000 and 2,000,000 simulations (depending on how quickly convergence was achieved) was run for two sets of initial values and results were based on a further 50,000 sampled simulations.

Differences between treatments were considered significantly significant at the 0.05 level if the 95% CrI for the odds ratio did not include 1. All p-values represent Bayesian p-values.

6.6.2. Results from the meta-analysis

Key results from the meta-analysis

- Tenofovir is the most potent nucleos(t)ide for reducing HBV DNA
- There is no statistically significant difference between nucleos(t)ides with regard to the proportion of patients achieving HBeAg seroconversion

Studies identified

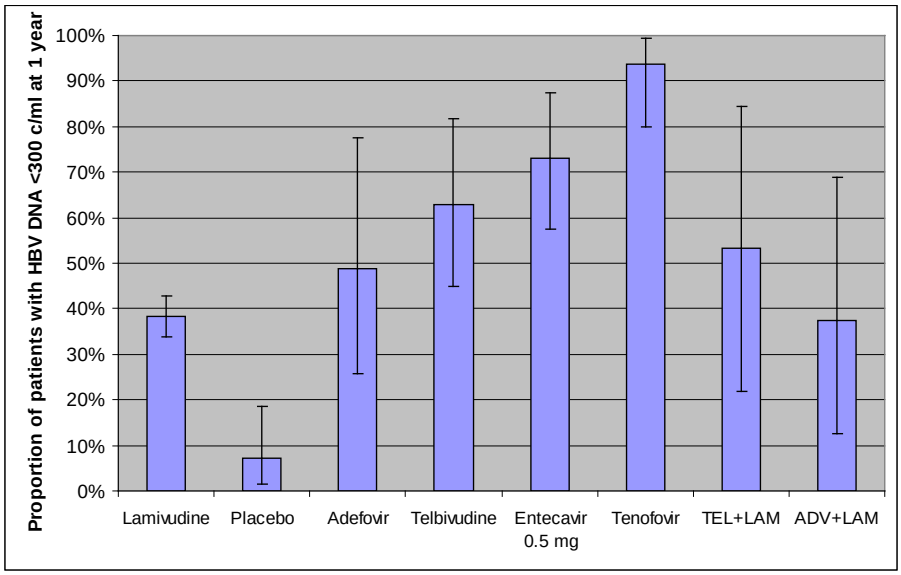
A total of 23 RCTs met the narrower inclusion criteria for the meta-analysis (Figure 1, Section 6.1), (13, 19, 20, 43, 44, 74, 76, 79, 87-104) of which 13 were on treatment-naïve patients with HBeAg-positive CHB (19, 43, 44, 76, 79, 87-94). Four RCTs met the criteria for the HBeAg-negative treatment-naïve subgroup (13, 20, 43, 74); five met the criteria for the HBeAg-positive lamivudine-resistant subgroup (95-103); and one met the criteria for the HBeAg-negative lamivudine-resistant subgroup (104).

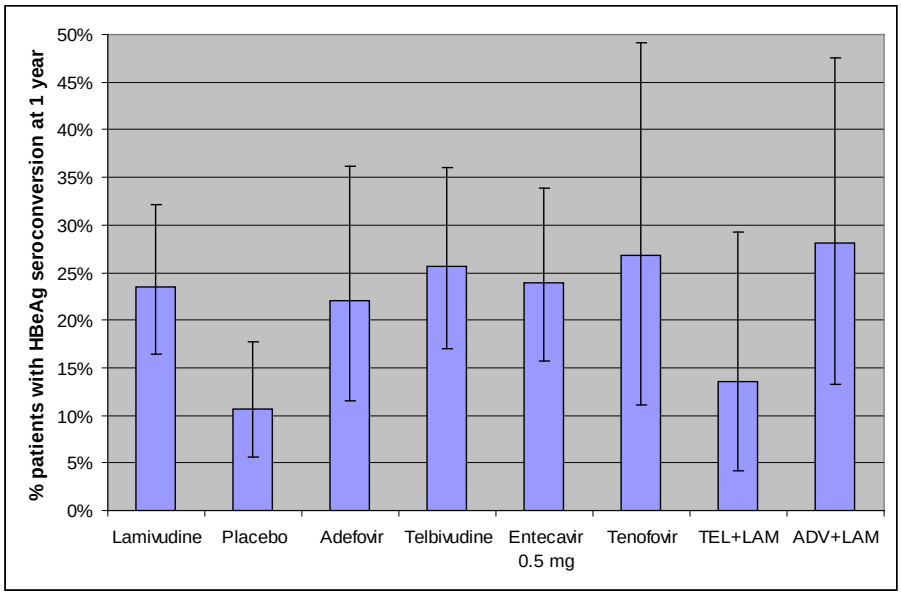
Results of the meta-analysis on HBeAg-positive nucleos(t)ide naïve patients
The analysis of HBV DNA was conducted using a random-effects model since significant heterogeneity was identified. This meta-analysis demonstrated that tenofovir had the highest probability of achieving HBV DNA levels undetectable by PCR after 1 year of therapy for HBeAg-positive nucleos(t)ide-naïve patients (Table 16, Figure 4). The probability of achieving undetectable HBV DNA with tenofovir was found to be significantly higher than that for all other treatments considered in the analysis at the 0.05 level, including entecavir and telbivudine. The analysis demonstrated that there is a 98% probability that tenofovir is the most potent nucleos(t)ide considered in this analysis in terms of this outcome.

All treatments were associated with a significantly higher chance of achieving undetectable HBV DNA than placebo and tenofovir, entecavir and telbivudine were also found to be significantly superior to lamivudine at the 0.05 level.

There is currently a shortage of evidence on combination therapy. Only two small RCTs evaluating nucleos(t)ide combination therapy met inclusion criteria (44, 92). Since both trials found combination therapy to have a slightly lower probability of undetectable HBV DNA than monotherapy ($p>0.05$), a similar non-significant trend was observed in the meta-analysis, but should be interpreted cautiously due to the small patient numbers.

Figure 4: Proportion of patients achieving undetectable HBV DNA or HBeAg seroconversion at 1 year with each nucleos(t)ide and for placebo. Error bars represent 95% credible (Bayesian probability) intervals (95% CrI)[i].





[i] Credible intervals are the Bayesian equivalent of confidence intervals. There is a 95% probability that the true value falls within the 95% credible interval.

Table 16: Key results of the meta-analysis of outcomes after 1 year of treatment. Full results can be seen in Appendix 4

Treatment (No. trials)	% pts HBV DNA <300 copies/mL (95% CrI)	OR vs LAM (95% CrI)	% pts HBeAg sero-converted (95% CrI)	OR vs LAM (95% CrI)
Tenofovir (1)	93.7% (80.0%, 99.3%)[l,p,*]	52.78 (6.427, 226.4)	26.7% (11.1%, 49.1%)[p]	1.275 (0.441, 2.984)
Entecavir (3)	73.1% (57.6%, 87.6%)[l,p]	4.941 (2.228, 11.6)	23.9% (15.7%, 33.9%)[p]	1.027 (0.758, 1.361)
Telbivudine (3)	62.9% (44.8%, 81.7%)[l,p]	3.091 (1.275, 7.517)	25.7% (17.1%, 36.1%)[p]	1.132 (0.827, 1.51)
Telbivudine + lamivudine (1[†])	53.3% (21.9%, 84.3%)[p]	2.576 (0.434, 9.292)	13.5% (4.2%, 29.3%)	0.532 (0.15, 1.289)
Adefovir (4)	48.8% (25.8%, 77.5%)[p]	1.861 (0.551, 5.715)	22.1% (11.6%, 36.1%)[p]	0.946 (0.467, 1.703)
Lamivudine (9[‡])	38.4% (33.9%, 42.8%)[p]	-	23.5% (16.4%, 32.1%)[p]	-
Adefovir + lamivudine (1[†])	37.5% (12.5%, 68.7%)[p]	1.182 (0.231, 3.651)	28.1% (13.2%, 47.6%)[p]	1.344 (0.536, 2.814)
Placebo (5[‡])	7.1% (1.5%, 18.5%)	0.129 (0.025, 0.373)	10.7% (5.6%, 17.7%)	0.393 (0.213, 0.65)

CrI, credible (Bayesian probability) interval; OR, odds ratio showing how many times higher probability of this outcome is with the treatment in question, compared with lamivudine.
[*] Significantly superior to all 7 treatments included in the analysis at the 0.05 level.
[l] Significantly superior to lamivudine at the 0.05 level.
[p] Significantly superior to placebo at the 0.05 level.
[†] n<60.
[‡] Data on patient achieving undetectable HBV DNA by PCR were unavailable for 3 placebo-controlled lamivudine trials.

The analysis was repeated for data on HBeAg seroconversion by one year. For this analysis, a fixed-effects meta-analysis was conducted since there was little heterogeneity between studies. All treatments other than telbivudine+lamivudine were found to significantly increase the probability of HBeAg seroconversion at 1 year relative to placebo at the 0.05 level (Table 16, Figure 4). However, this analysis identified no statistically significant differences between nucleos(t)ides for this outcome.

Results on the probability of HBV DNA <300 copies/mL in HBeAg-negative nucleos(t)ide naïve patients

- Sparse network of trials (four trials met inclusion criteria and reported this outcome (13, 33, 66, 74, 105-108)).
- Even when a fifth study (109) comparing lamivudine with placebo that met all criteria other than study length (two years vs one year), the analysis did not converge due to the small number of trials and the presence of zero cell counts in trial 438 (74).
- No meaningful data can be generated based on HBeAg-negative subgroup alone.
- An additional analysis combining trials on HBeAg-positive and HBeAg-negative patients in which the proportion of patients who were HBeAg-positive was considered as a covariate produced similar results to the HBeAg-positive subgroup.

Results for HBeAg-positive lamivudine-refractory HBV mono-infected patients

- Five RCTs met the inclusion criteria (95-103, 110, 111).
- A random effects model was used, in which the between-studies standard deviation was informed by data from a meta-analysis of placebo-controlled studies evaluating interferon-alpha (7).

- All treatments significantly increased the chance of achieving undetectable HBV DNA relative to lamivudine, although there were no statistically significant differences between other nucleos(t)ides.
- Analysis suggested that adefovir and adefovir+lamivudine may be the most effective in terms of both HBeAg seroconversion and viral suppression (p>0.05).

Results for HBeAg-positive lamivudine-refractory patients with or without HIV co-infection

- Seven RCTs met the inclusion criteria (23, 71, 95-103, 110, 111).
- A random effects model was used, in which the between-studies standard deviation was informed by data from a meta-analysis of placebo-controlled studies evaluating interferon-alpha (7).
- Tenofovir was found to be the most effective treatment in terms of achieving undetectable HBV DNA, with a 70% chance of being most effective.
- All treatments significantly increased the chance of achieving undetectable HBV DNA relative to lamivudine, although there were no statistically significant differences between other nucleos(t)ides.
- The analysis on HBeAg seroconversion did not converge and no meaningful results could be generated.

Results for HBeAg-negative lamivudine-resistant/refractory patients

- Only one RCT met the inclusion criteria (104).
- No MTC could be conducted.
- An analysis combining the results of trials on HBeAg-positive, HBeAg-negative, HBV monoinfected and HIV co-infected patients confirmed the results of other analyses, showing that tenofovir has the highest chance of achieving undetectable HBV DNA.

6.6.3. Conclusions of the meta-analysis

- The mixed treatment comparison meta-analysis demonstrated that tenofovir is the most effective nucleos(t)ide treatment evaluated in RCTs in terms of achieving undetectable HBV DNA (<300 copies/mL) at one year.

- Tenofovir was significantly superior to all other nucleos(t)ides for this outcome in HBeAg-positive nucleos(t)ide-naïve patients and for the analysis that combined data on HBeAg-positive and HBeAg-negative nucleos(t)ide-naïve patients together.

- Tenofovir was associated with the highest probability of achieving undetectable HBV DNA at one year in lamivudine-resistant patients and was significantly superior to lamivudine, although there were no statistically significant differences between other nucleos(t)ides.

- There were no statistically-significant differences between nucleos(t)ides in terms of HBeAg seroconversion, either in treatment-naïve or lamivudine-resistant patients.

6.7. Safety

6.7.1. Key results regarding tenofovir safety

Tenofovir continues to demonstrate a desirable safety profile at two years.

The results in patients with CHB are consistent with those observed in HIV, where there are currently 2 million patient years of safety data (34).

6.7.2. Safety evidence from RCTs

6.7.2.1. GS-US-174-0102

The safety analysis set included all randomised subjects who received at least one dose of study medication (RAT analysis set) (33). Tenofovir was well tolerated; the overall frequency of AEs was similar between groups (Table 17), and the majority were mild or moderate, and unrelated to treatment.

Adverse events classed as 'investigations' were significantly more frequent among subjects in the adefovir group (19/125 [15.2%]) than among those in the tenofovir group (19/250 [7.6%]) (p=0.029), due in part to the increased incidence of blood creatine phosphokinase (CPK) increased AEs and blood creatinine increased AEs in the adefovir group (CPK increased: 5/125 [4.0%] adefovir vs 1/250 [0.4%] tenofovir; creatinine increased: 4/125 [3.2%] adefovir vs 1/250 [0.4%] tenofovir) (33).

Table 17: **Treatment-emergent adverse events of any severity occurring in at least 5% of subjects in either treatment group (RAT analysis set).**

Adverse event	Tenofovir N=250	Adefovir N=125	P-value
Any adverse event	176 (70.4%)	92 (73.6%)	0.546
Headache	26 (10.4%)	16 (12.8%)	0.491
Nasopharyngitis	21 (8.4%)	12 (9.6%)	0.702
Back pain	18 (7.2%)	7 (5.6%)	0.664
Abdominal pain (upper)	17 (6.8%)	8 (6.4%)	1.000
Diarrhoea	16 (6.4%)	8 (6.4%)	1.000
Nausea	16 (6.4%)	5 (4.0%)	0.476
Fatigue	15 (6.0%)	8 (6.4%)	1.000
Arthralgia	15 (6.0%)	0 (0.0%)	0.003
Procedural pain	9 (3.6%)	9 (7.2%)	0.132

Other than arthralgia, which occurred in 15 subjects (6.0%) in the tenofovir group and no subjects in the adefovir group (p=0.003), there were no other significant differences in the frequency of treatment-emergent AEs of any severity. The incidence of study drug-related AEs was similar in the two groups (42/250 [16.8%] tenofovir and 24/125 [19.2%] adefovir). The only statistically significant difference between groups in terms of treatment-related AEs was for 'investigations', which occurred in 0.8% (2/250) of subjects receiving tenofovir compared with 7.2% (9/125) subjects in the adefovir group (p=0.001) (33).

Of the most frequently reported AEs of any severity, only headache was reported in more than 4% of subjects in either group at grade two or greater severity (4/250 [1.6%] with tenofovir; 6/125 [4.8%] with adefovir). Grade three or four AEs occurred in 22/250 (8.8%) and 11/125 (8.8%) of subjects receiving tenofovir and adefovir, respectively; the only grade 3/4 AE that occurred in more than 1% of subjects in

either group was increased ALT, which was reported in 5/250 (2.0%) of subjects receiving tenofovir and 1/125 (0.8%) of those receiving adefovir.

Serious AEs (SAEs) (12/250 [4.8%], tenofovir; 7/125 [5.6%], adefovir), and AEs resulting in permanent discontinuation (5/250 [2.0%] tenofovir and 2/125 [1.6%] adefovir) or in change in dose or interruption of study drug treatment (4/250 [1.6%] tenofovir and 1/125 [0.8%] adefovir) were infrequent. There were no deaths reported during the study (33).

Results from Week 48-96

Tenofovir treatment was well tolerated over the 96-week treatment period, and the safety profile between Week 48 and Week 96 was consistent with the results observed over the first 48 weeks of double-blind treatment and the known safety profile of tenofovir.

- The most common AEs during open-label tenofovir treatment were nasopharyngitis, headache, hypertension, and influenza. None required interruption or discontinuation of treatment.
- The frequency of SAEs during open-label treatment was similar in the TDF-TDF and ADV-TDF treatment groups (4.7% and 8.9% respectively). Only one SAE (mild renal impairment, which was managed with a dose reduction) was considered related to study drug.
- Three subjects discontinued open-label tenofovir due to AEs. The only AE that led to discontinuation in more than a single subject during any phase of tenofovir treatment was fatigue (two subjects).
- There was no evidence of renal failure, severe renal impairment, or renal toxicity and no bone events due to tenofovir.
- Two deaths (one from liver carcinoma and one from cervical carcinoma) were reported during the open-label period. Both were considered unrelated to tenofovir.

6.7.2.2. GS-US-174-0103

The safety analysis set included all randomised subjects who received at least one dose of study medication (RAT analysis set) (26). Tenofovir was well tolerated, and its safety profile was consistent with that observed in patients with HIV. The overall frequency of AEs was similar between groups (Table 18). Most were mild or moderate in severity, and unrelated to study drug; the incidence of AEs related to study drug, however, was higher in the tenofovir group (54/176 [30.7%]) than the adefovir group (15/90 [16.7%]) (p=0.018) due to a higher incidence of mild nausea in subjects receiving tenofovir. There were no AEs resulting in permanent discontinuation in the tenofovir group, and 1/90 (1.1%) in the adefovir group

Gastrointestinal disorders were significantly more frequent (p=0.011) in the tenofovir group due to the increased incidence of mild nausea compared with adefovir (24/176 [13.6%] vs 1/90 [1.1%]; p<0.001). All cases of nausea were mild, except for one subject with moderate nausea, and all resolved without treatment. Except for gastrointestinal disorders, the percentages of subjects with AEs in each system organ class were generally similar in the two treatment groups. With the exception of nausea, there were no significant differences between groups in the frequency of treatment-emergent AEs of any severity (26).

A total of six subjects (3.4%) receiving tenofovir and one subject (1.1%) receiving adefovir had AEs in the renal and urinary disorders system organ class, while 7

(4.0%) and 7 (7.8%) in the tenofovir and adefovir groups, respectively, had AEs in the hepatobiliary disorders system organ class. Laboratory abnormalities related to hepatic function that were reported as AEs included ALT increased (5.1%, tenofovir; 4.4%, adefovir), AST increased (1.7%, tenofovir; 2.2%, adefovir), total bilirubin increased (1.1%, tenofovir; 0%, adefovir), and prothrombin time prolonged (1.1%, tenofovir; 0% adefovir) (26).

Table 18: Treatment-emergent adverse events of any severity occurring in at least 5% of subjects in either treatment group (RAT analysis set).

Adverse event	Tenofovir N=176	Adefovir N=90	P-value
Any adverse event	141 (80.1%)	66 (73.3%)	0.216
Nausea	24 (13.6%)	1 (1.1%)	<0.001
Abdominal pain (upper)	13 (7.4%)	3 (3.3%)	0.277
Diarrhoea	12 (6.8%)	3 (3.3%)	0.399
Nasopharyngitis	21 (11.9%)	12 (13.3%)	0.844
Influenza	8 (4.5%)	5 (5.6%)	0.767
Upper respiratory tract infection	6 (3.4%)	6 (6.7%)	0.229
Headache	29 (16.5%)	14 (15.6%)	1.000
Dizziness	13 (7.4%)	2 (2.2%)	0.098
Fatigue	21 (11.9%)	8 (8.9%)	0.536
Influenza-like illness	10 (5.7%)	3 (3.3%)	0.552
Back pain	12 (6.8%)	3 (3.3%)	0.399
Myalgia	8 (4.5%)	5 (5.6%)	0.767
Arthralgia	5 (2.8%)	6 (6.7%)	0.191
ALT increased	9 (5.1%)	4 (4.4%)	1.000
Cough	8 (4.5%)	5 (5.6%)	0.767
Pharyngolaryngeal pain	8 (4.5%)	5 (5.6%)	0.767

ALT, alanine aminotransferase

A total of 54/176 (30.7%) of the tenofovir-treated subjects and 15/90 (16.7%) of the adefovir-treated subjects had at least one treatment-related AE (p=0.018). The difference between groups was largely driven by the increased incidence of mild nausea in the tenofovir group (15/176 [8.5%], tenofovir; 1/90 [1.1%], adefovir; p=0.014). All of these treatment-related AEs of nausea were Grade 1 events. Reproductive system and breast disorders were reported in 9/176 of subjects in the tenofovir group (5.1%) vs none in the adefovir group (p=0.031). All were Grade 1/2, and none were related to study drug. The incidence of Grade 2, 3, or 4 AEs was comparable between the two treatment groups (Table 19).

The proportion of subjects with SAEs was similar in the two treatment groups (15/176 [8.5%], tenofovir; 7/90 [7.8%], adefovir). Of these, 6/176 (3.4%) and 4/90 (4.4%), respectively, were considered related to study drug treatment. There were no deaths reported during the study period (26).

Table 19: Grade 2–4 treatment-emergent adverse events occurring in ≥3% of subjects in either treatment group (RAT analysis set).

Adverse event	Tenofovir N=176	Adefovir N=90	P-value
Any grade two, three, or four adverse event	55 (31.3%)	29 (32.2%)	0.890
Nasopharyngitis	1 (0.6%)	3 (3.3%)	
ALT increased	8 (4.5%)	4 (4.4%)	
Headache	4 (2.3%)	5 (5.6%)	0.171
Hepatitis or hepatitis B	2 (1.1%)	3 (3.3%)	

ALT, alanine aminotransferase

Results from Week 48-96

Tenofovir treatment was well tolerated over the 96-week treatment period, and the safety profile between Week 48 and Week 96 was consistent with the results observed over the first 48 weeks of double-blind treatment and the known safety profile of tenofovir.

- The most common AEs during open-label tenofovir treatment were nasopharyngitis, headache, abdominal pain upper, and cough. None of these required interruption or discontinuation of treatment.
- The frequency of SAEs during open-label treatment was similar in the TDF-TDF and ADV-TDF treatment groups. Three subjects had SAEs considered related to open-label tenofovir, including ALT increased in two subjects (on-treatment hepatic flares in the ADV-TDF group) and facial spasm in one subject.
- One subject in the TDF-TDF group discontinued open-label tenofovir treatment because of an AE of serum creatinine increased (a transient, unconfirmed increase of 0.5 mg/dL from baseline to a peak value of 1.3 mg/dL). No other subject in this study discontinued tenofovir for an AE.
- There was no evidence of renal failure, severe renal impairment, or renal toxicity and no bone events due to tenofovir.
- On-treatment hepatic flares occurred in 1.7% of subjects during open-label treatment (one subject in the TDF-TDF group and three in the ADV-TDF group). In the three subjects in the ADV–TDF group, the flares occurred 8–24 weeks after a change in therapy and were associated with enhanced viral clearance. One of these subjects subsequently lost HBsAg and then seroconverted to anti-HBs and anti-HBe. In the subject in the TDF–TDF group, the flare was associated with an increase in viral load which may have reflected poor compliance. No subject experienced associated symptoms or decompensation, and all flares were resolved or improving at the last assessment.
- No deaths were reported during the study period.

6.7.2.3. GS-US-174-0106

The safety analysis included all randomised subjects who received at least one dose of study medication (RAT analysis set). Data is from the first 48 weeks of treatment.

There were no deaths or discontinuations, dose interruptions, or dose modifications due to AEs. The overall incidence of AEs was similar in the two treatment groups (77% in the tenofovir group and 71% in the emtricitabine/tenofovir group). Grade 2–4 AEs, Grade 3–4 AEs, and SAEs were somewhat less frequent in the tenofovir group than in the emtricitabine/tenofovir group (38% vs. 50% for Grade 2–4 AEs, 2% vs. 8% for Grade 3–4 AEs and SAEs), but none of the differences were statistically significant.

The most frequent AEs in both treatment groups were nasopharyngitis (23% and 17% in the tenofovir and emtricitabine/tenofovir group), headache (19% and 15%), and fatigue (11% and 14%) (Table 20). The only statistically significant difference in the incidence of AEs was for upper abdominal pain, which occurred in 2% of subjects in the tenofovir group and 14% in the emtricitabine/tenofovir group ($p = 0.031$); however, this observation is considered questionable because unspecified abdominal pain was reported more frequently in the tenofovir group (9% vs. 4%), and the percentage of subjects with any abdominal pain AE was similar in the two groups (11% vs. 15%). Abdominal pain/upper abdominal pain AEs were mild in severity for

11 subjects and moderate for 3 subjects, and most were considered not related to study drug (12/14 subjects)

Table 20: Treatment-emergent adverse events of any severity occurring in at least 5% of subjects in either treatment group (RAT analysis set).

Adverse event	Tenofovir N=53	Emtricitabine/ tenofovir N=52	Overall N=105	P-value
Any adverse event	41 (77.4%)	37 (71.2%)	78 (74.3%)	0.509
Nasopharyngitis	12 (22.6%)	9 (17.3%)	21 (20.0%)	0.627
Urinary Tract Infection	4 (7.5%)	2 (3.8%)	6 (5.7%)	0.678
Abdominal Pain Upper	1 (1.9%)	7 (13.5%)	8 (7.6%)	0.031
Abdominal Pain	5 (9.4%)	2 (3.8%)	7 (6.7%)	0.437
Diarrhoea	3 (5.7%)	3 (5.8%)	6 (5.7%)	1.000
Nausea	3 (5.7%)	2 (3.8%)	5 (4.8%)	1.000
Fatigue	6 (11.3%)	7 (13.5%)	13 (12.4%)	0.775
Asthenia	7 (13.2%)	2 (3.8%)	9 (8.6%)	0.161
Headache	10 (18.9%)	8 (15.4%)	18 (17.1%)	0.797
Dizziness	2 (3.8%)	3 (5.8%)	5 (4.8%)	0.678
Pharyngolaryngeal Pain	5 (9.4%)	2 (3.8%)	7 (6.7%)	0.437
Blood Creatine Phosphokinase Increased	0	4 (7.7%)	4 (3.8%)	0.057
Alanine Aminotransferase Increased	0	3 (5.8%)	3 (2.9%)	0.118
Decreased Appetite	3 (5.7%)	0	3 (2.9%)	0.243

A total of 26% of subjects in the tenofovir group and 31% of subjects in the emtricitabine/tenofovir group had at least one AE considered by the investigator to be related to study drug. The most frequently reported AE considered related to study drug was headache (9% in the tenofovir group and 4% in the emtricitabine/tenofovir group).

One subject (2%) in the tenofovir group and 4 subjects (8%) in the emtricitabine/tenofovir group had at least one SAE. No SAE was reported in more than one subject. Only one SAE (ALT increased) was considered related to study drug; this event also met the protocol-specified criteria for an on-treatment hepatic flare.

No marked laboratory abnormality occurred in more than one subject, except for increased ALT levels in 3 subjects, increased creatine kinase in 2 subjects, and electrolyte abnormalities (decreased serum calcium levels, increased serum potassium levels, and decreased serum magnesium levels) that were unconfirmed and resolved while on continued treatment at the next study visit, and therefore were considered spurious. Among the 3 subjects with marked ALT abnormalities, 2 subjects (both in the emtricitabine/tenofovir group) met the criteria for on-treatment hepatic flare. The third subject was in the tenofovir group and had a single Grade 3 ALT value that resolved at the next visit.

Of the 2 subjects with hepatic flares, one had an increase in ALT to a Grade 4 value at Week 8, which was concomitant with a 3-log decrease in HBV DNA. The other subject had an increase in ALT to a Grade 4 value at Week 48. The HBV DNA level was similar to the baseline level at the time of the flare, possibly due to low adherence (55%) to the active component of the treatment regimen. These laboratory abnormalities were not accompanied by other changes in liver function

tests and resolved within 12–16 weeks. Neither subject showed any signs of decompensation.

No clinically important AEs related to renal function, bone events or fractures related to study drug, or clinically important changes in renal laboratory parameters were observed.

6.7.3. Conclusions regarding safety of tenofovir

- The overall incidence of AEs was comparable in patients receiving tenofovir or adefovir and in patients receiving tenofovir or emtricitabine/tenofovir
- The most common AEs across the studies included headache, nasopharyngitis, backpain, nausea, and fatigue
- The incidence of grade 3/4 AEs and SAEs was similar between treatment groups
- There were no deaths in the studies

These results in patients with CHB are consistent with those observed in HIV, where there are currently 2 million patient years of safety data (34).

6.8. Tenofovir non-RCT evidence

6.8.1. Details of how the relevant tenofovir non-RCTs have been identified and selected

Forty-six non-randomised studies were identified by the systematic review (Section 6.1 and Appendix 2). Five of these studies related to the use of tenofovir in HBV mono-infected patients and all were considered relevant (24, 25, 27-29, 31). These studies were used to provide data on the incidence of drug resistance.

In addition to these five relevant studies meeting the inclusion criteria, one additional study that was technically excluded from the systematic review on grounds of size is included here since it comprises one of only two studies that have evaluated tenofovir in patients who have failed to respond to adefovir (30, 31)[j].

[j] The abstract (30) and paper (31) by van Bommel et al were treated as a single study since the description of patients given in the two publications suggest that the patient populations overlap entirely.

6.8.2. Summary of methodology of relevant non-RCTs

A summary of the methodology of the relevant tenofovir non-randomised trials is shown in Table 21.

Table 21: Summary of methodology of relevant non-RCTS

Study	Objectives	Intervention	Participants	Duration	Study type	Outcome measures
van Bommel et al 2007 (25)	To study the effectiveness of tenofovir monotherapy in patients with HBV monoinfection with respect to virologic parameters and resistance	300 mg tenofovir o.d.	Patients with CHB infection with HBV DNA $>10^5$ copies/mL. 75 patients were lamivudine resistant	> 6 months	Uncontrolled, retrospective multi-centre analysis	• HBV DNA levels • Resistance • HBeAg seroconversion • HBsAg loss • ALT levels
van Bommel et al 2006 (24)	Long-term effectiveness of tenofovir with respect to virologic parameters and resistance development	300 mg tenofovir o.d.	Patients with lamivudine-resistant HBV infection and different co-morbidities. 24 patients HIV/HBV co-infected, 47 patients HBV mono-infected	9 – 61 months	Uncontrolled, retrospective long-term study	• HBV DNA levels • Resistance • HBeAg seroconversion • HBsAg loss • ALT levels
Im et al 2005 (27)	To compare the efficacy and tolerability of tenofovir and adefovir based combination therapy in patients with CHB	Group 1: Tenofovir + emtricitabine Group 2: tenofovir + lamivudine Group 3: adefovir + emtricitabine Group 4: adefovir + lamivudine	CHB patients. HIV negative. 20 patients had previously received ADV or LAM and were switched to combination therapy due to viral breakthrough or failure to achieve undetectable HBV DNA levels	> 6 months	Controlled, retrospective study	• Number patients achieving undetectable HBV levels • Normalisation of ALT • HBeAg seroconversion • Adverse events
Hann et al 2006 (28)	To compare the suppressive activities of tenofovir and adefovir against LAM resistant HBV	Group 1: Tenofovir Group 2: adefovir	CHB patients with lamivudine resistance	6 – 38 months	Controlled, retrospective study	• Reduction of HBV DNA • ALT normalisation • HBeAg loss
van Bommel et al 2004 (29)	To compare the effect of tenofovir and adefovir on HBV DNA suppression.	Group 1: Tenofovir 300 mg o.d. Group 2: adefovir 10 mg o.d.	CHB patients with high HBV DNA levels and genotypic evidence of lamivudine resistance. HIV/HBV co-infected patients included.	60 – 130 weeks	Prospective, active-controlled	• HBV DNA levels • ALT levels • Resistance • HBeAg seroconversion • HBsAg loss
van Bommel et al 2006 (30, 31)	To investigate whether the efficacy of viral suppression could be improved by replacing adefovir with tenofovir.	Tenofovir 300 mg o.d.	CHB patients with viral breakthrough during lamivudine therapy and persistent viral replication after adefovir monotherapy	3 – 24 months	Retrospective, uncontrolled	• HBV DNA levels • Resistance • HBeAg seroconversion • HBsAg loss • ALT levels

6.8.3. Critical appraisal of relevant non-RCTs

A critical appraisal of the relevant non-RCTs is given in Table 22. These studies were generally of low quality.

Table 22: Critical appraisal of relevant non-RCTs

Study	Critical appraisal
Van Bommel et al 2007 (25)	Non-randomised, retrospective study. One hundred and twenty-one patients treated with tenofovir were retrospectively analysed. Inclusion criteria were very brief. Published as an abstract only.
Van Bommel et al 2006 (24)	Non-randomised, retrospective study. Seventy-one lamivudine resistant patients treated with tenofovir were retrospectively analysed. Inclusion criteria were not defined. Presented as a poster (American Association for the Study of Liver Diseases).
Im et al 2005 (27)	Non-randomised, retrospective study. Patients receiving combination nucleos(t)ide therapy were identified from a database of HBV patients. Inclusion criteria were not defined. Thirteen patients received tenofovir based regimens and 17 received adefovir based regimens. Published as an abstract only.
Hann et al 2006 (28)	Non-randomised retrospective study. One hundred and nine lamivudine resistant patients treated with tenofovir or adefovir were retrospectively analysed. Forty-four patients received tenofovir and 65 received adefovir. Inclusion criteria were very brief. Presented as a poster (Digestive Disease Week).
Van Bommel et al 2004 (29)	Non-randomised prospective study. Fifty-three patients who developed lamivudine resistance were included in the study. The study gave defined patient inclusion criteria. Patients were enrolled consecutively according to the availability of tenofovir and adefovir. Thirty-five patients were treated with tenofovir and 18 with adefovir. Published as a full paper.
Van Bommel et al 2006 (30, 31)	Non-randomised, retrospective study. Twenty lamivudine resistant patients with an insufficient virological response to adefovir were switched to tenofovir and retrospectively analysed. This study has a small number of patients and does not meet the inclusion criteria of the systematic review, but has been included because it comprises one of only two studies that have evaluated tenofovir in patients who have failed to respond to adefovir. The study gave defined inclusion criteria. Published as a full paper.

6.8.4. Results of the relevant non-RCTs

The non-RCTs provide additional evidence on the safety and efficacy of tenofovir that in situations that have not been evaluated in RCTs (Table 23). In particular:

- Non-RCTs confirm the meta-analysis finding that tenofovir is more effective than adefovir (27-29).
- Studies suggest that tenofovir is safe and effective when used in combination with other antiviral medications, such as emtricitabine or lamivudine (27).
- Studies suggest that tenofovir is also an extremely effective treatment in patients who are lamivudine resistant (24, 25, 27-29) and in those who have both lamivudine resistance and have failed adefovir (30, 31).
- There is evidence of continued efficacy and safety in up to five years of continuous treatment (24).
- No studies identified any cases of virologic resistance to tenofovir (24, 25, 27-29, 31).

However, these findings must be interpreted cautiously due to the methodological weaknesses of these studies (Section 6.8.3).

Table 23: Results of the relevant non-RCTs

Study	Patient characteristics at baseline	Efficacy outcomes	Adverse events	Study conclusions
van Bommel et al 2007 (25)	121 patients; 87 male, mean age 45 ± 12 years, 70 HBeAg-positive. 105 had been treated with lamivudine and 75 consecutively with adefovir for lamivudine resistance. 14 patients were excluded with genotypic ADV resistance and 6 due to non-compliance to tenofovir.	• HBV DNA levels decreased from mean baseline of 6.7 ± 1.3 by a mean of 3.8 ± 1.1 and 4.1 ± 1.2 log copies/mL at weeks 24 and 48, respectively. • HBV DNA was undetectable (<400 copies/mL) in 72% and 91% of the patients at weeks 24 and 48, respectively. • No evidence of tenofovir resistance development • HBeAg seroconversion observed in 23% after mean tenofovir treatment of 9 ± 3 months. • HBsAg loss observed in 4% after 13 ± 6 months. • 78% patients had normal ALT levels at week 48 (70% had elevated ALT levels at baseline).	No significant side effects were observed.	Results demonstrate the high efficacy and lack of resistance of tenofovir monotherapy in nucleos(t)ide experienced and therefore difficult-to-treat mono-infected HBV patients.
van Bommel et al 2006 (24)	71 patients; 60 male, mean age 45 ± 11 years, 62 HBeAg-positive, 24 with HBV/HIV co-infection. All patients had previously been treated with lamivudine for a mean of 30 ± 4 months and had developed genotypic resistance and viral breakthrough. 24 patients were	• HBV DNA was <400 copies/mL in 63% and 90% of the patients at months 6 and 12, respectively. • At month 18, HBV DNA levels were under the lower limit of detection in all patients. • HBV mono-infected patients showed a significantly faster virologic response than HBV/HIV co-infected patients: the mean duration until HBV DNA <400 copies/mL was 4.6 vs. 9.3 months ($p<0.0001$). • No evidence of tenofovir resistance development	No significant side effects or increase of creatinine values were observed.	Results demonstrate the high long-term efficacy and the safety profile on tenofovir in patients with different co-morbidities. Resistance against tenofovir was not observed in the long term therapy.

Study	Patient characteristics at baseline	Efficacy outcomes	Adverse events	Study conclusions
	consecutively treated with adefovir monotherapy for a mean of 15 ± 6 months.	• HBeAg seroconversion observed in 43% after mean tenofovir treatment of 14 ± 2.1 months. • HBsAg loss observed in 9% after 15 ± 4.9 months.		
Im et al 2005 (27)	30 patients; median age 35 years, 77% male, 67% HBeAg positive, all HIV negative. 70% previously received adefovir or lamivudine monotherapy.	• Mean time to HBV DNA <160 c/mL was shorter in NA naive vs. experienced patients (4.5 vs 6.5 months), but longer in HBeAg-positive vs HBeAg-negative patients (7 vs 5 months). • 69% normalised ALT • HBeAg seroconversion observed in 2 patients • Median time to HBV DNA <160 c/mL was; 8 months for tenofovir + emtricitabine; 6.5 months for tenofovir + lamivudine; 5 months for adefovir + emtricitabine; 4.5 months for adefovir + lamivudine. • % patients achieving HBV DNA <160 c/mL at 6 months; tenofovir groups 38% and adefovir groups 52%; and at 12 months; tenofovir groups 80% and adefovir groups 71%.	No adverse events observed and serum creatinine was stable on therapy.	Adefovir based combination regimens achieved a more rapid fall in HBV DNA than tenofovir based regimens. Both tenofovir and adefovir regimens appear potent and well tolerated.
Hann et al 2006 (28)	109 patients; 86 male, mean age 46 years, 78% HBeAg positive.	• At 6 months, mean HBV DNA reduction (log_{10} copies/mL) was 3.65 ± 1.75 for tenofovir and 1.94 ± 1.98 for adefovir (p=0.001). • At 12 months, mean HBV DNA reduction was 5.03 ± 1.64 for tenofovir and 2.36 ± 2.37 for adefovir (p=0.001). • HBV DNA reduction >3 log at 12 months was 63% and 28% for tenofovir and adefovir respectively (p=0.013). • HBeAg loss in 24 months showed no difference; 4% for tenofovir and 7% for adefovir. • No patient developed tenofovir resistance during the entire observation period.	Not reported.	For lamivudine resistant HBV, tenofovir alone or in combination with lamivudine, exerts greater viral reduction than adefovir. There is no difference in HBeAg loss or ALT normalisation between tenofovir and adefovir.
van Bommel et al 2004 (29)	53 patients; 35 tenofovir treated and 18 adefovir treated. Mean age; tenofovir treated 47 ± 2 years and adefovir treated 45 ± 3.7 years. Male subjects, 32 tenofovir treated and 14 adefovir treated. HBeAg positive; 89% in both treatment groups.	• Decline of HBV DNA levels was faster in tenofovir-treated patients (2.9 log_{10} vs 1.9 log_{10} copies/mL at day 35; p=0.085). • % patients showing viral decline to $<10^5$ copies/mL at weeks 12, 24 and 48 was significantly higher in the tenofovir than adefovir group. • ALT levels normalised more rapidly in the tenofovir group than the adefovir group (week 24, 69% vs. 53%; week 36, 87% vs. 50%, p=0.006; week 48, 85% vs. 57%, p=0.008). • In all tenofovir treated patients HBV DNA levels became undetectable within 44 weeks of treatment and remained undetectable during the 130 week observation period. • Phenotypic resistance to tenofovir was not observed. • HBeAg loss occurred in 35% HBeAg-positive patients in the tenofovir group vs. 19% in the adefovir group. • HBsAg loss occurred in 14% patients in the tenofovir group vs 5.6% in the adefovir group.	No major clinical side effects were observed.	Data suggest that tenofovir has a stronger antiviral activity than adefovir.

Study	Patient characteristics at baseline	Efficacy outcomes	Adverse events	Study conclusions
van Bommel et al 2006 (31)	20 patients; 16 male, age range 19 - 76 years; 19/20 HBeAg positive. All patients had viral breakthrough during lamivudine therapy and were consecutively treated with adefovir. Patients were then switched to tenofovir due to insufficient virological response to adefovir.	• Median decrease of HBV DNA was -3.37 ± 1.0 log_{10} copies/mL and -3.7 ± 1.1 log_{10} copies at 3 and 6 months respectively. • Suppression of HBV DNA to an undetectable level was achieved in 19/20 patients. The only patient who remained viraemic had a reduced tenofovir dose due to renal insufficiency. • At the end of the observation period 16/20 patients had normal ALT values. • 4 patients lost HBeAg.	No significant side effects or changes in creatinine levels were observed.	Preliminary observations strongly suggest that tenofovir might be a highly effective rescue drug for HBV-infected patients with altered responsiveness to treatment with lamivudine and adefovir.

Abbreviations; c/mL, copies/mL; HBV, hepatitis B virus; ALT, alanine aminotransferase; vs, versus

6.9. Interpretation of clinical evidence

6.9.1. Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The pivotal phase III RCTs are highly relevant to the decision problem: in particular, they were conducted on the same patient population and consider use of 300 mg tenofovir in the primary position in which a recommendation is sought, namely use of tenofovir monotherapy in nucleos(t)ide-naïve patients (19, 20, 26, 33). In particular, these (and other) trials demonstrate that:

- Tenofovir has proven potency against HBV (17-20, 26, 33), including lamivudine-resistant viral strains (112-114).
- Ongoing phase III RCTs have demonstrated that tenofovir is superior to adefovir in terms of the primary endpoint[k] and in terms of reduction in HBV DNA levels to <400 copies/mL after 48 weeks of therapy (19, 20, 26, 33).
- Study 0103 has also demonstrated that tenofovir significantly increases the probability of HBeAg and HBsAg seroconversion compared with adefovir (18).
- During the 96 weeks of follow up completed to date, tenofovir was found to provide durable viral suppression and a low incidence of adverse events.
- A meta-analysis shows tenofovir to have a significantly greater probability of achieving undetectable HBV DNA levels than lamivudine, adefovir, telbivudine or entecavir (32).
- The overall incidence of adverse events (including grade 3/4) with tenofovir is comparable to adefovir (19, 20, 26, 33). Furthermore, the safety/tolerability profile tenofovir is supported by 2 million patient-years' of use in patient with HIV (34).
- Furthermore, no cases of virologic resistance to tenofovir have been observed to date during more than one thousand patient-years of therapy in controlled clinical trials (16, 23-26, 29, 33) (Section 6.10.1.5).

Since tenofovir has been shown to provide effective viral suppression (19, 20), superior potency compared with other nucleos(t)ides (32), an acceptable safety profile (17, 18) and no cases of virologic resistance identified to date, it is a particularly appropriate first-line treatment option. Furthermore, with tenofovir, these benefits are provided at a lower price than adefovir, entecavir or telbivudine (Table 34, Section 7.2.9.6).

6.9.1.1. The relationship between clinical trial outcomes and clinical benefits experienced by patients.

The primary endpoint of trials 0102 and 0103 was a composite virological and histologic response[l]. EASL guidelines recommend that virological response – HBV DNA levels of below 10^5 copies/mL – and histologic responses using a system that scores necro-inflammatory activity separately from fibrosis (such as the histology activity index) should be used as treatment endpoints (115). Secondary endpoints included changes in histology, viral load, ALT, HBeAg and HBsAg seroconversion and HBV DNA levels.

[k] Complete response at Week 48, defined as HBV DNA less than 400 copies/mL and histologic improvement

[l] Defined as suppression of HBV DNA levels below 400 copies/mL and a two-point or greater reduction in the Knodell necroinflammatory score.

Low or undetectable HBV DNA levels are associated with inactive disease and a reduced risk of hepatic inflammatory injury (52, 115). Lower HBV DNA levels are associated with a reduced risk of death from liver disease (116, 117), HCC (117-119), hepatic decompensation (117, 120) and cirrhosis (121), which are associated with reduced quality of life (37, 38) and increased mortality (115, 117, 122-127, 128 9, 129-133). Undetectable HBV DNA by PCR reduces the risk of drug resistance (66) and increases the chance of HBeAg (66) and HBsAg (134, 135) seroconversion. HBsAg seroconversion represents clearance of the infection and is associated with an extremely favourable prognosis.

The effect of treatments on these endpoints is, therefore, clinically relevant to patients seen in everyday clinical practice.

6.9.2. Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The inclusion criteria of the clinical trials closely match the proposed licensed indication (19, 20, 26, 33) and current clinical guidelines for patient selection. However, trial 0103 excluded patients who had ALT levels between 1 and 2 times the ULN (Section 6.3.2.1), who may be considered for treatment in practice (Appendix 1).

The HBV genotypes at baseline in the clinical trials occurred at different frequencies to those observed in England and Wales (136), however this is not expected to have any significant impact on the efficacy of tenofovir since no relationship has been observed between genotype and response rates for the related nucleotide adefovir (137, 138).

No RCTs have yet investigated tenofovir in lamivudine-resistant patients with HBV mono-infection[m], although its efficacy has been assessed in a subgroup of HIV co-infected lamivudine-resistant patients (23). A number of non-randomised trials also suggest that tenofovir is highly effective and well tolerated in patients with lamivudine-resistant HBV (24, 25, 28-31, 139).

All of the studies described above used the dose of tenofovir licensed for use in the UK and stated in the Summary of Product Characteristics (300 mg o.d., Appendix 1). Accordingly, the results of the tenofovir trials support the use of tenofovir within its licensed indication.

The criteria that should be used to assess whether patients are suitable for treatment are the same for most other antiviral medications and include (Appendix 1):

- ALT >ULN
- Evidence of active viral replication: this would be primarily based on HBV DNA, although the level of HBV DNA that would be considered an indication for treatment varies substantially between around 10^5 and 10^8 copies/mL depending on age, HBeAg status or the degree of liver damage/inflammation.

[m] Study 0121 is an ongoing study that is comparing the antiviral efficacy against HBV of tenofovir versus emtricitabine + tenofovir combination treatment in subjects with lamivudine resistance.

- Histological evidence of active inflammation and/or fibrosis
- No evidence of hepatic decompensation
- Over 18 years of age
- No hypersensitivity to tenofovir or to any of the excipients.

6.10. Other relevant clinical evidence

6.10.1. Tenofovir resistance

6.10.1.1. Key results regarding tenofovir resistance

Tenofovir continues to demonstrate 0% genotypic resistance at up to 2 years.

Despite widespread use of tenofovir, no clinically-significant cases of virologic resistance have yet been identified.

6.10.1.2. Resistance profile of tenofovir

As part of its strategy for evading the immune system, the HBV genome mutates rapidly. In particular, there are a number of polymorphic sites on the genome that vary substantially between and within virus populations and which rapidly evolve over time, with no known impact on the sensitivity of the virus to different medications. By contrast, all mutations known to confer drug resistance occur on conserved sites on the HBV DNA polymerase gene (114, 140, 141).

Resistance mutations can reduce the sensitivity of the virus to the drug by more than 100-fold (10, 142), lead to viral breakthrough ('virologic resistance') within 6–12 months (140) and produce a rise in ALT ('clinical resistance') approximately four months after viral breakthrough occurs (143).

To date, more than 600 HBV-infected patients have received tenofovir in clinical trials in which regular resistance monitoring was conducted (Table 25). Despite widespread use of tenofovir in large trials of HBV mono-infected patients (26, 33) and routine clinical use in HIV-1 co-infected patients, no clinically-significant cases of virologic resistance[n] have yet been identified *in vivo.*

6.10.1.3. In vitro tenofovir resistance data

In vitro work has demonstrated that tenofovir effectively suppresses replication of a wide range of HBV strains, including those resistant to multiple nucleos(t)ides (142, 144). In the isolates investigated by Brunelle et al (142), all the drugs had reduced sensitivity to the drug-resistant HBV strains (Table 24). However, all strains tested were less resistant to tenofovir than the other nucleos(t)ides tested: in particular, no strains reduced the EC_{50} (the effective concentration of tenofovir required to inhibit 50% of viral replication) for tenofovir by more than 2-fold, while the sensitivity of entecavir and lamivudine was reduced by at least 9-fold by all mutations tested. Since the clinical significance of the smaller fold-resistance changes (especially those <10) has yet to be determined, this study demonstrates that tenofovir remains

[n] Virologic resistance was defined as an increase in HBV DNA of ≥1 $\log_{10}$ copies/mL and the presence of mutations conferring drug resistance.

effective against a wide range of HBV strains that are resistant to other nucleos(t)ides.

Table 24: *In vitro* sensitivity of different isolates of HBV to tenofovir and other commonly-used nucleos(t)ides (142).

HBV strain	Fold resistance*			
	LAM	ADV	TDF	ETV
Wt1 (genotype H)	**1**	**1**	**1**	**1**
rtL180M/M204V	>1,000	1.5	1.1	175
rtL180M/A181V	800	2.7	1.4	28
rtV173L/L180M/A181V	1,000	4.8	1.6	50
rtV173L/L180M/A181V/M204V	>1,000	4.0	1.8	>800
rtV173L/L180M/A181V/M204V/N236T	>1,000	7.7	1.8	461
rtV173L/L180M/A181V/N236T	>1,000	>10	1.1	9
Wt2 (genotype E)	**1**	**1**	**1**	**1**
rtV173L/L180M/M204V*	>156	0.7	1.2	43
rtL180M/S202G/M204V*	>156	1.1	2	210

* Fold resistance is equal to mutant EC_{50} / wild-type EC_{50}. EC_{50} = effective concentration: i.e. the concentration at which virus replication is inhibited by 50%. For mutants rtV173L/L180M/M204V and rtL180M/S202G/M204V, the corresponding wt strain is wt1 (genotype H) and the fold resistance is equal to (mutant EC50)/(wt1 EC50). For the other mutants, the corresponding wt strain is wt2 (genotype E) and the fold resistance is equal to (mutant EC50)/(wt2 EC50).

Preclinical studies have identified three mutations (rtN236T, A181V and rtA194T) that reduce the sensitivity of the virus to tenofovir *in vitro*. In a study of HIV–HBV co-infected patients (n=43), the A194T mutation was identified in two patients who had persistently detectable HBV DNA despite 48–77 weeks of combination therapy with tenofovir and lamivudine (60, 113). The A194T mutation reduced the sensitivity of the virus to tenofovir by 7.6-fold *in vitro* (60), although this would not necessarily be considered to be clinically significant. However, these results do not agree with those of Delaney et al, whose *in vitro* analysis demonstrated that the A194T mutation did not cause a significant change in tenofovir susceptibility either as a single mutation or in combination with lamivudine resistance mutations (EC_{50} values changed 1.5 to 2.5 fold) (114).

Furthermore, the significance of the A194T mutation needs to be confirmed as the two cases reported above do not represent the typical clinical pattern seen in patients who develop antiviral-resistant mutations as their presentation was confounded by changes in CD4 count and interruptions of pharmacological therapy. Surveillance for other tenofovir resistance mutations should be continued.

6.10.1.4. Tenofovir resistance data in vivo: 0102, 0103 and 0106

As virologic HBV resistance to tenofovir has not yet been observed *in vivo*, the mutations conferring tenofovir resistance are not well characterised. Complete sequencing of the viral genome was therefore conducted at baseline on all patients participating in the 0102 and 0103 trials and repeat sequencing was conducted at 48, 72 and 96 weeks on all patients with detectable[o] HBV DNA (17, 18, 26, 33, 39). Similarly in study 0106, resistance surveillance was conducted at week 48, or at the point at which patients discontinued therapy. Annual resistance surveillance of studies 0102 and 0103 will continue until patients have received up to eight years of therapy, while that on patients participating in study 0106 will continue for 3.5 years.

[o] It is not possible to conduct sequencing on patients with undetectable viral load; as any clinically-meaningful drug-resistance are associated with viral breakthrough, this strategy ensures that all cases of drug resistance are rapidly identified.

Resistance surveillance in weeks 0-48 of studies 0102 and 0103
Within studies 0102 and 0103, a total of 39/426 (9.2%) tenofovir-treated patients had HBV DNA levels ≥400 copies/mL after the first 48 weeks or therapy, while 10/426 (2.3%) showed viral breakthrough[p] (26, 33, 39). Viral breakthrough has been confirmed to be associated with poor compliance in a number of these cases (22). Fourteen patients who were viraemic at week 48 or discontinued therapy early with detectable viral load showed mutations at polymorphic sites. However, the polymorphic site mutations occurring during the study were similar to those seen in baseline isolates and the presence/absence of polymorphic site mutations at baseline had no impact on response rates to tenofovir (39).

No patients with viral breakthrough had evidence of conserved site changes[q] (26, 33). Since the mutations that affect viral replication and sensitivity to medication generally occur in conserved regions of the viral genome, the absence of conserved site changes in conjunction with viral breakthrough suggests that the viral breakthrough was not related to drug resistance. Although two patients who did not achieve viral suppression to below 400 copies/mL had evidence of conserved site changes, these mutations (S74P/S and H156H/R) occurred outside the catalytic domain of the DNA polymerase and patients continued to show viral suppression with viral loads 5.3–6.6 $\log_{10}$ copies/mL lower than baseline and with no signs of viral breakthrough; subsequently, these cases were not considered to be signs of drug resistance.

In trials 0102 and 0103, no subjects developed substitutions in the HBV polymerase/ reverse transcriptase gene that are associated with resistance to tenofovir (39). Phenotypic analysis of serum HBV isolated from subjects with virologic breakthrough demonstrated full sensitivity to tenofovir *in vitro* (39).

Resistance surveillance in weeks 48-96 of studies 0102 and 0103
In study 0102 (17), six patients randomised to tenofovir were viraemic at the last time point at which they were receiving tenofovir monotherapy and evaluated to identify any mutations conferring genotypic resistance. Two of these patients had wild-type virus with changes at unique polymorphic sites compared with their baseline isolates. The remaining four patients had no changes from baseline in the sequence of HBV polymerase/reverse transcriptase. Two of the six patients switched to open-label emtricitabine/tenofovir, of whom one remained viraemic at Week 96 and had changes at polymorphic sites relative to their last isolates taken while on tenofovir monotherapy. No subject originally randomised to receive adefovir was viraemic at their last time point on tenofovir monotherapy.

In study 0103 (18), 18 patients initially randomised to tenofovir were included in resistance surveillance. None of these subjects developed conserved-site changes in the HBV polymerase. Two patients were found to have changes in conserved sites in other genes (compared with baseline) at the last observation while on tenofovir monotherapy, in the absence of virologic breakthrough. One patient had conserved site changes at the loci rtV173L, rtL180M, and rtM204V, while the other had the change rtL101F/L. Both subjects achieved a virologic response while on tenofovir monotherapy with a >6.0-$\log_{10}$ decrease in HBV DNA from baseline. In addition, clonal analysis of the baseline sample from the first subject demonstrated

[p] Defined as an increase in HBV DNA to ≥400 copies/mL after having HBV DNA <400 copies/mL and/or 1 $\log_{10}$ increase in HBV DNA above nadir.
[q] Conserved sites represent parts of the viral genome that are generally common to all viral strains and that evolve least over time.

the presence of the rtV173L, rtL180M, and/or rtM204V mutations at a frequency of 6.5%, suggesting that the subject was previously exposed to lamivudine treatment.

Resistance surveillance in weeks 0-48 of study 0106
Study 0106 recruited patients who have failed to achieve viral suppression with adefovir (including those who have already developed lamivudine resistance) and allowed patients initially randomised to tenofovir monotherapy to switch to tenofovir plus emtricitabine after week 24. Subsequently, this study is not included in the pooled resistance analysis. In this study, 10 out of 53 patients randomised to tenofovir monotherapy were viraemic at the end of Year 1, of whom two had viral breakthrough during the study. Although one of the patients with viral breakthrough had changes at polymorphic sites, neither had any changes at conserved sites Of the viraemic patients without viral breakthrough, one had changes at polymorphic sites relative to baseline, while four had changes at conserved sites in the HBV polymerase gene. Despite developing conserved site changes, none of these subjects experienced viral breakthrough, and all subjects had a positive viral response (at least 3.3 $\log_{10}$ copies/mL decrease from baseline in HBV DNA) at Week 48.

6.10.1.5. Tenofovir resistance data in vivo: pooled analysis

To calculate the incidence of resistance to tenofovir, a pooled analysis (Appendix 5) was conducted on all studies meeting the inclusion criteria for the systematic review (Appendix 2) (19, 20, 23-25, 29). Similar pooled analyses were conducted on other nucleos(t)ides (Appendix 5).

This confirmed the findings from studies 0102 and 0103, demonstrating that the incidence of virologic resistance to tenofovir[r] cannot be higher than 0.23% (1/432) in the first year of treatment in naïve patients, or more than 0.82% (1/122) in lamivudine-resistant patients (Table 25). It should be noted however, that to date there have been no cases of resistance with up to 2 years of tenofovir use in CHB (17, 18).

[r] Virologic resistance was defined as mutations reducing the sensitivity to treatment, accompanied by a ≥1 $\log_{10}$ increase in HBV DNA levels from nadir, or the reappearance of detectable HBV DNA after a period in which HBV DNA was undetectable by PCR.

Table 25: Pooled analysis of resistance to tenofovir (Appendix 5).
For studies 0102 and 0103, the numbers of patients in Year 1 of tenofovir therapy include those patients who were initially randomised to adefovir but switched to tenofovir at week 48, as well as the first year of therapy for those patients randomised to tenofovir. For example, in study 0102, the total count of 352 patients includes the 244 patients randomised to tenofovir who completed 48 weeks of therapy and the 108 patients randomised to adefovir who were receiving tenofovir monotherapy at 96 weeks.

	Definition of resistance	**Resistance, n/N (%)**						
		Year						
		1		**2**		**3**	**4**	**5**
		TDF†	**TDF/ FTC‡**	**TDF**	**TDF/ FTC‡**			
Nucleos(t)ide-naïve subjects								
Study 0102 (17, 20, 33) HBV mono-infection	Mutations conferring resistance and HBV DNA ≥400 copies/mL after having HBV DNA <400 copies/mL and/or 1 log_{10} increase in HBV DNA above nadir	0/352 (0%)*	0/0 (0%)	0/221 (0%)	0/2 (0%)	-	-	-
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Study 0103 (18, 19, 26) HBV mono-infection	Mutations conferring resistance and HBV DNA ≥400 copies/mL after having HBV DNA <400 copies/mL and/or 1 log_{10} increase in HBV DNA above nadir	0/224 (0%)*	0/13 (0%)	0/129 (0%)	0/15 (0%)	-	-	-
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
POOLED ANALYSIS	**Mutations conferring resistance and viral breakthrough**	**0/577 (0%)**	**0/13 (0%)**	**0/351 (0%)**	**0/17 (0%)**	**-**	**-**	**-**
Lamivudine-resistant patients								
907 (23) HIV-HBV co-infection	Conserved site mutations	0/10 (0%)*	-	-	-	-	-	-
van Bommel (29) 40% pts HBV mono-infected	"Phenotypic resistance" (definition not stated)	0/35 (0%)	-	0/35 (0%)	-	0/35 (0%)	-	-
van Bommel (25) HBV mono-infection	Breakthrough of HBV DNA >1log	0/121 (0%)*	-	-	-	-	-	-
van Bommel (24) 66% pts mono-infected	Re-increase of HBV DNA as a sign of HBV resistance	0/67 (0%)	-	0/55 (0%)*	-	0/38 (0%)*	0/27 (0%)*	0/8 (0%)*
POOLED ANALYSIS	Mutations conferring resistance and viral breakthrough	0/121 (0%)	-	0/55 (0%)	-	0/38 (0%)	0/27 (0%)	0/8 (0%)
Patients who have failed adefovir								
Study 0106 (16)	Mutations conferring resistance and HBV DNA ≥400 copies/mL after having HBV DNA <400 copies/mL and/or 1log_{10} increase in HBV DNA above nadir	0/53 (0%)		-	-	-	-	-
	Viral breakthrough	2/53 (3.8%)		-	-	-	-	-

	Definition of resistance	Resistance, n/N (%)						
		Year						
		1		2		3	4	5
		TDF†	TDF/ FTC‡	TDF	TDF/ FTC‡			
	Conserved site mutations	4/53 (7.5%)		-	-	-	-	-

* Data included in pooled analysis of resistance data. Since it was not possible to identify the extent to which the various publications by van Bommel et al. overlapped, only the publication with the largest sample size in each year of follow up was included in the pooled analysis.
† For studies 0102 and 0103, the data in this column includes both the Year 1 outcomes for patients initially randomised to tenofovir and the Year 2 outcomes for those patients who initially received adefovir but switched to tenofovir at week 48.
‡ The data shown in this column presents information for the subgroup of patients who received tenofovir monotherapy at the start of this period but switched to tenofovir plus emtricitabine part-way through the year. In Year 1, this column represents events that occurred between week 48 and week 96 of the study among patients who were randomised to adefovir but switched to tenofovir at week 48 and then added in FTC. In Year 2, this column represents events that occurred ween week 48 and week 96 of the study among patients who were randomised to tenofovir.
# Out of the 28 patients recieving TDF/FTC (across both treatment arms) only 5 were below <400 copies/mL after a mean treatment duration of 16 weeks.

Study 0106 was excluded from this pooled analysis as all patients were receiving adefovir at baseline with persistent viral replication and as patients were allowed to switch to tenofovir plus emtricitabine at 24 weeks if they did not have adequate viral suppression (16). Since no patients in this study developed virologic resistance to tenofovir, this pooled analysis will therefore underestimate the number of patients in whom tenofovir resistance surveillance has been conducted.

In summary, intensive resistance surveillance has involved more than 920 patient-years of exposure to tenofovir in nucleos(t)ide naïve patients, in addition to more than 50 patient-years of exposure in patients who have failed adefovir and 249 years of exposure in lamivudine-resistant patients. This means that the risk of developing tenofovir resistance is unlikely to be higher than 0.22% per year in nucleos(t)ide naïve patients. It should be noted, however, that to date there have been no cases of resistance with up to 2 years of tenofovir use in CHB (17, 18).

6.10.1.6. Conclusions regarding tenofovir resistance

- Despite widespread use of tenofovir, no clinically-significant cases of virologic resistance have yet been identified.
- These results are promising in comparison to the resistance profiles seen with currently used CHB drugs.

6.10.2. Tenofovir in lamivudine-resistant patients

This submission supports the routine use of tenofovir within its licensed indication, including in first-line use in nucleos(t)ide-naïve patients. Although the majority of clinical evidence on the efficacy and safety of tenofovir has been conducted in treatment-naïve patients, it is acknowledged that clinicians may *also* use tenofovir in patients who respond only partially to lamivudine or have already developed lamivudine resistance.

While no RCTs have yet evaluated the efficacy and safety of tenofovir in lamivudine-resistant patients with HBV mono-infection, a small number of patients who had

previously received lamivudine were included in studies 0102, 0103 and 0106 (16, 26, 33). Additionally, a subgroup analysis of an HIV trial also provides data on use of tenofovir in lamivudine-resistant patients with HIV/HBV co-infection (23), while more than six non-randomised trials have evaluated tenofovir in lamivudine-resistant patients (24, 25, 27-29, 31, 72).

A pooled analysis of the results of studies 0102 and 0103 demonstrated that among the 426 patients who received tenofovir across these two trials, there were no differences in virologic response between patients with prior lamivudine experience and those who were treatment-naïve, with 93% of patients in both groups having HBV DNA <400 copies/mL at Week 48 (39).

In study 0106, 13 subjects had lamivudine-resistant HBV at baseline. Seven of these 13 subjects were randomised to blinded therapy with tenofovir and 6 to emtricitabine/tenofovir. No substantive differences were observed between the lamivudine-resistant subgroup (13 subjects) and the non-resistant subgroup (92 subjects). The percentage of subjects with HBV DNA < 169 copies/mL at Week 48 was similar in the two subgroups (77% of lamivudine-resistant subjects and 72% of non-resistant subjects). The percentage of subjects with HBV DNA < 400 copies/mL at Week 48 was greater in the lamivudine-resistant subgroup (92% vs. 79%), although this difference was not apparent at earlier time points or when switch subjects were considered failures (77% vs. 71%). The percentage of subjects with normal and normalised ALT was similar among lamivudine-resistant and non-resistant subjects at Week 48 (69% and 70% with normal ALT, and 56% and 50% with normalised ALT, respectively) (69).

A subgroup analysis of trial 907 investigated tenofovir in anti-retroviral experienced patients with HIV/HBV co-infection (23). The mean decrease in HBV DNA levels was similar for patients with wild-type (5.3 $\log_{10}$) and lamivudine-resistant (4.6 $\log_{10}$) strains (23). No conserved-site mutations leading to tenofovir resistance were observed (23).

A total of 577 lamivudine-resistant patients receiving tenofovir were examined in six retrospective trials (24, 25, 27-29, 31, 72) (Appendix 5). After a year of tenofovir, 45–100% of patients had undetectable HBV DNA levels (24, 25, 27-29, 31, 72). One study found tenofovir therapy to be very effective in lamivudine-resistant patients who had had an inadequate response to adefovir: 100% of tenofovir-treated patients had undetectable HBV DNA after a year of therapy compared with 44% of those receiving adefovir (8/18) (29). Although one study observed viral breakthrough in a single patient (72), no case of tenofovir resistance was observed in up to 5 years of treatment (24, 25, 27-29, 31, 72). In a further study on patients who had failed adefovir as well as including lamivudine-resistant patients, patients treated with tenofovir had a mean decrease in HBV DNA levels of -3.1 $\log_{10}$ copies/mL [range 2.0-4.6] after 3 months of treatment and a reduction of -3.9 $\log_{10}$ copies/mL [range 1.9-4.6] after 6 months of treatment (30, 31).

These findings were supported by a study of lamivudine-resistant patients with HIV/HBV co-infection (146), in which tenofovir monotherapy had approximately the same efficacy as tenofovir plus lamivudine: 83% of patients in both groups achieved undetectable HBV DNA levels (<1,000 copies/mL) (146).

6.10.2.1. Conclusions regarding lamivudine-resistant patients

- The available evidence strongly suggests that tenofovir is a highly effective treatment for lamivudine-resistant patients as well as those who are treatment-naïve. However, it should be noted that the SPC for tenofovir neither specifically recommends use of tenofovir in lamivudine-resistant patients nor explicitly prohibits it (Appendix 1).

- The available evidence suggests that tenofovir is more effective than adefovir in both of these patient groups.

6.10.3. *Comparing tenofovir with interferons*

Interferon-alpha and peginterferon-alpha were not considered as comparators as interferons are generally given early in the treatment pathway to a different subgroup of patients, namely those who are likely to respond, have not received prior nucleos(t)ide therapy, are not contraindicated and are willing and able to tolerate the side-effects associated with interferon therapy. At this stage, it is unlikely that tenofovir would replace the use of peginterferon in the minority of patients deemed suitable for interferon-based therapy in UK clinical practice; based on the latest EASL guidelines, this subgroup comprises patients who are HBeAg-positive, have low viral load, ALT >3-fold higher than ULN and are ideally genotype A or B (8). This was confirmed by interviews with UK clinicians.

However, data from trial 0103 suggest that tenofovir may significantly increase the chance of HBsAg loss relative to adefovir and subsequently 4% of patients receiving tenofovir at week 96 have now achieved HBsAg seroconversion (Section 6.4.2) (18). If this promising finding is confirmed in future research, tenofovir may become an alternative to interferon therapy and this is certainly a position that should be explored in any future multiple technology appraisal conducted by NICE in this disease area. Furthermore, since peginterferon-alpha has been found to produce a lower probability of HBV DNA <400 copies/mL than lamivudine immediately after a 48-week course of treatment (80), it is likely that the meta-analysis would have found interferons to be less effective than tenofovir and other newer nucleos(t)ides if studies on interferon had been included in the meta-analysis.

7. Cost effectiveness

7.1. Published cost-effectiveness evaluations

7.1.1. Identification of studies

A systematic review was conducted to identify all papers relating to the use of nucleos(t)ides in the treatment of CHB. MEDLINE/PubMed and The Cochrane Library were searched on 31st August 2007. In addition, a number of other references were identified from the reference lists of reviews identified in literature searches, from data on file, from clinicians and from lists of abstracts being presented at AASLD 2007 and EASL 2008. Full details are given in Appendix 2 and Section 6.1. All economic analyses identified by the systematic review were flagged and examined to assess whether they met two additional inclusion criteria:

- Evaluated both costs and benefits
- Evaluated tenofovir monotherapy

Only studies meeting these criteria in addition to the inclusion criteria for the wider systematic review are presented here.

A total of 1,272 publications were identified for in inclusion in the systematic review (57 of which were identified by hand), 170 of which met the inclusion criteria.

7.1.2. Description of identified studies

Two studies were identified that fulfilled the inclusion criteria (Table 26) (147, 148).

Table 26: Economic analyses meeting the inclusion criteria

Study	Study title	Study aims
Deniz et al, 2008 (148)	Cost-effectiveness simulation analysis of tenofovir disoproxil fumarate, lamivudine, adefovir dipivoxil and entecavir of HBeAg negative patients with chronic hepatitis-B in Spain	To estimate cost and health outcomes of initiating treatment with tenofovir, lamivudine, adefovir or entecavir as 1st line therapy in patients with HBeAg-negative CHB in Spain
Deniz and Everhard, 2008 (147)	Cost-effectiveness simulation analysis of tenofovir disoproxil fumarate (tenofovir) in HBeAg negative patients with chronic hepatitis-B in Italy and France	To estimate cost and health outcomes of initiating treatment with tenofovir, lamivudine, adefovir or entecavir as 1st line therapy in patients with HBeAg-negative CHB in Italy and France

Methods

- A patient-level simulation model was developed to predict disease progression and the incidence and cost of CHB-related complications based on the HBV DNA viral suppression achieved with different antiviral treatments for CHB. The same model was used for the two studies, the only differences in methodology were the management costs of disease complications and medication costs inputs.
- Patients with CHB were assigned to one of the following first-line treatments at the start of the simulation: 1) tenofovir; 2) adefovir; 3) entecavir; 4) lamivudine. Patient demographic and clinical characteristics were similar in each group.

- Patients were then assigned to a level of viral suppression and risk of resistance specific to their HBV treatment.
- Three levels of viral suppression were included in the model to predict progression to compensated cirrhosis, and the incidence of decompensated cirrhosis or hepatocellular carcinoma (HCC):
    - HBV DNA < 300 copies/mL
    - 300 - 10^5 copies/mL
    - > 10^5 copies/mL
- During the simulation, the incidence of CHB-related complications (compensated cirrhosis, decompensated cirrhosis, HCC) were estimated as variables dependent on time and viral load. Patients who developed DCC or HCC were eligible for liver transplant.
- Patients remained on their initial first-line HBV treatment until they developed resistance to treatment, and/or experienced any major HBV complications.
- Patients who developed resistance were switched to a second-line regimen and assigned to a level of viral suppression and risk of resistance specific to their second-line regimen. Selection of the second-line treatment option was based on national treatment guidelines and/or minimising the risk of developing treatment resistance.
- Levels of viral suppression for different first and second line treatment were based on published literature and reported according to three categories. Rates of resistance were based on published literature.
- Rate of disease progression, complications and mortality were based on published literature.
- Annual management costs of disease complications were reflective of Spain or Italy and France health care systems (depending on the study) and applied over time.
- The simulation was run for 10,000 hypothetical patients over a 30-year time horizon. Both health and cost outcomes were discounted at 3% per year.

Results

The analyses demonstrated that first-line use of tenofovir generated more QALYs and reduced medical costs compared with first-line use of lamivudine, adefovir or entecavir in all three countries evaluated (Table 27 and Table 28). Both costs and health outcomes differed between countries due to the different inputs used in the analyses – particularly in terms of country-specific costs, the baseline characteristics of the populations modelled and probabilities of certain state transitions (e.g. the risk of cirrhosis).

Table 27: Cost and effectiveness results over 30 years in Spain

Outcomes	**Tenofovir**	**Lamivudine**	**Adefovir**	**Entecavir**
Average medical cost per patient	€70,589	€87,394	€95,859	€90,549
Life years	16.07	14.30	15.42	15.99
QALYs	**13.65**	**11.68**	**12.95**	**13.58**

Table 28: Cost and effectiveness results over 30 years in France and Italy

Outcomes		Tenofovir	Lamivudine	Adefovir	Entecavir
Average medical cost per patient	France	€103,237	€108,219	€129,094	€134,797
	Italy	€70,082	€88,989	€101,966	€101,896
Life years		16.73	14.79	16.04	16.66
QALYs		**14.53**	**12.27**	**13.71**	**14.47**

Relevance to decision making in the UK

Drug costs, disease management costs and the second-line treatments used to treat patients who developed resistance to their first-line therapy are likely to differ substantially between countries. However, since these economic evaluations have been published only as abstracts/podium presentations, it is not possible to assess the extent to which these factors differ between countries. In addition, there is some evidence that people in different countries placed different values or utilities on CHB disease states (36).

However, the finding that using tenofovir in place of entecavir or adefovir will reduce medical costs is likely to also be applicable to a UK setting, since the acquisition cost of tenofovir is 32.5% lower than of entecavir and 19% lower than that of adefovir in the UK (1) (Table 34).

Consequently, a *de novo* economic evaluation was conducted to assess the cost-effectiveness of tenofovir compared with lamivudine, entecavir, adefovir and combinations of these medications in the UK.

7.2. De novo economic evaluation(s)

The economic evaluation was conducted in accordance with the NICE reference case (Table 29).

Table 29: Important features of the NICE reference case

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years		

7.2.1. Technology

7.2.1.1. How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

Within the economic evaluation tenofovir is assumed to be used according to the licensed indication:

- At a dose of 300 mg/day tenofovir disoproxil fumarate taken as a single once-daily tablet.
- For the treatment of CHB in adult patients with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (Appendix 1).
- Duration of treatment is discussed in Section 7.2.1.2.

The licensed indication for tenofovir neither specifically recommends combination therapy nor does it advise against use in combination with other nucleos(t)ides other than adefovir. Therefore, the economic evaluation focuses on use of tenofovir monotherapy regimens, although secondary analyses of combination therapy regimens which may be considered clinically appropriate have been included for completeness to reflect current clinical practice: in particular the combination of tenofovir with 100 mg/day lamivudine.

7.2.1.2. Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

Patients are assumed to continue to receive tenofovir (and all other therapies) until they die, undergo HBeAg seroconversion, undergo HBsAg seroconversion or develop tenofovir resistance. Although tenofovir and entecavir are not licensed in patients with decompensated disease, it was assumed, based on expert opinion (Section 7.2.7.5 and Appendix 6), that treatment would not be withdrawn from patients if they developed decompensated cirrhosis, HCC or required a liver transplant. No clinicians interviewed said that they would discontinue treatment in a patient who had undergone hepatic decompensation. However, this assumption was varied in sensitivity analyses (Section 7.3.3).

However, since patients will generally continue therapy for 6-12[s] months after HBeAg seroconversion (Appendices 1 and 4), the cost of an additional 10.2 (SE: 1.2) months' of antiviral therapy was applied to all patients who underwent HBeAg seroconversion (Table 4, Appendix 9). Similarly, patients were assumed to continue treatment for 6 (SE: 5.6) months after HBsAg seroconversion is detected.

Expert opinion suggests that all patients receive regular monitoring of HBV DNA and ALT (which will detect the loss of efficacy associated with drug resistance) and that HBeAg-positive patients also receive regular monitoring of HBeAg and anti-HBe antibodies (Section 7.2.7.5 and Appendix 6, Appendix 10). Consequently, no additional monitoring will be required to implement these stopping rules.

7.2.2. Patients

7.2.2.1. What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patient group considered in the analysis comprised HIV-negative adults with CHB who meet the licensed indications for tenofovir (Appendix 1) and match the key inclusion criteria for clinical trials (26, 33), i.e. adults with HBeAg-positive or HBeAg-negative CHB who have compensated liver function, evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) or histologically active disease.

Patients co-infected with HIV were excluded from the economic evaluation since tenofovir is already licensed and recommended for use in HIV-infected patients by both the British HIV Association (BHIVA) (149) and the SMC (150-152). Children and young people under the age of 18 were excluded from the analysis since tenofovir is not licensed for this population.

[s] The number of months for which patients continued nucleos(t)ide therapy after HBeAg or after HBsAg seroconversion was varied over the range of values suggested by clinicians in one-way sensitivity analysis; this influenced only the cost of treatment and was assumed to have no impact on the durability of seroconversion or other outcomes. The length of time for which treatment continued after HBsAg seroconversion was varied independently of the length of time treatment continued after HBeAg seroconversion. For the purposes of discounting, the cost of treatment after seroconversion was applied at the point when seroconversion applied.

For simplicity, all patients were assumed to be nucleos(t)ide-naïve at the point when they entered the model. However, this assumption was varied in a sensitivity analysis (Section 7.3.3) and the analysis considered both first, second and third-line use of tenofovir by modelling all possible pathways of the treatments considered in the analysis.

The age and sex distribution of the cohort at baseline and the baseline distribution of patients between different disease states were based on a small audit of patients attending a London hepatology clinic (Appendix 7).

Among the patients attending this clinic, 62.7% were male, which is similar to the gender ratios previously reported in the literature, where males outnumber females 1.5-4.9 to 1 (129). In this population of adult patients, the mean age was 38.3 years ± a standard error of 1.25 years (range: 19-72 years). The average age of the cohort considered in the model was therefore assumed to be 38 (95% CI: 36-41) years and 62.7% of patients were assumed to be male; these demographic parameters were used to calculate the weighted average general population utilities (Section 7.2.8.3) and all-cause mortality.

The patients attending this clinic were classified into one of the 17 live disease states considered in the model (Appendix 8), based on clinical history, the presence/ absence of HBeAg, HBsAg, anti-HBeAg and anti-HBsAg and levels of ALT and HBV DNA (Appendix 7). These data were used to calculate the proportion of patients who were in each treated disease state at the start of the model by recalculating percentages after excluding patients in states that are outside the population considered in the economic evaluation (Table 30).

Table 30: Proportion of patients in each disease state. Disease states are defined in Appendix 8, while the data shown in the table are based on data from an audit of a London hepatology clinic (Appendix 7). The starting distribution of patients in the model was calculated by excluding the proportion of patients who are in disease states (indicated by ‡) where tenofovir is not licensed (Appendix 1) and recalculating the distribution by multiplying by 100%/54.4% so that the total patient distribution added up to 100%.

	Proportion of HBsAg+ patients in clinic cohort			Starting distribution in the model		
Disease state	**HBeAg-positive**	**HBeAg-negative**	**TOTAL**	**HBeAg-positive cohort**	**HBeAg-negative cohort**	**Mixed cohort**
Immunotolerant‡	5.7%	0.0%	5.7%	-	-	-
HBeAg seroconverted‡	-	35.7%	35.7%	0.0%‡	0.0%‡	0.0%‡
Active CHB	22.9%*	28.6%*	51.5%	94.04%	95.17%	94.7% (of whom 44% are HBeAg +ve)
Viral suppression	*	*	0.0%	0.00%	0.00%	0.0%
Compensated cirrhosis – detectable HBV DNA	2.9%	0.0%	2.9%	5.96%†	4.83%†	5.3% (of whom 44% are HBeAg +ve)
Compensated cirrhosis – undetectable HBV DNA	*	*	0.0%	0.0%	0.0%	0.0%
Decompensated cirrhosis‡	0.0%	0.0%	0.0%	0.0%‡	0.0%‡	0.0%‡
HCC‡	0.0%	1.4%	1.4%	0.0%‡	0.0%‡	0.0%‡
Liver transplant‡	1.4%	0.0%	1.4%	0.0%‡	0.0%‡	0.0%‡
Post-liver transplant‡	0.0%	1.4%	1.4%	0.0%‡	0.0%‡	0.0%‡
TOTAL	**68.6%**	**31.4%**	**100.0%**	**100%**	**100%**	**100.0%**
Total patients in states where tenofovir is indicated	**25.80%**	**28.60%**	**54.40%**	**-**	**-**	**-**

* Since the data on HBV DNA levels available from the audit data was based on an older assay giving viral load in IU rather than copies/mL, it was assumed that no untreated patients who had not undergone HBeAg or HBsAg seroconversion would have HBV DNA levels <300 copies/mL. Consequently, all non-cirrhotic, non-seroconverted patients with CHB were assumed to be in the active CHB state rather than have viral suppression; similarly it was assumed that all patients with cirrhosis were assumed to have detectable HBV DNA.

† Since patients with HBeAg-negative CHB are at least as likely to develop cirrhosis as those with HBeAg-positive CHB, it was assumed that 50% of all patients with compensated cirrhosis were HBeAg-negative.

‡ Since the proposed licensed indication for tenofovir is for patients with CHB who have compensated liver function, evidence of active viral replication, persistently elevated serum ALT or histologically active disease (Appendix 1), patients in the states indicated by ‡ would be outside the population considered in the model (Section 7.2.2.1).

7.2.2.2. Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Two separate base case analyses were conducted in line with the decision problem in order to assess the cost-effectiveness for a cohort of patients who are HBeAg-positive at the point when they start nucleos(t)ide therapy and a cohort who are HBeAg-negative. However, the model allows for the fact that a proportion of HBeAg-

positive patients will develop HBeAg-negative CHB following HBeAg seroconversion (e.g. by acquiring a precore mutation that prevents expression of HBeAg).

A number of additional subgroup analyses were conducted (Section 7.3.2):

- A mixed cohort that included patients with HBeAg-positive and those with HBeAg-negative disease
- HBeAg-positive patients who do not have cirrhosis when they start antiviral therapy
- HBeAg-positive patients who have compensated cirrhosis when they start antiviral therapy
- HBeAg-negative patients who do not have cirrhosis when they start antiviral therapy
- HBeAg-negative patients who have compensated cirrhosis when they start antiviral therapy

Results for these subgroups were analysed in the same way as the base case analysis and differed only in the distribution of patients across different starting states. Different transition probabilities were applied to patients in different starting disease states, as described in Section 7.2.6.1.2.

Two further subgroup analyses evaluated results in populations of patients who were lamivudine-resistant at baseline.

- HBeAg-positive patients who are lamivudine-resistant at the start of the period modelled
- HBeAg-negative patients who are lamivudine-resistant at the start of the period modelled

Different transition probabilities were applied to lamivudine-resistant patients, as described in Section 7.2.6.1.2.

In addition to these subgroup analyses, the time horizon used in the model was varied extensively in sensitivity analyses (Section 7.2.11). This analysis gives an indication of the cost-effectiveness of treatment in populations of patients who have a longer or shorter life expectancy than the average patient for reasons other than CHB. For example, the scenario analysis using a 10-year time horizon provides an indication of cost-effectiveness for patients who have a 10-year life expectancy due to advanced age or comorbidities, such as cancer or heart disease. However, the same baseline characteristics and transition probabilities were applied regardless of time horizon, whereas in reality, older patients may have a higher risk of cirrhosis. Consequently, sensitivity analyses varying time horizon should be interpreted with caution and should not be viewed as definitive estimates of the cost-effectiveness of tenofovir (or other drugs) in older patients.

7.2.2.3. Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

No subgroup analyses specific to men and women were conducted: although there is evidence that women are more likely to undergo HBeAg seroconversion or develop cirrhosis (115), there is a shortage of quantitative data that could be used to calculate transition probabilities for each sex, which meant that it was not possible to model these subgroups separately.

Additionally, we did not assess cost-effectiveness in other subgroups for which tenofovir is not licensed (e.g. patients with HCC or those who have undergone liver

transplantation) or in subgroups outside the decision problem (e.g. patients co-infected with HIV, HCV or HDV).

However, the analysis did not omit any subgroup analysis specified in the scope.

7.2.2.4. At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

In the base case analysis, patients enter the model immediately after the decision has been made to start therapy with a nucleos(t)ide or nucleos(t)ide combination. However, due to a shortage of UK data on the prevalence of HBeAg-negative CHB or cirrhosis among incident cohorts, these data inputs are based on a prevalent cohort treated at a London Hepatology clinic (Section 7.2.2, Appendix 7).

Patients remain in the model for 40 years (the healthy life expectancy of a 38 year-old) (Section 7.2.5) regardless of outcome, with mortality considered using an absorbing "dead" state.

7.2.3. Comparator technology. What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

This analysis differs from previous analyses (including that conducted by BMS for the entecavir STA (46)) in that it considers all logically possible sequences of treatments – not just those that are commonly used in practice. This was conducted in order to assess whether tenofovir is the most cost-effective strategy out of all of those that could be used in practice and to enable NICE to recommend the optimal sequence of treatments. Furthermore, clinical practice in CHB is evolving rapidly and the treatments that are not commonly used at present may become the most relevant comparators in the future.

The interventions considered in the analysis comprised the nucleos(t)ides tenofovir, adefovir, entecavir, lamivudine and the most commonly-used or most plausible combinations of these agents (adefovir plus lamivudine, entecavir plus adefovir[t] and tenofovir plus lamivudine).The licensed indication for tenofovir neither specifically recommends combination therapy nor does it advise against use in combination with other nucleos(t)ides other than adefovir. Therefore combination therapy regimens that clinicians felt are likely to be used in the UK have been included for completeness to reflect current clinical practice.

Best supportive care (BSC, defined as monitoring with no antiviral therapy) was also considered as a comparator for completeness. Historically, lamivudine followed by BSC was the only treatment option available for patients who had developed lamivudine resistance; consequently much of the published literature supports the cost effectiveness of this strategy even though it may not be considered clinically appropriate in the current setting (Appendix 2). Including lamivudine followed by BSC in the analysis enables assessment of whether tenofovir is the most cost-effective strategy out of all plausible nucleos(t)ide strategies (including lamivudine monotherapy). There is also some evidence that despite the improved treatment

[t] Although this combination is not commonly used in UK clinical practice, it was included in the analysis as it represents the most plausible entecavir combination that does not include concomitant use of tenofovir. In particular, it would not be appropriate to use entecavir in combination with lamivudine due to cross-resistance (14).

options for CHB, some patients who have not been appropriately referred to specialist care may still receive no pharmacological treatment, which means that this comparison may be clinically relevant for some patients (153). However, expert interviews (Section 7.2.7.5 and Appendix 6) suggested that the vast majority of patients with raised ALT currently receive some pharmacological treatment.

Interferon-alpha and peginterferon-alpha were not considered as comparators as interferons are generally given early in the treatment pathway to a specific subgroup of patients, namely, those who are likely to respond, have not received prior nucleos(t)ide therapy, are not contraindicated and are willing and able to tolerate the side-effects associated with interferon therapy. At this stage, it is unlikely that tenofovir will replace interferon or peginterferon use in the minority of patients who receive these products in UK clinical practice. This was confirmed by UK clinicians. However, data from trial 0103 suggest that tenofovir may significantly increase the chance of HBsAg loss relative to adefovir (26, 154) (Section 6.4). If this promising finding is confirmed in future research, tenofovir may become an alternative to interferon therapy.

Telbivudine was not considered as a comparator since it is not recommended by NICE (56) and KOL interviews (Section 7.2.7.5 and Appendix 6) suggested that it is rarely used in the UK: one clinician did not use telbivudine at all, one used it only in clinical trials, while one used telbivudine last-line in a small number of patients and another did not start any new patients on telbivudine but continued treatment in a small number of patients who were already on this treatment. [redacted] (Table 50). Furthermore, telbivudine is more expensive (1) and less potent (32) (Appendix 4) than tenofovir, and is associated with resistance rates of 2.3-5% after one year (43), whereas no cases of virologic resistance to tenofovir have yet been identified (Appendix 5). Subsequently, telbivudine is likely to be "strictly dominated"[u] by tenofovir, since tenofovir is less expensive and likely to generate more QALYs. It is therefore highly unlikely that including telbivudine as a comparator would affect the conclusions drawn.

Although there is a small amount of evidence supporting off-label use of other treatments such as emtricitabine or emtricitabine plus tenofovir in CHB (155), expert interviews (Section 7.2.7.5 and Appendix 6) suggested that HBV mono-infected patients rarely receive unlicensed or off-label treatments in the UK.

Only the three combination therapy regimens that were suggested in expert interviews or advisory boards as being the most common or most plausible combinations likely to be used in UK clinical practice were included in the analysis: adefovir plus lamivudine, entecavir plus adefovir and tenofovir plus lamivudine. Of these, adefovir plus lamivudine is most commonly used at present. Entecavir plus lamivudine is unlikely to be an effective treatment in practice due to the cross-resistance between these two agents and this combination was not suggested by any clinicians interviewed. Similarly, tenofovir is not licensed for use in combination with adefovir (Appendix 1) and this combination is unlikely to reduce the risk of resistance below that with tenofovir monotherapy as these drugs are chemically similar. The efficacy of combinations for which there is no RCT data were based on the assumptions described in Section 7.2.6.1.2.

[u] The term "strictly dominated" indicates that the treatment in question (in this case telbivudine) is both more costly and less effective than its comparator (in this case tenofovir).

In order to identify the most cost-effective sequence of treatments and evaluate the cost-effectiveness of both first and second-line tenofovir relative to all alternatives, all logically-plausible combinations of up to three treatments in sequence were considered in the analysis.[v] For practical reasons, the longest sequence of treatments that could be modelled is three treatments followed by BSC. BSC was included at the end of each treatment pathway as a fixed fourth-line treatment to which patients cannot become resistant. Patients were assumed to not continue to receive monotherapy with an agent to which they have developed resistance as there is RCT evidence suggesting that this has no impact on outcomes (156) and as previous analyses suggested that this was not a cost-effective treatment strategy (65).

A number of criteria were used to exclude strategies in which patients would be resistant to their third-line agent before starting therapy due to prior exposure to that drug or a closely related molecule:

- Pathways that included the same treatment or treatment combination twice were excluded.
- Use of BSC was only ever considered at the end of a treatment pathway.[w]
- Strategies in which adefovir monotherapy was used after tenofovir monotherapy were excluded.
- Strategies that included use of treatment A, treatment B and combination therapy with A+B in any order were excluded.
- Strategies in which lamivudine was used first-line followed by tenofovir (or vice versa), with either adefovir or lamivudine+adefovir being used third-line were excluded.
- Strategies in which entecavir was used first-line with tenofovir second-line (or vice versa), followed by third-line therapy with either adefovir or entecavir+adefovir.
- Strategies such as lamivudine then tenofovir+lamivudine then adefovir where they will be resistant to the third-line strategy before they start third-line treatment were excluded.
- Strategies such as those in which entecavir+adefovir are used last line after both lamivudine and tenofovir were excluded.

All sequences of up to three different treatments that did not meet any of these exclusion criteria were included in the analysis.

The complete list of all 211 strategies (accounting for all the various treatment pathways and sequences mentioned) considered in the analysis is shown in Appendix 11 along with the full base case results.

[v] For simplicity, the word ‘treatment’ is used within this section to include both monotherapy and combination therapy regimens: for example, use of adefovir in combination with lamivudine was termed a ‘treatment’. Similarly, the word ‘switch’ is used to include both switches and the addition of the next treatment: for example, adding in adefovir to ongoing lamivudine therapy is described as a ‘switch’ to combination therapy (lamivudine to adefovir plus lamivudine). However, patients were assumed to discontinue one monotherapy regimen before starting the next, except where otherwise stated.

[w] Although BSC as a treatment strategy was permitted only last-line, it should be noted that patients who undergo HBeAg or HBsAg seroconversion were assumed to cease antiviral therapy for the duration of the time that they spent in that disease state.

7.2.4. Study perspective

The analysis was conducted from the perspective of the NHS and personal and social services in line with current NICE guidelines (157). The analysis therefore excluded patients' out-of-pocket expenses and lost productivity. It is likely that the majority of costs associated with CHB would be incurred by the NHS, other than lost productivity. However, the productivity losses associated with morbidity and premature mortality caused by severe liver disease are likely to be substantial.

7.2.5. Time horizon

A lifetime time horizon was used in the base case analysis in order to ensure that all differences in costs and benefits between the different treatments considered in the analysis were captured. Based on an audit of patients attending a London Hepatology clinic (Appendix 7), the average age of patients diagnosed with CHB is 38 (Section 7.2.2). Consequently, the time horizon used in the analysis was based on the healthy life expectancy of 38-year-old patients. Based on Government Actuary's Department data for Scotland, the life expectancy of a 38-year-old man is 38.5 years, while that for a woman of the same age is 42.6 (158). A 40-year time horizon was therefore used in the base case analysis based on the weighted average of these two figures and assuming that 62.7% of patients with CHB are male (Section 7.2.2). However, the time horizon was varied between 30 and 50 years in the sensitivity analyses conducted to create the tornado diagrams and was varied between five and 60 years in the sensitivity analyses conducted to generate Table 45 and Table 47.

7.2.6. Framework

a) Model-based evaluations

7.2.6.1. Model description

CHB was modelled using a Markov model that included 10 main disease states:

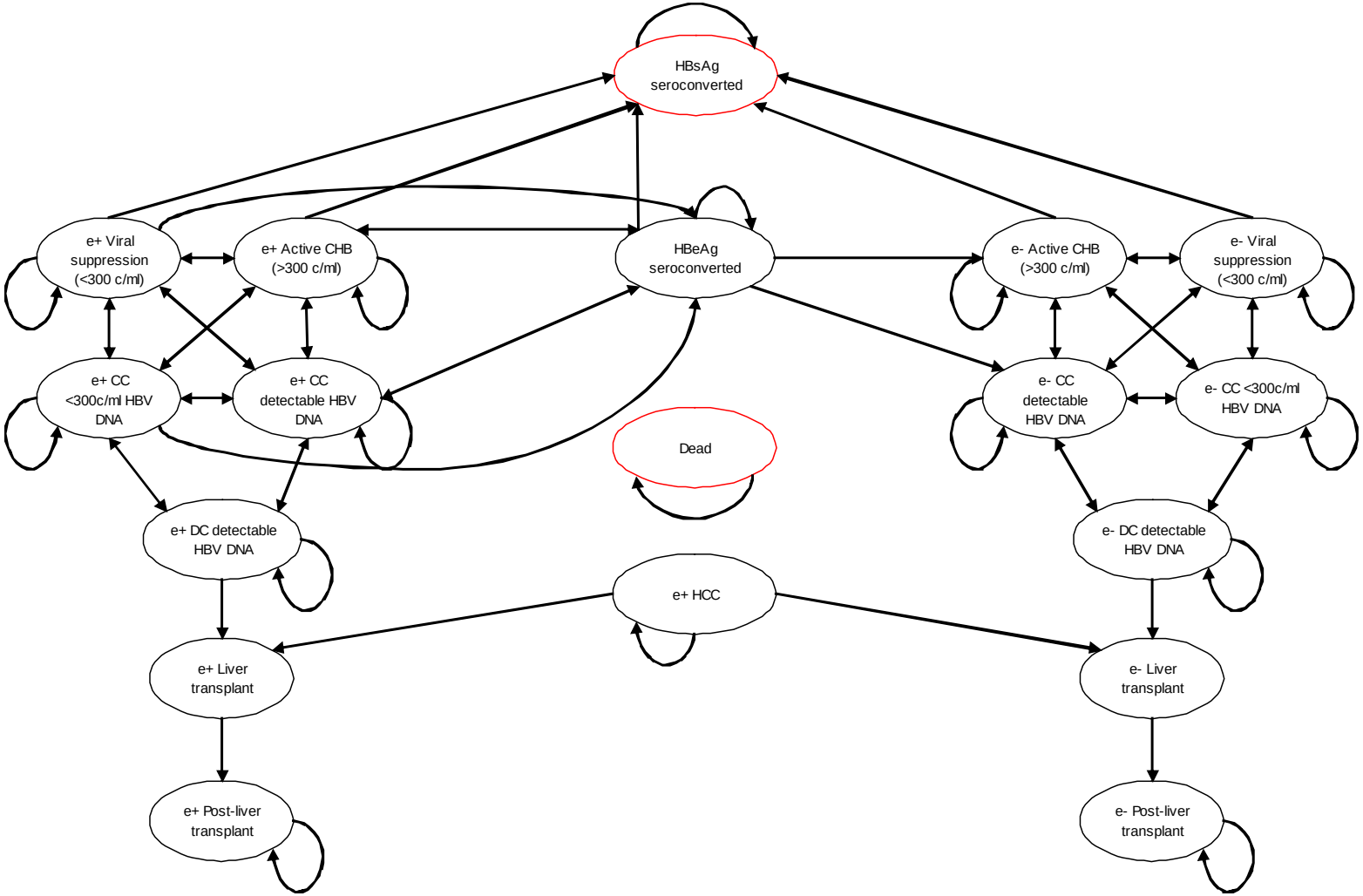
- HBsAg seroconverted
- HBeAg seroconverted
- Active CHB (HBV DNA ≥300 copies/mL[x])
- Viral suppression (HBV DNA <300 copies/mL)
- Compensated cirrhosis with detectable HBV DNA (HBV DNA ≥300 copies/mL)
- Compensated cirrhosis with undetectable HBV DNA (HBV DNA <300 copies/mL)
- Decompensated cirrhosis
- Liver transplant (year in which transplantation occurs[y])
- Post-liver transplant (≥9 months since transplantation)
- Hepatocellular carcinoma (HCC)
- Death

[x] "Undetectable" HBV DNA was defined as <300 copies/mL since this comprises the LLQ of many commonly used assays and matches the threshold used in the meta-analysis used to calculate key transition probabilities (Appendix 4) since this comprises the most commonly used threshold HBV DNA level reported in the trials included in the meta-analysis. Use of this threshold instead of the 400 copies/mL threshold that formed the primary endpoint of studies 0102 and 0103 is unlikely to have had any impact on the results of the analysis.

[y] For the purposes of calculating disease management costs, it was assumed that the liver transplant operation took place three months into the year, such that the liver transplant state encompasses three months prior to the operation and nine months afterwards.

These states are defined in more detail in Appendix 8. However, all states other than HBeAg seroconverted, HBsAg seroconverted, HCC and death were duplicated to allow for HBeAg-positive and HBeAg-negative patients. This produced a total of 18 disease states (Figure 5). The immunotolerant state, which represents the initial quiescent phase of CHB in patients who were infected at birth or early in life, was omitted from the model since this economic evaluation concerned only those patients who had raised ALT at baseline.

Figure 5: State transition diagram illustrating the Markov model



In addition to the transitions shown, patients may die or develop HCC from any disease state; these arrows are omited to improve clarity.
Abbreviations: CC, compensated cirrhosis; c/mL, copies/mL; DC, decompensated cirrhosis; e-, HBeAg-negative; e+, HBeAg-positive.

The Markov model was run using cohort simulation (i.e. running an entire cohort of patients through the model simultaneously) rather than using patient-level simulation (generating individual hypothetical patients and running them through the model one at a time) in order to minimise the processing time required to run the model and increase the range of sensitivity analyses that could be run. Where it was practical to do so, any aspects of patient history that were likely to have a significant effect on cost-effectiveness were modelled by using time-variant transition probabilities and/or by duplicating disease states. The simplest example of this is the distinction between the liver transplant tunnel state (which covers the 12 month period in which transplantation occurs) and the post-liver transplant state (which covers all subsequent years between transplantation and death).

Transitions between treatments and variation in the risk of drug resistance and the probability of HBeAg seroconversion and/or viral suppression were taken into account by replicating the 18 main disease states for each of the situations outlined below. There were therefore 15 copies of each of the main 18 states, to give a separate set of 18 states to cover each of the following situations:

- **Treatment 1:** this set of states covered the entire period for which patients are receiving Treatment 1 (the therapy designated the first-line option in that strategy). Since all patients considered in the model are suitable for treatment at baseline, all patients start to receive Treatment 1 at the very beginning of the model and time-variant transition probabilities and resistance rates can be applied and linked to the cycle. For example, the transition probabilities applicable to patients' first year of therapy were applied to Cycle 1, while the resistance rates and transition probabilities applicable to patients' second year of therapy were applied to Cycle 2.
- **Resistant to Treatment 1:** this set of states covered the year in which patients develop resistance to Treatment 1. The way in which state transitions, utilities and costs were applied to the year in which resistance occurred is described in Section 7.2.6.1.1 below. Patients were only permitted to stay in this state for one cycle, before progressing onto ‘Treatment 2, Cycle 1’ or ‘BSC’.
- **Treatment 2, Cycle 1:** this set of states represented the first year that patients spend on Treatment 2. Patients were only permitted to stay in this state for one cycle, before progressing onto ‘Treatment 2, Cycle 2’ or ‘Resistant to Treatment 2’.
- **Treatment 2, Cycle 2**
- **Treatment 2, Cycle 3**
- **Treatment 2, Cycle 4**
- **Treatment 2, Cycle 5 and subsequent years**
- **Resistant to Treatment 2**
- **Treatment 3 , Cycle 1**
- **Treatment 3 , Cycle 2**
- **Treatment 3 , Cycle 3**
- **Treatment 3 , Cycle 4**
- **Treatment 3 , Cycle 5 and subsequent years**
- **Resistant to Treatment 3**
- **BSC:** all patients who develop resistance to third-line treatment were assumed to continue to receive BSC with no antiviral therapy until death/seroconversion or for the remainder of the time horizon.

Patients were assumed to move from one set of states to another depending on the strategies selected and whether or not they developed drug resistance.

The key assumptions used in the analysis were as followed:

- A half-cycle correction was applied (Section 7.2.6.7).
- It was assumed that patients can die or develop HCC from any live disease state, although the probability of death or HCC varied between states based on the transition probabilities derived from the literature (Appendix 9).
- Other than transitions to death or HCC, it was assumed that no patients can move between disease states except where shown on the arrows on Figure 5.
- It was assumed, based on expert opinion, that patients can only develop HBeAg-negative CHB from the HBeAg seroconverted disease state. Clinicians felt that it was unlikely that any patient would develop HBeAg-negative CHB without first undergoing HBeAg seroconversion (since it is only the selective pressure of anti-HBe antibodies that permit the selection of HBeAg-negative viral strains). In reality, some patients may undergo HBeAg seroconversion and develop mutations enabling the development of HBeAg-negative CHB within the same 12-month period, although expert opinion suggests that this occurs rarely in practice and the risk of developing HBeAg-negative CHB has previously been shown to have negligible impact on cost-effectiveness (65).
- It was assumed that once patients enter the HBeAg-negative active CHB disease state or any other HBeAg-negative disease state other than HBeAg seroconverted, patients could not move back to any HBeAg-positive disease state.
- Three specific transition probabilities (the probability of HBeAg seroconversion, the probability of achieving undetectable HBV DNA and the probability of reverting from decompensated to compensated cirrhosis) were assumed to differ between the first and subsequent years of treatment (Section 7.2.6.1.2; Appendix 9). However, all other transition probabilities were assumed to be constant over time; this was validated by expert opinion.
- Resistance rates were assumed to vary over time during the first five years of treatment with any given therapy. However, due to a shortage of data beyond Year 5 and the complexity of modelling time-variant resistance rates, resistance rates were assumed to remain constant at the values used in Year 5 for all subsequent years.
- HBeAg seroconversion was assumed to have the same outcomes regardless of whether the patient had previously been cirrhotic. However, movement directly from the HBeAg seroconverted state to compensated cirrhosis was permitted since this has been observed in natural history studies (127, 128, 159, 160).
- It was assumed that HCC patients could not also undergo hepatic decompensation.

7.2.6.1.1 Modelling the development and consequences of drug resistance

All patients receiving nucleos(t)ide therapy will be at risk of developing drug resistance at a rate that depends on the medication received and how long they have been receiving therapy (Appendix 5). The development of drug resistance was taken into account within the model by identifying those patients developing resistance in any given year and moving them into a separate set of disease states, as described above. For simplicity, it was assumed that the risk of drug resistance was the same for all disease states in which treatment was given. Although there is evidence that the risk of resistance is higher in patients with higher viral load (11, 66), assuming that the risk of resistance is independent of viral load is likely to bias the analysis slightly against tenofovir: the most effective treatments will enable more patients to maintain undetectable HBV DNA and after a number of years, the resistance rates

associated with these potent nucleos(t)ides may decline as the number of patients with detectable HBV DNA decreases over time.

In order to avoid overestimating the length of time elapsing between the development of resistance and switching therapy, patients developing drug resistance in any given cycle were identified at the start of the cycle, before any transition probabilities were applied. Subsequently, the model first calculated the proportion of patients in each state who will develop drug resistance in any given year and applied a separate set of transition probabilities associated with drug-resistant patients to this subset of patients during that year.

In most patients, the development of genotypic resistance to any given medication will lead to raised levels of HBV DNA (termed virologic resistance) within around 6-12 months (140). If patients continue to receive the same therapy, most patients with virologic resistance will develop biochemical resistance (raised ALT) after a median of four months (143). ALT flares associated with biochemical resistance may precipitate hepatic decompensation or even death and/or hasten the worsening of liver damage and the development of cirrhosis (9). Furthermore, virologic resistance alone is likely to reduce the chance of improvement in the patient's condition and increase the chance of worsening to a level similar to that observed in untreated patients.

Expert interviews (Section 7.2.7.5 and Appendix 6) suggested that in practice most patients receiving antiviral therapy visit the clinic and undergo HBV DNA quantification and liver function tests every 3-6 months[z]; [redacted] At most centres, patients who show increased viral load are first asked about their level of compliance. In patients who show an increase in HBV DNA despite complying with therapy, treatment is generally changed within 0-3 months. At present, genotypic monitoring is not conducted at routine consultations in the UK on cost grounds, although interviews suggested that some centres would conduct sequencing in patients who show virologic/clinical signs of resistance. Given this level of monitoring, cases of drug resistance will generally be identified before biochemical resistance develops, thereby preventing the risk of cirrhosis, decompensation or death increasing to above the risk experienced by untreated patients.

Since genotypic screening is not currently conducted routinely in the UK, the resistance rates used in the model (Section 7.2.7.2.2) were based on the incidence of virologic resistance (a ≥1 $\log_{10}$ copies/mL increase in HBV DNA from nadir (low point) or the reappearance of detectable HBV DNA by PCR in cases where HBV DNA had been undetectable previously). Within the model, it was conservatively assumed that patients would switch therapy an average of 1.5 months after virologic resistance developed. This was based on the assumption that (on average) viral load will increase approximately halfway between the routine quarterly checkups and the assumption that patients' therapy would be switched as soon as the change in viral load was identified. In practice, the interval between the development of virologic resistance and switching therapy is likely to vary. Consequently, this parameter was varied between 0.5 and 4.5 months within the one-way sensitivity analyses used to construct tornado diagrams and values up to 12 months were tested in further sensitivity analyses (Section 7.3.3).

[z] Although patients are currently monitored quarterly, regardless of which nucleos(t)ide they are receiving, clinicians stated that six-monthly checkups may be sufficient for tenofovir and entecavir due to their low risk of drug resistance (Appendix 7).

During the year in which resistance develops, the probability of improvement or disease progression was assumed to be the same as the transition probabilities for non-resistant treated patients[aa] during the 10.5-month period before virologic resistance develops (Figure 6). Annual transition probabilities were converted into probabilities over a 10.5-month period using standard formulae.[bb] After 10.5 months, virologic resistance was assumed to occur. By definition, the development of virologic resistance will involve the reappearance of detectable HBV DNA. Consequently, any patients who would otherwise have been in the viral suppression state at the point when virologic resistance develops were assumed to move to active CHB, while those in the compensated cirrhosis with undetectable HBV DNA state were assumed to move to compensated cirrhosis with detectable HBV DNA. For the remaining 1.5 months of this year, patients were assumed to continue treatment with the same therapy (since resistance has not yet been detected), but receive the transition probabilities associated with untreated patients. Untreated transition probabilities were applied since an RCT comparing continuation of lamivudine with no treatment in lamivudine-resistant patients found no differences in HBV DNA or disease progression between the two groups (156). No increased risk of decompensation was applied to resistant patients since resistance was assumed to be picked up before hepatic flares occur. The annual transition probabilities for untreated patients were converted into probabilities over 1.5 months, as before.[cc]

At the start of the next cycle (1.5 months after virologic resistance developed), resistance was assumed to be identified in a routine consultation and treatment was assumed to be switched immediately. The cost of one or more additional consultations was therefore applied to the cost of the cycles in which resistance developed (Section 7.2.9). After a year in the set of states specific to resistant patients, patients were assumed to move into Cycle 1 of the next treatment in the pathway. Although patients' quality of life may be reduced by drug resistance, the QALYs accrued during the year in which resistance develops were based only on the state that patients were in at the end of the cycle.

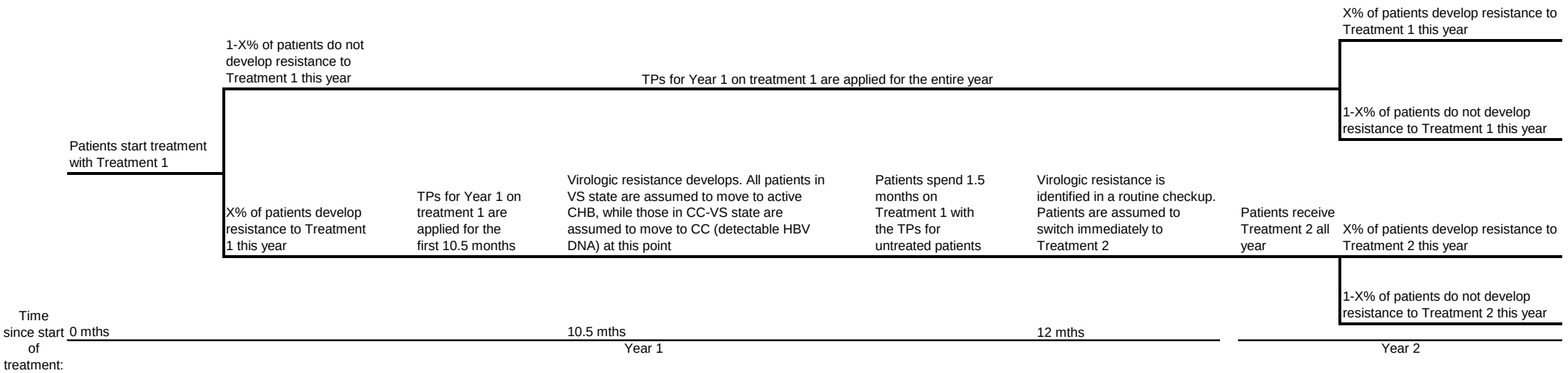
Although Lampertico et al. found that identifying drug resistance early (before clinical resistance develops) led to improved long-term outcomes (such as improved response to second-line treatment and a reduced risk of decompensation and death (162-164)) it was conservatively assumed that the speed with which resistance was detected had no long-term effect on prognosis other than that resulting from any change in disease state that occurred before treatment was switched.

[aa] For simplicity, the transition probabilities for all patients (regardless of how long they had been receiving therapy) in the year when drug resistance develops were based on the transition probabilities calculated for patients who have been receiving that treatment for more than one year. This assumption may bias the analysis slightly against treatments with very high resistance rates, where a significant number of patients may become resistant during Year 1.

[bb] Risk over X months (X=10.5 in the base case analysis) was assumed to equal: $1-e^{(-(-\ln(1-\text{annual risk}))/(12/X))}$ (Miller 1994 (161)).

[cc] Risk over Y months (Y=1.5 in the base case analysis) was assumed to equal: $1-e^{(-(-\ln(1-\text{annual risk}))/(12/Y))}$ (161).

Figure 6: Decision-tree illustrating the way in which resistance was applied within the model.



Abbreviations: CC, compensated cirrhosis with detectable HBV DNA (≥300 copies/mL); CC-VS, compensated cirrhosis with undetectable HBV DNA (<300 copies/mL); TP, transition probability; VS, viral suppression.

7,2.6.1.2. Outline of transition probability calculations

Each year, patients can make either or both of two types of transitions: patients can move from one of the 18 CHB disease states to another and they can develop drug resistance if they are in a disease state where treatment is given and if they are receiving pharmacological therapy. The main assumptions used to calculate the probability of transitions between states are described in this section, while the methods used to calculate the risk of resistance are given in Section 7.2.7.2.2.

Since nucleos(t)ides vary in potency, separate matrices of transition probabilities were used for each treatment, although due to expert opinion or lack of data, some parameters were assumed to be either unaffected by treatment or assumed to be the same for all nucleos(t)ides.

Additionally, separate transition probability matrices were used for the first year of any given treatment. The probabilities for undergoing HBeAg seroconversion, achieving undetectable viral load and moving from decompensated to compensated cirrhosis were assumed to be higher in the first year of treatment than in subsequent years. This assumption was made based on data from study 438 (165) and other long-term trials (99, 166-170) and was also supported by expert opinion (Appendix 9).

The full set of transition probabilities used in the model are shown in Appendix 9, along with further details on the methods used to calculate probabilities and references for all probabilities. However, the main assumptions used in the calculation of transition probabilities are summarised in Section 7.2.7.6.

7.2.6.1.3. Summary of data inputs, their ranges and sources

The model included around 290 data inputs. All inputs are given in Sections 7.2.7.2.2, 7.2.6.1.2, 7.2.9 and appendices 5, 9 and 10 along with their ranges, distributions and sources. However, in summary, the data inputs include:

- Mean age, sex distribution and starting state distribution of the cohort (Section 7.2.2.1): based on an audit of a London hepatology clinic (Appendix 7)
- Transition probabilities and relative risks (Section 7.2.6.1.2 and Appendix 9): these were based on the meta-analysis described in Section 6.6 and Appendix 4 wherever possible, supplemented by data from RCTs, natural history studies, published economic evaluations and expert opinion (in descending order of preference).
- Annual risks of developing drug resistance (Section 7.2.7.2.2 and Appendix 5): these were based on a pooled analysis of studies evaluating each drug in naïve or lamivudine-resistant populations (Appendix 5).
- Drug costs (Section 7.2.9.6): these were based on UK list prices (1).
- Disease management costs for each disease state (Section 7.2.9.5.2): the costs for the most severe disease states were based on published patient-level costing analyses on patients with hepatitis C (38, 171, 172) that were used in the 2005 NICE appraisal of adefovir (63, 64). The costs of less severe disease states were calculated from the bottom up based on clinicians' estimates of the frequency of monitoring and the tests conducted at each consultation (Appendix 10).
- Utilities for each disease state (Section 7.2.8.3): the majority of utilities were based on a published utility analysis (36, 37), although the utilities for HBeAg and HBsAg seroconverted were based on UK population norms (173).

7.2.6.2. Why was this particular type of model used?

CHB was modelled using a Markov model since CHB progresses in a dynamic fashion, with different patients progressing to different disease states at different times via different pathways, which cannot be modelled realistically within a decision-tree framework.

Cohort simulation was used instead of patient-level simulation in order to allow extensive sensitivity analyses to be performed rapidly. Aspects of patient history were accommodated through use of additional states, as described above.

7.2.6.3. What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The disease states used in the model and the transitions that were permitted were based on previous economic evaluations, expert interviews and evidence from the literature. The flow diagram and key assumptions were validated by KOLs working in this field in England or Scotland.

The model structure described in Section 7.2.6.1 models all of the key events associated with CHB and is very similar to that used by SHTAC in the 2004 NICE appraisal of adefovir (64) and that used by BMS in the 2008 STA of entecavir (46).

However, the current analysis models resistance in a different way to either of these appraisals, using a duplication of all 18 disease states to model outcomes in the year in which resistance develops instead of modelling all flares and resistance intervals through use of a single disease state (46); our method therefore allows for the fact that resistance can occur after cirrhosis develops and allows for the impact of losing viral suppression and the risk of disease progression during the interval between developing drug resistance and switching therapy.

Furthermore, our model allows for the fact that patients who initially have HBeAg-positive disease may develop active HBeAg-negative disease after HBeAg seroconversion (e.g. through the development of a precore mutation), which has (to our knowledge) been considered in only one previous analysis (63).

7.2.6.4. What were the sources of information used to develop and inform the structure of the model?

Details of the data used in the analysis and the sources of such data are described in detail in Sections 7.2.7.2.2, 7.2.6.1.2, 7.2.9 and appendices 5, 9 and 10. The main data sources were (in descending order of priority):

- The mixed treatment comparison meta-analysis described in Appendix 4, Section 6.6 and the EASL poster (32). This was used to define the probability of HBeAg seroconversion or viral suppression for each treatment.
- Pooled resistance analysis described in Appendix 5, which included a subset of the RCTs and non-randomised studies identified in the systematic review that met a number of further inclusion criteria. This was used for all resistance rates.
- RCTs identified in the systematic review described in Appendix 2. These were used to define transition probabilities that were not calculated in the meta-analysis.

- Non-randomised studies identified in the systematic review described in Appendix 2. These were used to define the probability that treated patients would make transitions on which no RCT data were available.
- Published costing or quality of life studies presenting the mean costs or mean utilities for a cohort of patients. These were used to define the costs for severe disease states and the utilities for all states.
- Published natural history studies and/or economic evaluations were used to provide transition probabilities for untreated patients that were not available from the meta-analysis.
- Conservative assumptions and/or expert opinion collected using the methods described in Section 7.2.7.5 and Appendix 6. Expert opinion was used as a source of up-to-date data on the quantities of resources use for patients in mild disease states and the duration of treatment after HBeAg seroconversion and was also used to validate assumptions.
- Unit costs were assembled from national tariffs (1, 174), supplemented where necessary by provider-provider tariffs.

7.2.6.5. Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model structure reflects all the essential features of the condition. Aspects of the condition that are not captured are listed below:

- All-cause mortality was not assumed to increase with increasing age or differ between patient subgroups.
- Transition probabilities and utilities were also assumed to be independent of patients' age.†
- The probability of undergoing liver transplant was assumed to be independent of the number of other patients indicated for liver transplant that year.†
- Cirrhotic patients who underwent HBeAg or HBsAg seroconversion were assumed to have the same risk of HCC or returning to the compensated cirrhosis state as patients who were non-cirrhotic when they seroconverted, although the transition probabilities for the HBeAg seroconverted state were based on natural history studies that included patients with cirrhosis.
- Treatment was assumed to have no benefits for patients with HCC.†

However, we are not aware of any previous models in this disease area that have allowed for any of these features of the disease that are marked with the symbol †.

7.2.6.6. For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

A one-year cycle length was used in the model. This cycle length matches that used in most previous economic evaluations in this disease area (46, 64, 175-178), although the manufacturer submission for the telbivudine STA used a six-month cycle length for their "viral load" model (176).

In general annual cycles reflect the minimum time over which state transitions will occur: in particular, patients are unlikely to make two state transitions in the space of a year (e.g. it is highly unlikely that patients would move from active CHB to compensated cirrhosis and on to decompensated cirrhosis in the space of a year). Although the development and impact of drug resistance can occur in less than a year, the structure of the model allows for these changes as described in Section 7.2.6.1.1.

7.2.6.7. Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction was applied such that for the purposes of calculating costs and utilities patients were assumed to move between disease states halfway through each cycle. This was conducted by adding on the QALYs and costs associated with six months in the patients' starting states and subtracting half of the discounted QALYs and costs incurred in the final cycle considered in the analysis from the total costs and benefits accrued over the time horizon. With the exception of the first and last cycles, utilities and disease state management costs were applied based on the states that patients were in at the end of the cycle.

7.2.6.8. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Costs and benefits were extrapolated beyond the trial follow-up periods. More detail on the assumptions and data used is given in Sections 7.2.6.1.2 and 7.2.7.2.2 and associated appendices, although the main assumptions are outlined here:

- Separate resistance rates were used for each year for which at least 20 patients were treated with the drug in question and monitored for resistance data in clinical trials (Appendix 5). In cases where fewer than 20 patients have been monitored in any given year of therapy, the resistance rates in that year were based on the rates observed in the previous year. The resistance rate applied to Year 5 and all subsequent years was the weighted average of the values for each year (weighted by the number of patients monitored for that period of time).
- Different transition probability matrices were used for the first year of any given treatment from any subsequent year. This was done as clinicians interviewed felt that the probability of undergoing HBeAg seroconversion or achieving undetectable viral load is likely to be highest in the first year of therapy. This was confirmed by data from Year 2 of study 438, which showed that the probability that a patient with detectable HBV DNA at week 48 would achieve undetectable HBV DNA in Year 2 was higher for patients who switched from adefovir to placebo than for those who remained on adefovir (165).[dd] A review of the cumulative proportion of patients achieving HBeAg seroconversion or undetectable HBV DNA by PCR within long-term follow up of the largest RCTs evaluating treatments other than lamivudine[ee] (99, 166-170) suggested that the probability that a patient who did not achieve undetectable HBV DNA in the first year of therapy would achieve undetectable HBV DNA in the second or subsequent year is 62.3% (between-studies SD: 35.8%) of the probability in Year 1. Similarly, the probability of undergoing HBeAg seroconversion in the second or subsequent year of therapy was assumed to be 95.2% (between-studies SD: 57.8%) of the probability in Year 1 (167, 168). These relative risks were used for all treatments; subsequently the relative risks showing how many times more

[dd] The probability of a patient with abnormal ALT at Week 48 normalising ALT in Year 2 was also higher for patients who switched from adefovir to placebo than for those who remained on adefovir (165).
[ee] Treatment arms in which patients received lamivudine monotherapy were excluded from this analysis since the high resistance rate is likely to hinder identification of the patients who achieved viral suppression during Year 2.

effective one treatment are than another are assumed to be constant over time.

- Based on a study on adefovir (179), it was assumed that 13.57% of any patients who started second or third-line treatment while they were in the decompensated cirrhosis disease state would revert to compensated cirrhosis in their first year on this treatment. However, since clinicians felt that the probability of making this transition would be substantially lower in the second or subsequent year of therapy while no published data provided a basis for this transition probability, it was conservatively assumed that no patients would move from decompensated cirrhosis to compensated cirrhosis after their first year of treatment.
- Other transition probabilities were assumed to not differ between the first and subsequent years of therapy.
- The model allowed for additional secondary care consultations or renal monitoring during patients' first year of treatment, although the costs and utilities associated with each disease state were otherwise assumed to be constant over time.

b) Non-model-based economic evaluations

7.2.6.9. Was the evaluation based on patient-level economic data from a clinical trial or trials?

N/A

7.2.6.10. Provide details of the clinical trial, including the rationale for its selection.

N/A

7.2.6.11. Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

N/A

7.2.6.12. Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

N/A

7.2.6.13. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

N/A

7.2.7. Clinical evidence

7.2.7.1. How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Transition probabilities for untreated patients were based either on the placebo arms of RCTs or on data from natural history studies or previous economic evaluations; these studies were identified through the literature searches conducted as part of the 2004 and 2007 systematic reviews and through additional searches. The transition probabilities used in the model and details of how they were calculated are given in Appendix 9.

7.2.7.2. How were the relative risks of disease progression estimated?

7.2.7.2.1. Transition probabilities for treated patients

The transition probabilities used in the model and details of how they were calculated are given in Appendix 9. Transition probabilities for treated patients were based on the meta-analysis described in Section 6.6 and Appendix 4 where possible. In cases where it was not possible to conduct a meta-analysis, probabilities were based on RCTs wherever possible, or on non-randomised clinical trials where no RCT evidence was available. RCTs and non-randomised studies were identified through the systematic review described in Appendix 2. In cases where evidence existed only for adefovir and/or lamivudine but was not available for other drugs, transition probabilities were based on the results of the trials that were available and there was assumed to be no difference in efficacy between drugs. Furthermore, evidence on the probability of regaining detectable HBV DNA[ff] were available only for telbivudine and lamivudine; subsequently, the probability of regaining detectable HBV DNA with adefovir was based on that for lamivudine, while that for entecavir or tenofovir were based on the probability with telbivudine. Conservative assumptions were made when no published data were available.

7.2.7.2.2. Resistance rates

Resistance rates were based on the pooled analysis of resistance rates shown in Appendix 5. Full details of the methodology used to create this analysis are shown in Appendix 5, along with the resistance rate data used in the model. Briefly, the analysis pooled all resistance rate data for the largest available studies on each treatment.

The pooled resistance analysis demonstrated that resistance rates are generally higher in patients who are already resistant to lamivudine (Appendix 5). Consequently, separate resistance rates were applied to treatment-naïve and lamivudine-resistant patients within the model. Due to a shortage of data on patients who are resistant to nucleos(t)ides other than lamivudine, the resistance rates for lamivudine-resistant patients were also applied to patients who were resistant to adefovir, tenofovir or entecavir.

No cases of virologic HBV resistance to tenofovir have been observed to date, over two years of follow up of the pivotal studies (17, 18), in smaller studies (16, 23-25, 29) or in routine clinical practice. Nevertheless, experience with older nucleos(t)ides

[ff] The "probability of regaining HBV DNA" refers to the risk that a patient will show an increase in HBV DNA levels from <300 copies/mL to a level above this threshold ***without*** developing mutations conferring drug resistance. This transition probability determines the annual risk of moving from the viral suppression state to the active CHB state (or from the compensated cirrhosis with undetectable HBV DNA to compensated cirrhosis with detectable HBV DNA).

suggests that it is possible that some cases of drug resistance may eventually be observed over time. In order to calculate resistance rates for the model that allow for the possibility of tenofovir resistance developing, an adjustment was made in any cases where no resistance was observed in any particular year by assuming that the next patient to be treated and monitored (e.g. the first patient recruited to the next study on tenofovir) would develop virologic resistance. For example, since 0% (0/130) of lamivudine-resistant patients receiving tenofovir in Year 1 developed resistance, the highest that the incidence of resistance with tenofovir can be is 0.76% (1/131). The model therefore assumed that 0.76% of all lamivudine-resistant patients receiving tenofovir would become resistant in Year 1. The resistance rates calculated in this way therefore represent the maximum rates that we can expect to see given the available evidence and are consequently likely to overestimate the actual risk of resistance. Furthermore, study 106 was excluded from the pooled analysis as all patients had failed adefovir prior to entering the study and patients were allowed to switch to tenofovir plus emtricitabine at 24 weeks if they did not have adequate viral suppression (16). Additionally, three studies by the same author were assumed to have entirely overlapping patient populations (24, 25, 29). Since none of these studies identified any cases of virologic resistance to tenofovir, this means that the maximum risk of tenofovir resistance is overestimated.

No resistance data were available for tenofovir plus lamivudine or entecavir plus adefovir. However, studies evaluating the efficacy of the adefovir plus lamivudine combination provide data on how many times lower the risk of resistance is with combination therapy compared with monotherapy. Within the RCT by Sung et al. (92), 2% (1/49) of nucleos(t)ide-naïve patients receiving adefovir+lamivudine developed virologic resistance to lamivudine, compared with 20% (10/49) patients receiving lamivudine monotherapy. This suggests that the relative risk of lamivudine resistance when used in combination is 0.10 (95% CI: 0.01, 0.75) compared with monotherapy in naïve patients. Consequently, use of combination therapy in treatment-naïve patients was assumed to reduce the risk of resistance to 10% of the risk of resistance that is associated with the component with the highest resistance rate. For example, if the risk of resistance with tenofovir is 0.173% and that with lamivudine is 19%, it was assumed that 1.9% of patients receiving lamivudine+tenofovir would develop [lamivudine] resistance. This assumption may underestimate the advantages of first-line combination therapy, since the combination therapy regimen may continue to provide effective viral suppression even after patients become resistant to one component – particularly when a potent agent, such as tenofovir, forms part of the combination therapy regimen. However, there is currently little/no evidence to support a more optimistic assumption about the efficacy of combination therapy (in particular, Sung et al did observe viral breakthrough at the time of lamivudine resistance in three out of 54 patients receiving adefovir+lamivudine combination therapy (92)) and the data underpinning this assumption represents the best available evidence on the efficacy of combination therapy. However, this was varied in a sensitivity analysis.

Although no RCTs comparing lamivudine plus adefovir in lamivudine-resistant patients have used adequate sample sizes to detect adefovir resistance in this population, a large historical control study by Lampertico et al. (164) found that 7.6% (21/277) of lamivudine-resistant patients receiving adefovir monotherapy developed adefovir resistance, compared with 0% (0/294) of patients receiving adefovir+lamivudine. Applying the same adjustment for zero cell counts that was used for other resistance rate data suggests that use of adefovir+lamivudine in lamivudine-resistant patients reduces the risk of adefovir resistance by 0.0447 (95% CI: 0.01, 0.33) relative to adefovir monotherapy. The same relative risk was applied

to all combination therapies when used in patients who are resistant to at least one nucleos(t)ide.

7.2.7.3. Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Trials reported intermediate outcomes such as HBeAg seroconversion and loss, HBsAg seroconversion and loss, HBV DNA concentrations, ALT normalisation and histological changes. These outcomes are recommended by EASL guidelines, which specifically advise that virological response – HBV DNA levels of below 10^5 copies/mL – and histologic responses using a system the scores necro-inflammatory activity separately from fibrosis (such as the histology activity index) should be used as treatment endpoints (115). There is a great deal of evidence linking these outcomes with progression to severe liver disease.

Low or undetectable HBV DNA levels are associated with inactive disease and a reduced risk of hepatic inflammatory injury (52, 115). Lower HBV DNA levels are associated with a reduced risk of death from liver disease (116, 117), HCC (117-119), hepatic decompensation (117, 120) and cirrhosis (121), which are associated with reduced quality of life (37, 38) and increased mortality (115, 117, 122-127, 128 9, 129-133). Achieving HBV DNA levels that are undetectable by PCR also reduces the risk of drug resistance (66) and increases the chance of HBeAg (66) and HBsAg (134, 135) seroconversion.

HBeAg seroconversion comprises an inactive stage of the disease in which inflammation and liver damage are reduced and in which patients have a lower risk of cirrhosis (127, 128, 159, 160) or HCC (115, 119, 122, 124, 129) than patients who have not undergone seroconversion. However, HBeAg seroconversion does not comprise a permanent quiescence as some patients can lose anti-HBe (115, 129, 180) or develop HBeAg-negative active CHB (124, 180-182). HBsAg seroconversion represents clearance of the infection and is associated with an extremely favourable prognosis (115).

Two of the main outcome measures used in pivotal clinical trials (HBeAg seroconversion and achieving HBV DNA levels <300 copies/mL (26, 33)) were translated into final endpoints (QALYs) using the Markov model. The number of patients who underwent HBeAg seroconversion or achieved undetectable HBV DNA (<300 copies/mL) in the first 48 weeks of each trial were used in the meta-analysis described in Section 6.6 and Appendix 4. The values from the meta-analysis of treatment-naïve patients were used as transition probabilities for the first year of treatment in naïve patients (Section 7.2.6.1.2 and Appendix 9). Relative risks and the results of other meta-analyses were applied for other years and other subgroups (Section 7.2.6.1.2 and Appendix 9). The transition probabilities were used within the Markov model to calculate the number of patients who were in each disease state in each year of the model. This patient distribution was used to calculate costs and QALYs using the costs and utilities described in Sections 7.2.9 and 7.2.8.3

7.2.7.4. Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

All of the nucleos(t)ides included in the analysis have been found to be well tolerated in trials and routine clinical practice (183-185) (Appendix 1). With the exception of lamivudine (which carries a significant risk of ALT elevations and exacerbations of hepatitis due to its high resistance rate (183)), the majority of side-effects associated with nucleos(t)ide treatment comprise laboratory abnormalities, such as raised creatine phosphokinase (CPK), raised creatinine or hypophosphataemia (184, 185) (Appendix 1). Further details on the main side-effects associated with each treatment are shown in Appendix 12.

Tenofovir has been shown to be at least as well tolerated as 10 mg adefovir (26, 33), which has in turn been found to have a safety profile similar to that of placebo (74, 76). Furthermore, tenofovir has a safety profile in 2 million patient-years of routine clinical practice in HIV (34). By contrast, there is less clinical experience with entecavir and telbivudine.

Since all nucleos(t)ides are well tolerated and the incidence of their various side-effects occurs at a similarly low rate, with most side-effects having no impact on quality of life, no cost or disutility associated with adverse events was included in the model. Additionally, since few patients experience side-effects warranting treatment discontinuation, it was assumed that no patients would switch or discontinue therapy due to adverse events.

7.2.7.5. Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

It was necessary to seek the opinions of clinical specialists working in this disease area in order to gain a thorough understanding of the disease area, validate the assumptions used in the model and to obtain estimates for the small number of model parameters that could not be obtained from the literature, such as up-to-date estimates of the healthcare resources used by people with active CHB and those who have undergone HBeAg/HBsAg seroconversion.

A total of ten clinicians and one specialist nurse were interviewed. Additional clinicians were contacted through advisory boards.

Preliminary expert interviews conducted in 2004
As part of the adefovir resubmission to the SMC and the Gilead NICE submission for adefovir, six interviews were conducted, involving a sample of five clinical hepatologists and one nurse specialist working at diverse clinics across the UK. Interviews were conducted face-to-face and were generally conducted using open-ended questions with the help of an interviewer-completed questionnaire.

No specific data inputs were taken from these interviews, however, they helped to define and validate the model structure that was later developed into that shown in Figure 5.

Recent expert interviews

Further interviews were conducted in 2007 and 2008 with the following aims:

- Identify how management of CHB has changed over the past three years and how it is currently managed.
- Identify how tenofovir is likely to fit into the treatment pathway.
- Identify and confirm the most appropriate comparators.
- Validate the amended model structure and key assumptions.
- Obtain updated data on the resource use associated with the active CHB, viral suppression, HBeAg seroconverted and HBsAg seroconverted disease states.
- Obtain data on a small number of other inputs, such as the frequency of routine monitoring of treated patients and the length of time that treatment continues after HBeAg and HBsAg seroconversion.
- Obtain data on the dose and cost of HBIG.

Four interviews were conducted by telephone using an interviewer-completed questionnaire; [redacted] Additional questions were posed by email, as required. A fifth clinician answered questions only by email.

The initial interview with a clinician working in England was conducted to get a general overview of disease management patterns, validate the key assumptions and model structure and identify the most appropriate assumptions for use in the meta-analysis and in the model. However, this interview was not used for any data inputs other than the dose and cost of HBIG.

Four clinicians were shown a version of Figure 5 and were talked through the diagram, as well as being asked general questions on treatment pathway and comparators (Appendix 6, Table 1). Five clinicians provided estimates of the frequency of secondary care consultations received by different patient groups and estimates of the duration of treatment after HBeAg or HBsAg seroconversion. Three clinicians provided information on the tests and investigations conducted at each consultation. The two Scottish clinicians were shown a copy of the tables of resource use data shown on pages 212, 213, 217 and 218 of the SHTAC technology appraisal report (64), while the clinician from Manchester was shown a copy of the mean resource use estimates from the Scottish clinicians; these tables were used as the basis for a discussion on the frequency of monitoring and on the types of tests and investigations conducted at each consultation. Four clinicians were also asked whether a detailed list of assumptions used in the analysis were reasonable; this list of assumptions was added to as the model was developed and as the interviews progressed, while a fifth clinician validated a subset of the most important assumptions by email. The information provided by each clinician is tabulated in Appendix 6.

[redacted]

7.2.7.6. What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

The main assumptions used in the calculation of transition probabilities and resistance rates are summarised below:

- In cases where two nucleos(t)ides were used in combination, it was assumed that the efficacy of the combination was equal to that of the most effective component of that combination. This assumption was validated in an expert interview. For example, the probability of undergoing HBeAg seroconversion with tenofovir+lamivudine was assumed to be equal to the probability of seroconversion with tenofovir monotherapy, since tenofovir is more effective than lamivudine based on the results of the meta-analysis. Since meta-analyses on lamivudine-resistant patients suggested that adefovir+lamivudine may be superior to adefovir (Appendix 4; not statistically significant), this assumption may mean that the benefits of combination therapy are underestimated.
- It was also conservatively assumed that nucleos(t)ide treatment has no impact on the probability of HBsAg seroconversion since relatively few of the trials meeting the inclusion criteria for the meta-analysis reported data on HBsAg seroconversion and as the incidence of HBsAg loss and seroconversion within the main adefovir trials (2-5% (166, 167)) was similar to that observed in untreated patients (7, 124). However, study 0103 suggested that tenofovir is associated with a significantly higher incidence of HBsAg loss than adefovir (3.2% vs 0.0% at 48 weeks; p=0.018) (26); consequently, this assumption may be highly conservative, especially since the number of patients with HBsAg loss in this group appears to rise over time.

[redacted]

- For a number of different transitions that may be influenced by treatment, data were only available for adefovir or lamivudine. In these cases, all treated patients were assumed to have the same chance of improvement/progression regardless of which nucleos(t)ide they were receiving. These transitions were predominantly those associated with the risk of disease progression in patients with severe liver disease, such as the probability of moving between decompensated and compensated cirrhosis and the probability of dying from the decompensated cirrhosis, liver transplant and post-liver transplant states (Appendix 9).
- It was assumed that patients could only develop HBeAg-negative CHB via the HBeAg seroconverted state.
- In the base case analysis, it was conservatively assumed that patients could not move from compensated cirrhosis to the active CHB or viral suppression states, regardless of viral load or treatment. Although some studies have reported regression of cirrhosis following nucleos(t)ide therapy (186, 187) and nucleos(t)ide therapy has been shown to improve necroinflammation, with some treated patients also showing improvement in fibrosis (26, 33, 74, 76, 79), no data were available on which to base data on the probability of regression of cirrhosis.

- Although some studies have suggested that nucleos(t)ide therapy reduces the risk of viral reactivation in patients with HCC (188, 189), it was conservatively assumed that nucleos(t)ide therapy would have no impact on mortality for patients with HCC.
- It was also assumed that treatment would have no impact on the mortality associated with compensated cirrhosis as most studies evaluating nucleos(t)ides in patients with compensated cirrhosis did not report mortality (120, 163, 190, 191), while Liaw 2004 et al. found lamivudine-treated patients to have a similar mortality to those receiving placebo (120). An expert interview suggested that this assumption is likely to be conservative.
- To avoid the risk of double-counting the benefits of treatment, it was conservatively assumed having undetectable viral load had no impact on the chance of undergoing HBeAg seroconversion.
- An adjustment was used to estimate the maximum risk of resistance for any drug that has not been associated with resistance (Section 7.2.7.2.2). This assumption is highly conservative and biases the analysis against tenofovir.
- The relative risk of resistance with combination therapy compared with monotherapy was based on studies on adefovir+lamivudine (Section 7.2.7.2.2). This assumption comprises the best available evidence, but may underestimate the benefits of combination therapy that includes potent drugs, such as tenofovir or entecavir.

7.2.8. Measurement and valuation of health effects

7.2.8.1. If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects were expressed in QALYs.

7.2.8.2. Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The model encompassed the below health effects:

- Viral suppression (i.e. achieving HBV DNA levels <300 copies/mL)
- HBeAg seroconversion
- HBsAg seroconversion
- Drug resistance
- Progression to cirrhosis, hepatic decompensation, HCC, liver transplantation
- Mortality

7.2.8.3. How were health effects measured and valued?

Literature searches and a review of published economic evaluations (64, 128, 175, 177, 178, 192-196) identified only one study that provides utilities for the main disease states that are based on direct utility measurement or generic utility questionnaires completed by patients with CHB (36, 37). One further study surveyed CHB patients with the Health Utilities Index questionnaire (197), but did not report utilities for all disease states used in the model.

A number of studies have reported utilities for patients with chronic hepatitis C (38, 198). [redacted] Consequently, the utilities used in the model were based on those reported by Ossa et al. (36, 37).

Ossa et al. directly elicited utilities using both standard gamble and a visual analogue scale (VAS) from both members of the general public and from patients with CHB within six countries (36, 37). All participants rated the quality of life associated with six different disease states (chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, liver transplant [Year 1], post-liver transplant [after year 1] and HCC) based on descriptions of the states defined by the Liver Disease Quality of Life instrument and a panel of hepatologists. Patients with CHB also rated their own disease state. The utility data collected were broadly similar across both populations and across both methods of utility collection, although there were statistically significant differences in the utility values from different countries. Although the uninfected sample of patients had VAS scores that were consistently lower than those from standard gamble (in accordance with economic theory and previous empirical work), patients with CHB assigned lower standard gamble weightings than uninfected patients. Furthermore, the standard gamble utilities from infected patients were frequently lower than VAS values for some disease states; this may reflect risk-seeking attitudes among patients infected with HBV.

Since utilities varied between countries, the utilities used in the model were based on those from the UK sample reported in the 2005 poster presentation of the study (37). Utilities were based on standard gamble valuations, since this technique is choice-based, produces utilities rather than values and is considered to be more robust than VAS. Utilities were based on values from the 93 infected patients providing valuations in order to ensure that the utilities used reflect the preferences of those people who will benefit from treatment. The utilities used in the model were based on the values of the health state descriptions supplied since the sample included few patients in the severe disease states (70% of patients had pre-cirrhotic CHB). However, other sets of utility data from the study were used in sensitivity analyses. The values used in the model are shown in Table 31.

Uninfected respondents largely comprised staff and students at local universities as well as members of the general population (36). Infected respondents were recruited consecutively from two UK liver disease treatment centres and clinics, transplant centers, and hospital hepatology units (36). Response rates were not reported. Details of the interview methods used and respondent characteristics can be found in the original publications (36, 37).

Table 31: Utilities used in the base case analysis

Disease state	Mean	SE	Lower 95% CI	Upper 95% CI	Reference
HBsAg seroconverted	0.86	0.0039	0.852	0.868	Age-dependent population norm for all ages (173) and its standard error.
HBeAg seroconverted	0.85	-	-	-	UK age-dependent population norm multiplied by 0.99. Wong: utility for HBeAg-/HBsAg+ chronic hepatitis based on clinicians using TTO and SG: 0.99 (124). The quality of life of the general population was varied over its 95% CI, while the disutility associated with detectable HBsAg was varied between 0% and 15% in sensitivity analyses but was not varied in PSA.
Active CHB	0.77	0.0255	0.71	0.81	Ossa, 2005 (37)
Viral suppression	0.77	0.0255	0.71	0.81	Assumed to be the same as for active CHB
Compensated cirrhosis, HBV DNA+	0.73	0.0306	0.65	0.77	Ossa, 2005 (37)
Compensated cirrhosis, HBV DNA-	0.73	0.0306	0.65	0.77	Assumed to be the same as for compensated cirrhosis with detectable HBV DNA
Decompensated cirrhosis	0.34	0.0357	0.25	0.39	Ossa, 2005 (37)
HCC	0.36	0.0332	0.28	0.41	Ossa, 2005 (37)
Liver transplant	0.56	0.0332	0.49	0.62	Ossa, 2005 (37)
Post transplant	0.67	0.0357	0.59	0.73	Ossa, 2005 (37)

The study by Ossa et al. did not provide utilities for the HBeAg or HBsAg seroconverted states or investigate the relationship between viral load and quality of life. Although the reductions in liver inflammation and infectivity that are associated with viral suppression may improve patients' quality of life, it was conservatively assumed that patients in the viral suppression state would have the same quality of life as that of patients in active CHB and that all cirrhotic patients would have the same quality of life regardless of viral load.

HBsAg seroconverted patients were assumed to revert to the quality of life typical for members of the general population (173) since they have effectively resolved the infection. This study included responses from 3,395 of 6,080 questionnaires sent out to a representative sample of the UK adult population (173) and used the EQ-5D instrument. Utilities were calculated based on the standard UK TTO tariff for EQ-5D, which used valuations from the same sample (199).

Although HBeAg seroconverted patients will generally have good liver function and will not normally experience any symptoms, a panel of experts convened as part of the economic evaluation by Wong et al. felt that the presence of detectable HBsAg would influence the activities of daily living (notably sexual behaviour) and would therefore reduce patients' quality of life by around 1% (124). Subsequently, the utility for HBeAg seroconverted patients was assumed to be 0.85 (the utility for the general population [0.86] multiplied by 0.99).

A range of different sets of utility data were used in sensitivity analyses (Appendix 11). These include utilities from non-infected patients, visual analogue utilities from infected patients and utilities from the NHS HTA study on hepatitis C (38).

7.2.8.4. Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 7.2.11).

N/A

7.2.8.5. Were any health effects excluded from the analysis? If so, why were they excluded?

The effect of adverse effects was not considered in the analysis since (as described in Section 7.2.7.4) adverse events associated with nucleos(t)ides are generally mild and common to all drugs included in the analysis.

Additionally, neither normalisation of ALT or histological improvement or fibrosis were directly included in the model as it was necessary to use a single definition of response within the model in order to allow calculation of transition probabilities from published studies. Suppression of HBV DNA was chosen since it influences a wide array of outcomes (Section 7.2.7.3) and is measured reported consistently in almost all recent trials. By contrast, studies use a wide range of measures of histological improvement (e.g. Ishak, HAI, Scheuer or METAVIR scales (200)) that are not necessarily comparable.

7.2.9. Resource identification, measurement and valuation

7.2.9.1. What resources were included in the evaluation?

7.2.9.1.1. Outline of the source of resource use data

The healthcare resources and costs associated with CHB were calculated in one of two ways. For the four least severe disease states (HBeAg seroconverted, HBsAg seroconverted, active CHB and viral suppression), costs were built from the bottom up based on expert opinion, resource use estimates from the SHTAC economic evaluation (64) and unit costs. For the more severe disease states (compensated cirrhosis, decompensated cirrhosis, HCC, liver transplant and post-liver transplant), costs were based on large UK costing studies on hepatitis C (38, 171, 172). These disease states were dealt with in different ways since the audits recording actual healthcare resource use for individual patients were thought to give a more accurate estimate of the cost of managing these severe disease states than expert opinion. It is likely that the bulk of NHS costs for severe liver disease are associated with complications of liver disease rather than being specific to the virus causing the disease. This assumption was validated by expert interviews [redacted] However, for mild symptoms, expert opinions can be more easily elicited and treatment costs, such as the frequency of monitoring and the tests conducted are more likely to vary between hepatitis B and C.

7.2.9.1.2. Resources included in bottom-up costing of mild disease states

The following resources were included in the costing analysis of mild disease states:

- Antiviral medication.
- Staff costs and overheads associated with pulling out notes, etc for consultations with nurses or clinicians in secondary care clinics.
- Tests conducted during secondary care consultations or on separate occasions, including: HBV DNA sequencing for resistance mutations; HBV DNA quantification; serology testing for HBeAg, anti-HBe or HBsAg; liver

biopsy; alpha-fetoprotein; abdominal ultrasound; full blood count; liver function tests; urea and electrolytes; prothrombin time; and ECG.
- Renal monitoring required in line with tenofovir SPC.

The types of healthcare resources consumed by patients in each disease state were identified through discussions with consultant hepatologists and hepatology nurses working at various hospitals across the UK (Section 7.2.7.5 and Appendix 6) and through examination of the tables of resource use from the SHTAC report (64).

All clinicians providing detailed information on resource use were asked about the frequency of GP consultations relating to CHB, although all agreed that patients would rarely see their GP regarding CHB. However, one other clinician who did not provide detailed resource use data said that some patients would see their GP, but did not provide information on the frequency of such consultations.

7.2.9.3. Resources included in costing of severe disease states

The following resources were included in the published costing analyses conducted by Wright et al. (38) and Longworth et al. (171, 172):
- Inpatient days and type of ward.
- Outpatient consultations to see a clinician, nurse or to A&E.
- Procedures such as: colonoscopy; endoscopy; sphincterectomy; liver biopsy; gastric biopsy; paracentesis; angiograms; venograms; radiofrequency, laser or alcohol ablation of the liver; bone scan; and liver aspiration.
- Investigations, such as: x-rays; ultrasound; MRI or CT scans.
- Blood tests, such as: HIV, liver function tests, alpha-fetoprotein or U&E. Although these included HCV-specific tests (e.g. viral genotyping, anti-HCV or HCV RNA quantification), it is likely that the cost and frequency of the HBV-specific tests for patients with severe liver disease associated with CHB would be similar to that of patients with CHC of the same severity.
- Medication.

In addition, the cost of HBIG and antiviral medication was added to these costs based on expert opinion.

7.2.9.2. How were the resources measured?

7.2.9.2.1. Bottom-up calculation for less severe disease states

The quantities of resource use typically required by patients in these disease states were based on interviews with two Scottish hepatologists (Section 7.2.7.5 and Appendix 6). The clinicians interviewed were first asked how many consultations would typically be received each year by patients with CHB who are in the disease states shown in Table 32.

Table 32: Consultations typically received by patients in each of the main mild disease states considered in the model. Responses from each clinician can be found in Appendix 10.

Disease state	No. consultations per year			
	Mean	SE	Min	Max
Active CHB or VS – treated	3.340	0.419	2	4
Active CHB or VS – untreated	2.500	0.612	1.5	4
HBeAg seroconverted	1.588	0.478	1	3
HBsAg seroconverted	0.820	0.455	0	2.5
Number of additional consultations required in the year when resistance develops	1.500	0.707	0	4
Number of additional consultations required in Year 1 (excluding the consultation in which treatment is initiated)	0.800	0.490	0	2

Clinicians were then asked to define the resources that would typically be used in each consultation (Appendix 10). In order to ensure that all relevant resources were captured, clinicians were shown a copy of the resource use tables produced by SHTAC as part of the 2004 NICE appraisal of adefovir (64) and asked to comment on how their current clinical practice differs from what was used in England in 2004. Based on the clinician interviews, no distinction was made between detailed and standard consultations, although allowance was made for differences in the types of tests given to patients who are not receiving nucleos(t)ide therapy. The clinicians interviewed agreed that patients would be seen substantially less frequently than the 11 consultations assumed by SHTAC, with most treated patients attending clinic every 3-6 months; [redacted]

Patients receiving BSC and those who are in the HBeAg or HBsAg seroconverted disease states were assumed to have the less frequent but slightly longer checkups applicable to untreated patients (costing £121.21/consultation), while those in other disease states accrued the cost of the more frequent monitoring given to treated patients (£114.69/consultation) for the periods in which they were receiving nucleos(t)ides.

In addition to the consultations occurring during treatment, all patients other than those receiving first-line BSC were assumed to have an initial consultation at the start of the first cycle in which treatment was initiated (cost: £240.60). A small number of tests were conducted at this visit to establish baseline values (Appendix 10), and a proportion of patients were assumed to undergo liver biopsy at this stage.

Where the experts disagreed about the average resource use, parameters were varied with the mean value taken as the base case and the minimum and maximum estimates used to define the upper and lower bounds; the standard error across the clinician interviews was used to define the distribution used in PSA.

In addition to the resource use suggested by clinicians, all patients receiving tenofovir were assumed to receive renal monitoring 14 times in the first year (one initial visit and every four weeks thereafter) and every three months in all subsequent years, as indicated in the SPC (Appendix 1). This resource use was included in order to ensure that tenofovir was used within its licensed indication, even though clinicians interviewed stated that in reality renal monitoring is only conducted four times a year during the first year regardless of treatment. Since clinician interviews indicated that all treated patients would receive quarterly testing of U&E during their quarterly

outpatient consultations (Appendix 10), the cost of 10 additional U&E tests and nine consultations with a practice nurse in a GP surgery[gg] were added to the disease management cost of tenofovir in the first year.

7.2.9.2.2. Measurement of resources for severe disease states

The costs of managing compensated cirrhosis, decompensated cirrhosis and HCC were based on a large retrospective micro-costing study conducted as part of a health technology assessment (HTA) economic appraisal of treatment for mild hepatitis C, which was conducted at three UK centres (London, Newcastle and Southampton) (38). The costs for liver transplantation and post-liver transplantation were taken from a similar large UK audit of patients undergoing liver transplantation for hepatitis C (38, 171, 172). Further details of these studies are given in Appendix 10 and details of the prices and quantities of resources used in each state can be found in the original publications.

Within the NHS HTA study, the quantities of resources used by a sample of 358 HCV-positive patients who were admitted to one of three hepatology centres or attended an outpatient appointment at one of these centres between March 1998 and April 2000 were included in the sample if they met the definition of these disease states (38). Resource use data were collected from the patient's hospital case notes and from histopathology, virology and pathology databases. Resource use that was definitely unrelated to hepatitis C (e.g. hip replacement) was excluded. The study evaluating the cost of liver transplant patients used a similar methodology to the NHS HTA trial (38, 171, 172).

7.2.9.3. Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

The evidence used to measure resources did not overlap with the evidence used for the transition probabilities for treated or untreated patients since we are not aware of any published RCTs evaluating nucleos(t)ides that have collected resource use data.

7.2.9.4. Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Disease management costs were applied to all disease states (other than the dead state) for the entire period modelled. For the severe disease states, the disease management costs (excluding cost of antiviral therapy and additional renal monitoring received by tenofovir-treated patients) were assumed to be constant over time and were assumed to be the same for all treatments and for untreated patients. Based on expert opinion, untreated patients were assumed to receive fewer secondary care consultations than those receiving treatment and patients were assumed to receive additional consultations in their first year of treatment (Table 32).

[gg] A clinician specialised in this field confirmed that any renal monitoring that might be conducted between patients' quarterly outpatient consulations would be conducted in primary care. Patients were assumed to consult their practice nurse directly without requiring a GP consultation.

7.2.9.5. What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

7.2.9.5.1. Valuation of resources for mild disease states

The cost for each unit of the resources used by patients in the mild disease states was valued based on published databases of unit costs (174), drug tariffs (1), hospital tariffs and, where necessary, costs reported in the SHTAC HTA report (64).[hh] Unit costs used in the analysis are tabulated in Appendix 10.

In PSA, unit costs were assumed to be known with certainty, while all quantities of resources were assumed to follow gamma distributions defined by the mean and SE given in Appendix 10, which were based on the mean and SD across clinicians' estimates. Quantities of resources were varied independently over the range of values suggested by clinicians in one-way sensitivity analyses, while unit costs were assumed to be fixed.

7.2.9.5.2. Valuation of resources for severe disease states

Wright et al. collected data on unit costs from each of the three centres participating in the costing analysis, which are stated in the HTA report (201). Drug costs were based on the BNF (1). The study on liver transplant patients is described as using a similar methodology to the NHS HTA study (201). The cost of HBIG was based on prices provided by a UK transplant centre and the doses suggested by a clinician working at this centre. No adjustment was made to exclude HCV-specific expenditure, such as interferon-alpha with/without ribavirin, since such treatment would not be given to patients with decompensated cirrhosis or HCC and medication accounted for only 2.5% of the total annual cost of compensated cirrhosis.

Costs were inflated to 2006/7 values using the Hospital & Community Health Services (HCHS) pay and prices index (174) (Table 33). The cost of the year in which transplantation occurs was calculated from the costs for the different stages in the process using the methods described in Appendix 10.

For each disease state, the mean cost per patient per year was used as the base case value in our economic analysis and this value was varied over its 95% confidence interval in one-way sensitivity analyses (Table 33). In PSA, costs were assumed to follow a gamma distribution defined by the means and standard errors shown in this table.

[hh] Costs from the SHTAC report were adjusted for inflation using the HCHS pay and prices index (174) and assuming that costs were originally in 2004/5 values.

Table 33: Cost of disease management for the five most severe disease states

Disease state	No. pts	2002/3 values		2006/7 values (inflated using HCHS (174))			
		Mean cost	SD	Mean cost	SE	Lower 95% CI	Upper 95% CI
Compensated cirrhosis (38)	115	£1,138	£2,479	£1,341	£272	£807	£1,876
Decompensated cirrhosis (38)	40	£9,120	£9,610	£10,750	£1,791	£7,240	£14,261
HCC (38)	20	£8,127	£8,541	£9,580	£2,251	£5,167	£13,992
Liver transplant: waiting list phase (3 mths) (38)	*67*	*£3,727*	*£6,338*	*£4,393*	*£913*	*£2,604*	*£6,182*
Liver transplant: transplant operation (excluding HBIG) (38)	*67*	*£27,330*	*£23,613*	*£32,215*	*£3,400*	*£25,550*	*£38,880*
Liver transplant: first 8 mths' post-transplant follow up (excluding HBIG) (38)	*67*	*£6,305*	*£13,904*	*£7,432*	*£2,002*	*£3,508*	*£11,357*
*Liver transplant: HBIG**	-	-	-	*£16,250*	-	*£13,750*	*£18,750*
Total cost of liver transplant	-	-	-	£60,291	-	-	-
Post-liver transplant (excluding HBIG) (38)	*67*	*£1,385*	*£2,906*	*£1,633*	*£418*	*£812*	*£2,453*
*HBIG in post-transplant**	-	-	-	*£5000*	-	-	-
Total cost of post-transplant	-	-	-	£6,333	-	-	-

* Cost of hepatitis B immunoglobulin (HBIG) was based on personal communications with the Birmingham Hepatology centre.

7.2.9.6. What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The doses and costs for the nucleos(t)ide therapies included in the model were based on the doses licensed in the UK for the treatment of CHB (Table 34). Based on acquisition cost alone, giving tenofovir instead of adefovir or entecavir would save the NHS up to £1,496.50 per patient per year.

Table 34: The costs of various nucleos(t)ide treatments for CHB patients.

Treatment	Mean dose	Mean daily cost*	Mean annual cost*
Lamivudine (Zeffix®) for CHB	100 mg/day	£2.79	£1,018.35
Adefovir (Hepsera®)	10 mg/day	£10.50	£3,832.50
Entecavir (Baraclude®) - for naïve patients	0.5 mg/day	£12.60	£4,599.00
Entecavir (Baraclude®) – for lamivudine resistant patients	1 mg/day	£12.60	£4,599.00
Tenofovir (Viread®)	245 mg/day†	£8.50	£3,102.50

* All costs are derived from the BNF (1). Annual costs are based on 365 days in a year. The cost of tenofovir tablets indicated for hepatitis B is the same as that for the tablets indicated for HIV (202).
† Tenofovir was assumed to be used at a dose of 245 mg of tenofovir, which is equivalent to 300 mg of tenofovir disoproxil as fumarate.

In accordance with licensed indications, entecavir was assumed to be given at a dose of 1 mg/day in lamivudine-resistant patients and at 0.5 mg/day in all other patients; the former dose was assumed to be given as a single 1 mg tablet once daily.

Lamivudine is available as two different formulations: 100 mg Zeffix tablets (which are licensed for CHB) and 150 mg Epivir tablets, which are licensed for use in HIV. Within the base case analysis, it was assumed that patients would receive the licensed Zeffix formulation. However, since expert interviews suggested that some patients may receive off-label treatment with the cheaper Epivir tablets, the cost of these tablets (£2.54 per patient-day) was used in a sensitivity analysis.

7.2.9.7. Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

The introduction of tenofovir into UK clinical practice will not require any additional infrastructure to be put in place.

However, there is evidence that many patients with CHB are not diagnosed (51, 203) and therefore receive no treatment until they develop severe liver disease. Diagnosing and treating these patients early would improve health outcomes and is potentially cost-effective, but would require additional infrastructure to screen high-risk groups and set up additional clinics to monitor and treat the new patients who are diagnosed. However, the costs and benefits of screening for CHB are outside the scope of this decision problem.

7.2.9.8. Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

The methods used to value and measure resources were conducted in line with the NICE reference case (157). In summary:

- Drug costs are based on national list prices (1).
- Only resources under the control of NHS and PSS are included and such resources are valued based on the costs relevant to the NHS/PSS.
- Costs incurred in additional years of life that relate to CHB are included, but those associated with other conditions are not.
- VAT is excluded from the economic evaluation but included in budget impact calculations.

7.2.9.9. Were resource values indexed to the current price year?

The reference year for costs was 2007, since the 2008 volumes of some unit cost publications, such as the PSSRU, are not yet published.

7.2.9.10. Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

- Patients were not assumed to visit their GP regarding CHB (based on expert interviews)
- In the base case analysis, it was assumed that all tenofovir-treated patients will receive renal monitoring every four weeks in the first year (and quarterly

thereafter) in line with licensed indications (Appendix 1), although this is not always conducted in practice (Section 7.2.9.2.1).

7.2.10. *Time preferences. Were costs and health benefits discounted at the rates specified in NICE's reference case?*

Costs and benefits were discounted at a rate of 3.5% per year in line with current NICE guidelines (157). However, discount rates were varied independently between 0% and 6% in sensitivity analyses.

7.2.11. Sensitivity analysis

Uncertainty surrounding the model inputs was taken into account through extensive deterministic sensitivity analyses and probabilistic sensitivity analysis (PSA). All parameters used in the model were systematically and independently varied over their 95% CI or the range of values that they could plausibly take to produce tornado diagrams; these ranges/intervals are given in Sections 7.2.6.1.2, 7.2.7.2.2, 7.2.8.3 and associated appendices.

Threshold analyses were then conducted on the 10 variables having the greatest impact on the cost/QALY, in order to identify the threshold values for these inputs at which the ICER for each of the main comparisons reached £20,000 or £30,000/QALY gained. This approach to sensitivity analysis was chosen in order to identify the factors having greatest impact on the results and identify the values that influential parameters would need to take in order to change the conclusions drawn.

Various multi-way sensitivity analyses were also conducted to assess the cost-effectiveness of tenofovir in particular scenarios, such as varying all disease management costs ±25%, testing the impact of increasing the resistance rate for tenofovir and varying the interval between development of virologic resistance and switching therapy.

7.2.11.1. Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The parameters varied in sensitivity analyses included the below structural assumptions:

- Discount rates
- Time horizon
- Amending the stopping rules used in the analysis (e.g. assuming that patients discontinue treatment when they develop decompensated [or even compensated] cirrhosis]
- Varying the interval between development of virologic resistance and switching therapy.

7.2.11.2. Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

All variables in the analysis were varied in sensitivity analysis <u>except</u> for those listed below:

- Unit costs for drugs
- Unit costs for tests and investigations, staff costs or clinic overheads

7.2.11.3. Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analysis (PSA) was conducted in order to investigate the impact of varying all uncertain parameters simultaneously and quantify the degree of uncertainty in the analysis. In this analysis, all parameters other than unit costs were assigned a distribution:

- Probabilities and utilities were assumed to follow beta distributions: alpha and beta were calculated from the means and standard errors (SE) defined in Section 5.7 and associated appendices: alpha=$mean^2*(1-mean)/SE^2$; beta=$(mean*(1-mean)/SE^2)$-alpha.
- Total costs and quantities of resource use were assumed to follow gamma distributions: alpha and beta were calculated from the means and SE given in Section 7.2.9 and associated appendices: alpha=$mean^2/SE^2$; beta=SE^2/mean.
- Although relative risks would normally be assumed to follow log-normal distributions, a gamma distribution was used in this model in order to minimise the risk of very high relative risks appearing that would increase probabilities to above 100%. The formulae used to calculate alpha and beta are the same as those used for costs.

Where no SEs were available from the literature, the SE was estimated from the range of values given in published studies by assuming that the range equated to a 95% CI. All parameters were varied independently in PSA and there were assumed to be no correlations between parameters.

7.2.12. Statistical analysis

7.2.12.1. How were rates or probabilities based on intervals transformed into (transition) probabilities?

Rates were converted to probabilities using the formula:

$$\text{Risk} = 1\text{-}e^{\text{-rate}} \quad (1)$$

Probabilities based on time periods other one year were converted into annual transition probabilities using the formula:

$$\text{Risk for x years} = 1 - e^{\frac{-(-\ln(1-\text{risk for y years}))}{y/x}} \quad (2)$$

Equation 2 was also used to convert annual transition probabilities into probabilities over 1.5 or 10.5 months to reflect the probability of making transitions in the year in which resistance developed (Section 7.2.6.1.1).

Both formulae and the definitions of rates and risks used in the report are based on the paper by Miller et al (161).

7.2.12.2. Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Time-dependent transition probabilities were included for a total of three different transitions for each treatment, which were assumed to be different in the first year on any given therapy from all subsequent years:

- The probability of HBeAg seroconversion
- The probability of achieving undetectable HBV DNA
- The probability of reverting from decompensated to compensated cirrhosis

In addition to these transition probabilities, tunnel states were used to allow for the fact that resistance rates will vary with the duration of treatment (Appendix 5) and that costs, utilities and transition probabilities are likely to differ between the first year after liver transplantation and subsequent years.

For simplicity, all other transition probabilities were assumed to the constant over time - largely due to a shortage of long term data from RCTs. This assumption was validated by expert opinion and is likely to be a reasonably realistic simplifying assumption, with the below exceptions:

- In reality, all-cause mortality will increase as patients get older. However, patients' life expectancy was limited by the time horizon considered in the analysis (Section 7.2.5) consequently, the assumption of constant all-cause mortality is unlikely to affect cost-effectiveness of treatments for the total population considered in the analysis.
- The probability of losing anti-HBe, developing HBeAg-negative active CHB and/or developing cirrhosis may be higher in the first year after HBeAg seroconversion than in subsequent years.
- Mortality may continue to fall in the third and subsequent years after liver transplantation.

7.2.13. Validity

The model and economic evaluation has been subjected to internal validation and "bug checking". Furthermore, the key assumptions have been validated by clinicians (Section 7.2.7.5 and Appendix 6).

The model described in this report has been adapted from those used in submissions to the Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG). Both the SMC and the AWMSG carefully examined the methods and assumptions used in this analysis and reviewed the model used in the analysis. The SMC commented positively on both the methods employed and approach taken (204).

7.2.14. Presentation and interpretation of results

Two alternative methods were used to identify which treatment strategy is most cost-effective out of the 211 antiviral treatment strategies that may be used to treat patients with CHB: the net benefit approach and the cost-effectiveness frontier. Both methods lead to the same conclusions, although the choice of approach can affect the ease with which the results can be interpreted.

The net benefit approach (205, 206) compares the total monetary benefits of each treatment with those for all other possible treatment strategies. Total net benefits are calculated by multiplying the number of QALYs accrued over a lifetime by the ceiling ratio (the maximum society is willing to pay to gain one QALY) and subtracting the total healthcare costs accrued over a lifetime.

$$TotalNetBenefit_{TreatmentX} = QALYs_{TreatmentX} \bullet CeilingRatio - Cost_{TreatmentX}$$

The treatment with the highest total net benefit at any given ceiling ratio is considered to be the optimal treatment at this willingness to pay threshold. Within this report, net

benefits are presented at three ceiling ratios (£10,000, £20,000 and £30,000 per QALY gained). However, conclusions are primarily based on cost-effectiveness at a £20,000/QALY threshold, since statements from NICE indicate that interventions with ICERs of £20,000/QALY or below are generally considered to be cost-effective (207).

Results were also interpreted using the cost-effectiveness frontier, which links all the treatments that have the highest net benefit at certain ceiling ratios and are therefore potentially cost-effective (depending on how much society is willing to pay to gain one QALY). All treatments that do not lie on the cost-effectiveness frontier are dominated by other treatment options by either strict or extended dominance. Strict dominance means that the treatment in question is less costly and more effective than its comparator, while extended dominance means that the treatment in question is more effective and has lower cost-effectiveness ratios than its comparator compared with the next most effective treatment lying on the frontier (208).

Within PSA, the mean ICER was calculated as the ratio of the mean incremental costs divided by the mean incremental QALYs. Where possible, 95% CI were calculated using the percentile method, counting all cost-effectiveness ratios lying in the north-west quadrant of the cost-effectiveness plane (in which treatment is more costly and less effective than its comparator) as having an arbitrarily high ICER indicating that treatment was dominated by its comparator; however, 95% CI were considered to be undefined if >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).

7.3. Results

Summary of key results

- First-line use of tenofovir monotherapy was found to be the most cost-effective nucleos(t)ide strategy for managing CHB for both HBeAg-positive and –negative patients.
- It is more cost-effective to give tenofovir monotherapy first-line than to wait until patients have developed lamivudine resistance.
- First-line use of tenofovir monotherapy was cost-effective in all of the main patient subgroups investigated.
- For those patients who have already developed lamivudine resistance, tenofovir monotherapy is the most cost-effective treatment.
- Extensive deterministic and probabilistic sensitivity analyses demonstrated that these results are extremely robust, remaining unchanged despite substantial changes to the data inputs used.

7.3.1. Base-case analysis (see also Section 10.1, addendum to 7.3.1)

The results shown in this section are based on the deterministic base case analysis. The results of PSA are shown in Section 7.3.3.

7.3.1.1. What were the results of the base-case analysis?

Base case results were generated for a total of 211 different treatment pathways covering all logically-plausible sequences of the eight antiviral treatments/treatment combinations considered in the analysis (lamivudine, adefovir, tenofovir, entecavir, adefovir+lamivudine, tenofovir+lamivudine, entecavir+adefovir and BSC). The results of all 211 treatment strategies for a mixed cohort of cirrhotic and non-cirrhotic HBeAg-positive patients can be seen in Table 1 of Appendix 11, while those for a mixed cohort of cirrhotic and non-cirrhotic HBeAg-negative patients can be seen in Table 2 of Appendix 11; the results for the most commonly used or most cost-effective strategies are described in more detail in Sections 7.3.1.1.1-2.

7.3.1.1.1. Deterministic base case results for HBeAg-positive patients

For this population, BSC is the least expensive and least effective treatment, with lamivudine followed by BSC when patients develop lamivudine resistance (termed ‘LAM-BSC’) having higher costs and greater numbers of QALYs than BSC, but being less costly than any other treatment (Table 35 and Table 36). After lamivudine then BSC, the next least expensive treatment strategy was lamivudine followed by tenofovir. Giving lamivudine first-line, followed by second-line use of tenofovir monotherapy in patients who develop lamivudine resistance would cost either £21,463 or £22,472 per patient over a lifetime (depending on whether or not entecavir was used as third-line therapy for the small number of patients who may develop tenofovir resistance); this strategy generated 18.84 or 18.86 QALYs per patient, respectively (Appendix 11).

Table 35: Disaggregated base case results for HBeAg-positive patients (based on deterministic base case).
Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.
For clarity, only the treatment strategies lying on the frontier, the strategies most commonly used in the UK are shown in this table and the most cost-effective treatment in each cluster of strategies with similar costs and benefits are shown.

Treatment strategy	1st line drug cost	2nd/3rd linedrug cost	Disease management cost	Total cost/pt		Life years/pt (Undisc)	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£9,483	£9,483	£14,338	25.45	16.81	20.68
LAM then BSC	£3,063	£0	£9,836	£12,899	£18,377	26.28	17.42	21.46
LAM then TDF	£3,063	£8,403	£9,997	£21,463	£34,337	28.53	18.84	23.37
LAM then ADV	£3,063	£9,292	£10,165	£22,520	£34,785	27.63	18.28	22.60
LAM then ETV	£3,063	£11,584	£10,500	£25,147	£35,375	26.32	17.34	21.36
LAM then TDF+LAM	£3,063	£12,471	£10,158	£25,692	£42,764	28.80	18.99	23.57
TDF then BSC	£17,338	£0	£11,346	£28,684	£44,076	29.60	19.56	24.32
TDF then LAM	£17,338	£31	£11,350	£28,718	£44,147	29.62	19.57	24.33
TDF then ETV	£17,338	£245	£11,362	£28,944	£44,554	29.61	19.57	24.32
TDF then TDF+LAM	£17,338	£331	£11,371	£29,040	£44,886	29.66	19.60	24.36
TDF then TDF+ LAM then ETV	£17,338	£332	£11,372	£29,041	£44,889	29.66	19.60	24.36
ADV then LAM	£19,262	£322	£12,118	£31,701	£45,725	28.41	18.79	23.28
LAM then ADV+LAM	£3,063	£17,854	£10,982	£31,899	£51,607	27.94	18.34	22.71
ADV then TDF	£19,262	£2,283	£12,344	£33,889	£50,584	28.80	19.01	23.58
ADV then TDF+LAM	£19,262	£3,399	£12,403	£35,063	£53,271	28.88	19.05	23.64
ADV then ADV+LAM	£19,262	£4,385	£12,515	£36,161	£55,132	28.69	18.92	23.46
ETV then LAM	£25,594	£96	£12,629	£38,320	£57,443	29.38	19.40	24.10
ADV+LAM then TDF+LAM	£22,751	£2,678	£13,384	£38,812	£58,874	28.72	18.99	23.55
ETV then TDF	£25,594	£682	£12,692	£38,968	£58,932	29.49	19.47	24.19
ETV+ADV then LAM	£47,942	£39	£16,001	£63,982	£95,798	29.48	19.46	24.18

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

First-line use of tenofovir monotherapy was associated with lifetime costs of between £28,684 and £29,384 and between 19.56 and 19.60 QALYs per patient, with the choice of second and third-line agents used in case of tenofovir resistance having minimal effect on results.

Table 36: Base case results for the 20 most commonly used or most cost-effective strategies in HBeAg-positive patients based on a 40-year time horizon. Results are given per patient treated and are based on the deterministic base case analysis.

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs LAM then BSC	Cost/ QALY vs next most effective strategy on frontier[¥]	NB £10,000 ceiling ratio	NB £20,000 ceiling ratio	NB £30,000 ceiling ratio
Strategies that would lie on the cost-effectiveness frontier[¥] if LAM-BSC and BSC are considered to be relevant comparators							
BSC	16.81	£9,483	-	-	£158,569	£326,621	£494,673
LAM then BSC	17.42	£12,899	-	£5,549	£161,308	£335,516	£509,723
LAM then TDF	18.84	£21,463	£6,014	£6,014	£166,985	£355,433	£543,881
TDF then LAM	19.57	£28,718	£7,344	£9,940	£167,029	£362,776	£558,523
TDF then TDF+LAM	19.60	£29,040	£7,412	£10,055	£166,943	£362,926	£558,909
TDF then TDF+ LAM then ETV	19.60	£29,041	£7,413	£36,583	£166,942	£362,926	£558,909
Other strategies dominated by treatment pathways on the cost-effectiveness frontier[¥]							
LAM then ADV†∞	18.28	£22,520	£11,216	-	£160,265	£343,050	£525,835
LAM then ETV†∞	17.34	£25,147	Dominated§	-	£148,293	£321,732	£495,172
LAM then TDF+LAM†	18.99	£25,692	£8,153	-	£164,206	£354,104	£544,002
TDF then BSC†	19.56	£28,684	£7,362	-	£166,964	£362,611	£558,259
TDF then ETVº	19.57	£28,944	£7,469	-	£166,746	£362,437	£558,127
ADV then LAMº∞	18.79	£31,701	£13,703	-	£156,227	£344,156	£532,085
LAM then ADV+LAMº∞	18.34	£31,899	£20,598	-	£151,533	£334,965	£518,396
ADV then TDFº	19.01	£33,889	£13,204	-	£156,215	£346,320	£536,424
ADV then TDF+LAMº	19.05	£35,063	£13,617	-	£155,422	£345,907	£536,392
ADV then ADV+LAMº	18.92	£36,161	£15,540	-	£153,015	£342,192	£531,369
ETV then LAMº	19.40	£38,320	£12,825	-	£155,710	£349,739	£543,768
ADV+LAM then TDF+LAMº	18.99	£38,812	£16,462	-	£151,136	£341,085	£531,033
ETV then TDFº	19.47	£38,968	£12,747	-	£155,690	£350,348	£545,006
ETV+ADV then LAMº	19.46	£63,982	£25,035	-	£130,630	£325,243	£519,855

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; NB, [Total] net benefit; QALY, quality-adjusted life-year; TDF, tenofovir.

[¥] The cost-effectiveness frontier links all the treatments that are not dominated by other options (by either strict or extended dominance) and are therefore potentially cost-effective. Strict dominance means that the treatment in question is less costly and more effective than its comparator, while extended dominance means that the treatment in question is more effective and has lower cost-effectiveness ratios than its comparator (208).

º First-line use of tenofovir shows strict dominance over this treatment strategy, since it is less costly and generates more QALYs.

† First-line use of tenofovir shows extended dominance (208) over this treatment strategy, since it generates more QALYs and has a lower incremental cost-effectiveness ratio compared with LAM then BSC.

∞ Second-line use of tenofovir (in lamivudine-resistant patients) shows strict dominance over this treatment strategy, since it is less costly and generates more QALYs.

‡ Second-line use of tenofovir (in lamivudine-resistant patients) shows extended dominance (208) over this treatment strategy, since it generates more QALYs and has a lower incremental cost-effectiveness ratio compared with LAM then BSC.
§ When base case assumptions were applied, entecavir then lamivudine was found to be less effective and more costly than lamivudine then no treatment as the meta-analysis found entecavir to have a non-significantly lower risk of HBeAg seroconversion than placebo in lamivudine-resistant patients. Since the meta-analysis on trials recruiting lamivudine-resistant patients did not converge as well as the analysis on trials on naïve patients and included fewer studies, this finding should be interpreted with caution.

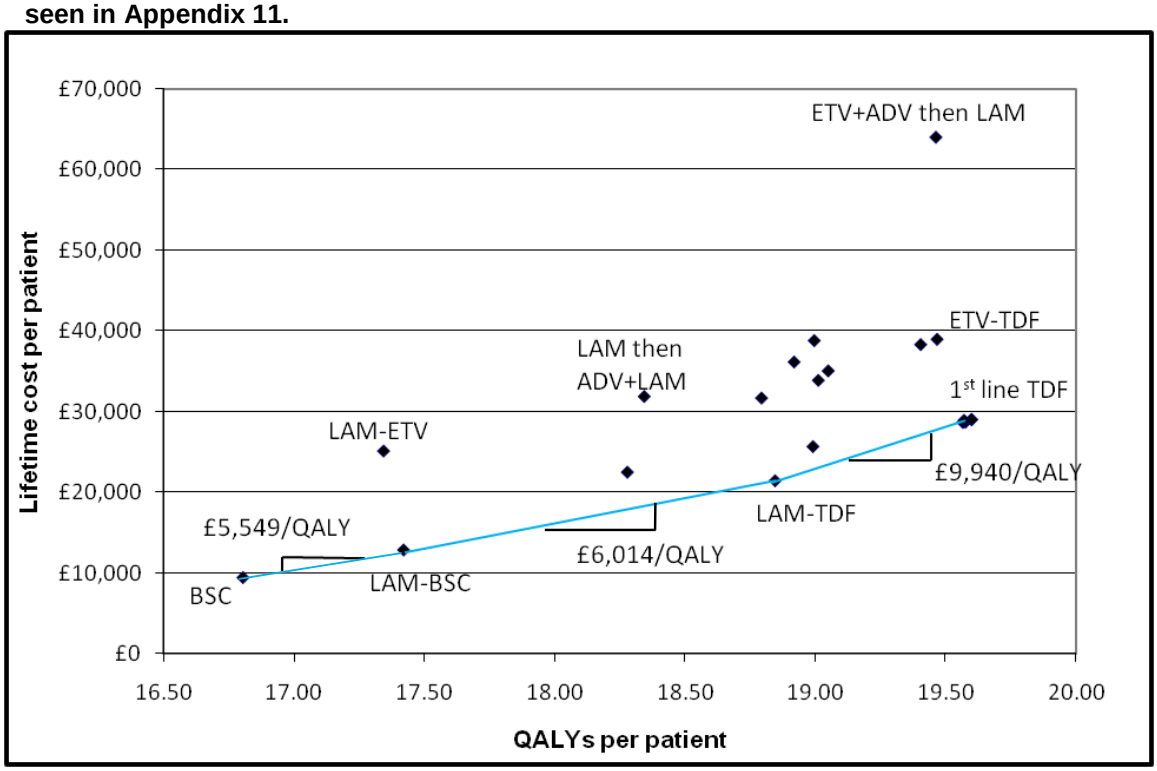
In order to assess which treatment strategy is most cost-effective at any particular ceiling ratio that represents the amount that society is willing to pay in order to gain one QALY, the costs and benefits of all treatment options were plotted on the cost-effectiveness plane (Figure 7) and net benefits were calculated (Table 36).

Analysis of net benefit demonstrated that if the NHS were willing to pay £20,000/QALY gained, the 17 best strategies out of the total list of 211 analysed would comprise the 17 strategies involving first-line use of tenofovir monotherapy (Appendix 11).

The cost-effectiveness frontier (the blue line on Figure 7) joins the treatments that may be cost-effective (depending on our cost-effectiveness threshold) – i.e. those that are not dominated by any other treatment by either strict[ii] or extended[jj] dominance. The treatments lying on the frontier also have the highest net benefit at one or more ceiling ratio. Treatments that lie above or to the left of the frontier are dominated by those that lie on the frontier and are therefore not cost-effective regardless of how much the NHS is willing to pay for a QALY if the agents on the frontier are also available. The gradient of the line that joins any two treatments represents the cost-effectiveness ratio for the treatment on the top right end of the line relative to the treatment on the bottom-left end of the line.

ii Strict dominance means that the 'dominant' treatment is both more effective and less costly than its comparator. For example, first-line tenofovir dominates first-line entecavir as tenofovir is generates more QALYs and is less costly.
jj Extended dominance means that one treatment is more effective *and* has lower cost-effectiveness ratios than the 'dominated' treatment. For example, giving lamivudine followed by adefovir (LAM-ADV) is dominated by LAM-BSC and TDF-LAM through extended dominance, as TDF-LAM generates more QALYs than LAM-ADV and is more cost-effective than LAM-ADV (i.e. the ICER for TDF-LAM relative to LAM-BSC is lower than that for LAM-ADV vs LAM-BSC). Extended dominance also means that a combination of LAM-BSC and TDF-LAM (e.g. a small proportion of patients receiving LAM-BSC, while most receive TDF-LAM) would generate more QALYs and be less costly than LAM-ADV.

Figure 7: Results on the cost-effectiveness plane for the HBeAg-positive patient population. Results are based on the deterministic base case analysis. The blue line represents the cost-effectiveness frontier; treatments that lie on this line are cost-effective at some ceiling ratio, while those that lie above the line are dominated. For clarity, only the main clusters of strategies are labelled and this figure includes only the 20 strategies shown in Table 36. A scatter graph including all 211 treatment strategies included in the analysis and the data used to produce these figures can be seen in Appendix 11.



For the HBeAg-positive population, the treatments falling on the cost-effectiveness frontier are (in order of increasing cost and effectiveness): BSC; lamivudine then no further treatment; lamivudine then tenofovir; tenofovir then lamivudine; tenofovir, then tenofovir+lamivudine; and tenofovir, followed by tenofovir+lamivudine, followed by entecavir.

All other treatment strategies (including all strategies involving first-line use of entecavir) were dominated by the treatment strategies on the frontier. In particular:

- First-line use of entecavir was dominated by first-line use of tenofovir, with entecavir being both more costly and less effective.
- Both lamivudine then BSC and lamivudine then tenofovir showed extended dominance over giving lamivudine then entecavir.
- First-line use of tenofovir monotherapy showed strict dominance over all strategies in which combination therapy was used first-line. However, this finding should be interpreted cautiously due to the shortage of data on the efficacy of combination therapy and the assumptions used to estimate resistance rates and transition probabilities for these treatments.
- When base case assumptions were applied, entecavir then lamivudine was found to be less effective and more costly than lamivudine then no treatment as the meta-analysis found entecavir to have a non-significantly lower risk of HBeAg seroconversion than placebo in lamivudine-resistant patients. Since the meta-analysis on trials recruiting lamivudine-resistant patients did not converge as well as the analysis on trials on naïve patients and included fewer studies, this finding should be interpreted with caution. If the probability

of HBeAg seroconversion with entecavir in lamivudine-resistant patients were the same as that for BSC, lamivudine then entecavir would generate lifetime costs of £22,966 and an average of 17.71 QALYs per patient, which would mean that this strategy would cost £34,990/QALY gained relative to lamivudine then BSC and be extendedly dominated by tenofovir then lamivudine and strictly dominated by lamivudine then tenofovir.

Which of the treatments lying on the cost-effectiveness frontier is cost-effective depends on how much society is willing to pay per QALY gained.

- If society were willing to pay less than £5,549 per QALY gained (the ICER for lamivudine then BSC vs BSC), BSC would comprise the most cost-effective treatment for CHB (having the highest total net benefit over this range of ceiling ratios).
- Lamivudine followed by BSC would be the most cost-effective treatment for this population (and have the highest net benefits) if society were willing to pay between £5,549 and £6,014/QALY.
- Lamivudine followed by tenofovir would be the most cost-effective treatment if society were willing to pay between £6,014 and £9,940/QALY gained relative to lamivudine then BSC.
- Tenofovir then lamivudine would be the most cost-effective at ceiling ratios between £9,940 and £10,055/QALY.
- Tenofovir then tenofovir+lamivudine would be the most cost-effective at ceiling ratios between £10,055 and £36,583/QALY.
- Tenofovir then tenofovir+lamivudine then entecavir would be the most cost-effective if society were willing to pay at least £36,583/QALY gained.

Since the NHS is generally considered to be willing to pay between £20,000 and £30,000/QALY gained (207), tenofovir followed by tenofovir+lamivudine is the most cost-effective strategy considered in this analysis since this treatment costs £10,055/QALY relative to tenofovir then lamivudine and has a total net benefit of £362,926 per patient at a £20,000/QALY ceiling ratio.

However, all strategies involving first-line use of tenofovir generated very similar numbers of QALYs (difference between highest and lowest: 0.034 QALYs) and very similar total lifetime costs (difference between highest and lowest: £700) since the resistance rate associated with tenofovir is so low[kk] that very few patients will progress onto second or third-line therapy. Due to the minimal differences in cost and effect, the cost-effectiveness ratios between different strategies involving first-line use of tenofovir vary substantially between different patient subgroups and are very sensitive to the input parameters. Additionally, the model suggests that the average patient will receive tenofovir for 12 years before developing tenofovir resistance, dying or undergoing seroconversion; subsequently a large number of additional antiviral agents are likely to become available before most tenofovir-treated patients require second-line therapy.

In particular, it should be noted that no RCTs have yet evaluated tenofovir+lamivudine in HBV mono-infected patients (Appendix 2) and that the UK licensed indications for nucleos(t)ides neither specifically mention combination

[kk] No cases of virologic resistance to tenofovir have yet been identified *in vivo* – either during up to 96 weeks of follow up of the pivotal clinical trials (17, 18, 26, 33), in smaller studies (23-25) or in routine clinical practice. However, the model conservatively assumed that 0.173% of patients would become resistant in Year 1 and that 0.285% of patients would develop resistance in each subsequent year, based on the pessimistic assumption that the first patient recruited to the next trial would develop resistance to tenofovir (Section 7.2.7.2.2; Appendix 6).

therapy nor advises against use in combination therapy. However, expert interviews suggest that clinicians would consider using this treatment in clinical practice. Consequently, there is particular uncertainty about the true costs and benefits of this combination.

Additionally, expert interviews suggest that most clinicians would not switch patients from tenofovir to lamivudine monotherapy due to concerns over viral breakthrough and would instead add in lamivudine in combination with continued tenofovir. If all strategies involving switching from tenofovir to lamivudine and all of those involving use of tenofovir or entecavir in combination with other antiviral medications were removed from the analysis, tenofovir then BSC would comprise the strategy with the highest net benefit at a £20,000/QALY threshold, with tenofovir then lamivudine plus adefovir.

7.3.1.1.2. Base case results for HBeAg-negative patients

HBeAg-negative patients accrued up to 31% fewer QALYs, up to 29% fewer life years and had lifetime costs that were up to 366% higher than those accrued by patients with HBeAg-positive disease (Table 35 and Table 37).

Table 37: Disaggregated base case results for HBeAg-negative patients (based on deterministic base case). Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum. (See Section 10.2 Addendum to 7.3.1.1.2, Table 37)

Treatment strategy	1st line drug cost	2nd/3rd linedrug cost	Disease management cost	Total cost/pt		Life years/pt (Undisc)	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£14,331	£14,331	£21,573	18.39	11.75	13.90
TDF then LAM	£4,283	£0	£14,852	£19,135	£27,218	18.77	11.99	14.18
TDF then TDF+LAM	£4,283	£24,481	£18,073	£46,837	£75,643	23.78	14.70	17.84
TDF then TDF+LAM then ETV	£4,283	£23,294	£17,597	£45,173	£68,555	20.90	13.08	15.62
LAM then BSC	£4,283	£17,945	£15,750	£37,978	£52,853	20.18	12.80	15.23
LAM then ETV	£4,283	£38,287	£19,005	£61,575	£103,675	24.97	15.30	18.67
LAM then ADV	£42,557	£0	£17,390	£59,948	£96,041	26.59	16.39	20.10
LAM then TDF	£42,557	£99	£17,423	£60,079	£96,295	26.63	16.41	20.13
ADV then LAM	£42,557	£680	£17,446	£60,683	£97,387	26.66	16.42	20.15
TDF then BSC	£42,557	£1,340	£17,558	£61,455	£99,278	26.83	16.51	20.27
TDF then ETV	£42,557	£1,345	£17,558	£61,460	£99,291	26.83	16.51	20.27
LAM then TDF+LAM	£38,739	£942	£17,355	£57,037	£83,536	22.81	14.23	17.16
LAM then ADV+LAM	£4,283	£41,955	£19,406	£65,644	£108,567	23.31	14.33	17.33
ADV then TDF	£38,739	£8,494	£18,559	£65,792	£101,661	24.40	15.04	18.28
ADV then TDF+LAM	£38,739	£13,112	£18,892	£70,743	£112,246	24.79	15.23	18.55
ADV then ADV+LAM	£38,739	£14,419	£18,980	£72,138	£114,395	24.23	14.91	18.10
ETV then LAM	£59,224	£299	£17,411	£76,933	£119,660	25.88	15.99	19.55
ETV then TDF	£51,400	£10,145	£19,315	£80,860	£125,610	24.16	14.83	18.02
ADV+LAM then TDF+LAM	£59,224	£2,619	£17,746	£79,589	£125,450	26.36	16.23	19.89
ETV+ADV then LAM	£113,307	£128	£17,995	£131,431	£204,248	26.30	16.20	19.85

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

BSC was the least expensive and least effective treatment, followed by the "lamivudine then BSC" strategy (Table 38). After "lamivudine then BSC", the next least expensive treatment strategy was "lamivudine followed by entecavir", although this strategy produced fewer QALYs than using adefovir or tenofovir after lamivudine resistance develops. Giving lamivudine first-line, followed by tenofovir monotherapy, cost between £46,837and £50,085 per patient over a lifetime and generated between 14.70 and 14.86 QALYs per patient (Appendix 11). First-line use of tenofovir monotherapy was associated with lifetime costs of between £59,948 and £62,736 and between 16.39 and 16.51 QALYs per patient (depending on the second and third-line agents used).

Table 38: Base case results for the 20 most commonly used or most cost-effective strategies in HBeAg-negative patients based on a 40-year time horizon. Results are given per patient treated and are based on the deterministic base case analysis.

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs BSC	Cost/ QALY vs LAM then ETV	Cost/QALY vs next most effective strategy on frontier¥	NB £10,000 ceiling ratio	NB £20,000 ceiling ratio	NB £30,000 ceiling ratio
Strategies that would lie on the cost-effectiveness frontier¥ if LAM-BSC and BSC are considered to be relevant comparators								
BSC	11.75	£14,331	-	-	-	£103,130	£220,591	£338,052
TDF then LAM	16.41	£60,079	£9,811	£6,118	£9,811	£104,010	£268,099	£432,189
TDF then TDF+LAM	16.51	£61,455	£9,895	£6,325	£13,854	£103,628	£268,710	£433,792
TDF then TDF+LAM then ETV	16.51	£61,460	£9,896	£6,326	£20,781	£103,625	£268,710	£433,794
Other strategies dominated by treatment pathways on the cost-effectiveness frontier¥								
LAM then BSC†‡	11.99	£19,135	£19,897	£23,293				
LAM then ETV†‡	12.80	£37,978	£22,512	-	-	£89,987	£217,952	£345,917
LAM then ADV†‡	13.08	£45,173	£23,137	£25,457	-	£85,618	£216,410	£347,201
LAM then TDF†	14.70	£46,837	£10,994	£4,647		£100,191	£247,219	£394,247
ADV then LAM†∞	14.23	£57,037	£17,192	£13,293	-	£85,265	£227,567	£369,870
TDF then BSC†	16.39	£59,948	£9,826	£6,116	-	£103,939	£267,825	£431,712
TDF then ETV§	16.42	£60,683	£9,907	£6,258	-	£103,564	£267,811	£432,058
LAM then TDF+LAMº	15.30	£61,575	£13,285	£9,417	-	£91,447	£244,468	£397,489
LAM then ADV+LAMº∞	14.33	£65,644	£19,884	£18,081	-	£77,623	£220,889	£364,156
ADV then TDFº	15.04	£65,792	£15,626	£12,401	-	£84,602	£234,996	£385,390
ADV then TDF+LAMº	15.23	£70,743	£16,182	£13,452	-	£81,579	£233,901	£386,223
ADV then ADV+LAMº	14.91	£72,138	£18,263	£16,152	-	£76,976	£226,089	£375,203
ETV then LAMº	15.99	£76,933	£14,765	£12,214	-	£82,926	£242,785	£402,644
ETV then	16.23	£79,589	£14,555	£12,120	-	£82,708	£245,005	£407,302

Treatment strategy	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs BSC	Cost/ QALY vs LAM then ETV	Cost/QALY vs next most effective strategy on frontier[¥]	NB £10,000 ceiling ratio	NB £20,000 ceiling ratio	NB £30,000 ceiling ratio
TDF[º]								
ADV+LAM then TDF+LAM[º]	14.83	£80,860	£21,540	£21,039	-	£67,487	£215,834	£364,180
ETV+ADV then LAM[º]	16.20	£131,431	£26,274	£27,434	-	£30,599	£192,628	£354,658

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; NB, [Total] net benefit; QALY, quality-adjusted life-year; TDF, tenofovir.

[¥] The cost-effectiveness frontier links all the treatments that are not dominated by other options (by either strict or extended dominance) and are therefore potentially cost-effective. Strict dominance means that the treatment in question is less costly and more effective than its comparator, while extended dominance means that the treatment in question is more effective and has lower cost-effectiveness ratios than its comparator (208).

º First-line use of tenofovir shows strict dominance over this treatment strategy, since it is less costly and generates more QALYs.

† First-line use of tenofovir shows extended dominance (208) over this treatment strategy, since it generates more QALYs and has a lower incremental cost-effectiveness ratio compared with LAM then BSC.

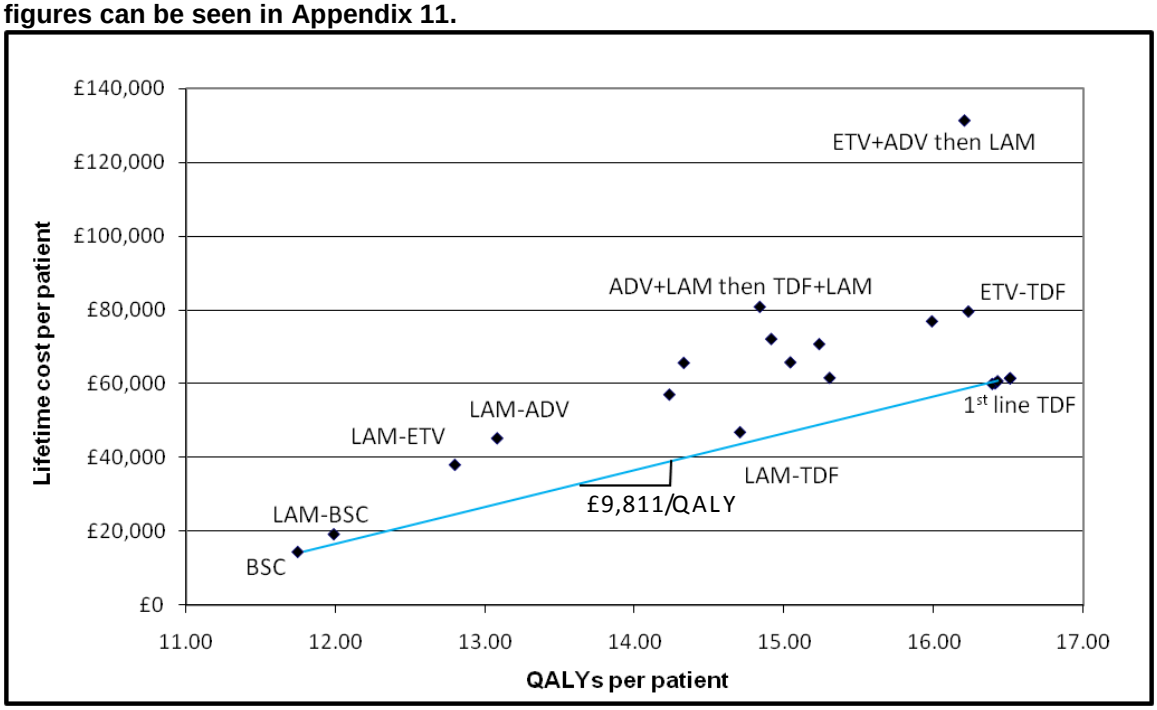
∞ Second-line use of tenofovir (in lamivudine-resistant patients) shows strict dominance over this treatment strategy, since it is less costly and generates more QALYs.

‡ Second-line use of tenofovir (in lamivudine-resistant patients) shows extended dominance (208) over this treatment strategy, since it generates more QALYs and has a lower incremental cost-effectiveness ratio compared with LAM then BSC.

§ A more effective strategy involving first-line use of tenofovir shows extended dominance over this strategy.

The relative costs and benefits of different treatments differed between HBeAg-positive and negative patients, as did the shape of the cost-effectiveness frontier. For HBeAg-negative patients, both “lamivudine then BSC” and “lamivudine then tenofovir” lay just above the cost-effectiveness frontier and were extendedly dominated by first-line use of tenofovir (Figure 8).

Figure 8: Results on the cost-effectiveness plane for the HBeAg-negative patient population. The blue line represents the cost-effectiveness frontier; treatments that lie on this line are cost-effective at some ceiling ratio, while those that lie above the line are dominated. For clarity, only the main clusters of strategies are labelled and this figure includes only the 20 strategies shown in Table 36. A scatter graph including all 211 treatment strategies included in the analysis and the data used to produce these figures can be seen in Appendix 11.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

In this population, first-line use of tenofovir monotherapy was dominant over all other treatment strategies, including:

- First-line use of tenofovir showed strict dominance over first-line use of adefovir, entecavir or combination therapy, being less costly and more effective.
- Both first-line and second-line tenofovir showed extended dominance over lamivudine followed by BSC, entecavir or adefovir.
- Tenofovir then tenofovir+lamivudine showed extended dominance over tenofovir then entecavir.

Based on the treatments lying on the cost-effectiveness frontier:

- BSC would be cost-effective if the NHS were not willing or able to pay £9,811 per QALY gained.
- Tenofovir then lamivudine would be the most cost-effective strategy antiviral strategy if the NHS used a ceiling ratio between £9,811 and £13,854/QALY gained.
- Tenofovir then tenofovir+lamivudine would be optimal at ceiling ratios between £13,854 and £20,781/QALY gained.
- Tenofovir then tenofovir+lamivudine then entecavir would be optimal if society were willing to pay at least £20,781 per QALY gained.

This means that the optimal treatments to be used if/when tenofovir resistance occurs are highly dependent on society's willingness to pay: at a £20,000/QALY threshold, tenofovir then tenofovir+lamivudine would be most cost-effective, while

tenofovir then tenofovir+lamivudine would be optimal at a £30,000/QALY threshold. However, tenofovir was the most cost-effective first-line strategy at all ceiling ratios above £9,811.

As for the HBeAg-positive population, all strategies involving first-line use of tenofovir generated very similar numbers of QALYs (difference between highest and lowest: 0.12 QALYs) and very similar total lifetime costs (difference between highest and lowest: £2,736) due to the low resistance rate for tenofovir. As described above, tenofovir then lamivudine is also less likely to be used in practice, while results for combination therapy are dependent on a number of assumptions.

Conclusions of the base case analysis

The base case analysis demonstrates that first-line use of tenofovir monotherapy is the most cost-effective antiviral strategy for managing both HBeAg-negative and HBeAg-positive CHB if the NHS is willing to pay between £20,000 and £30,000 per QALY gained.

- In HBeAg-positive patients, first-line tenofovir cost £9,940/QALY compared with the next most effective treatment on the frontier (lamivudine then tenofovir).
- In HBeAg-negative patients, first-line tenofovir cost £9,811/QALY compared with the next most effective treatment on the frontier (BSC)
- Consequently, first-line use of tenofovir would be cost-effective at any ceiling ratios above £9,811/QALY.

First-line use of tenofovir monotherapy is less costly and generates more QALYs than first-line use of entecavir, adefovir or combination therapy. It is also more cost-effective to use tenofovir first line than to wait until after lamivudiner resistance has developed.

Although the choice of second or third-line treatment has minimal impact on total costs or benefits over a lifetime, second-line use lamivudine+tenofovir in any patients who may develop tenofovir resistance is likely to be most cost-effective.

It should be noted that although no cases of virologic resistance to tenofovir have yet occurred, the model uses a conservatively high estimate of the risk of developing tenofovir resistance (Section 7.2.7.2.2). Subsequently, analysis may underestimate the true benefits of tenofovir, even when the two years of follow up in studies 0102 and 0103 are taken into account.

7.3.2. Subgroup analysis

7.3.2.1. What were the results of the subgroup analysis/analyses if conducted?

Subgroup analyses were conducted based on patients' starting state (Table 39) and based on prior treatment (Table 40).

The overall shape of the cost-effectiveness frontier was similar for the four main patient subgroups categorised by starting state (Table 39 and Appendix 11), although ICERs and exactly which treatments lay on the cost-effectiveness frontier varied between subgroups (Table 39).

For a mixed cohort of patients in which 69% of patients were HBeAg-positive and 5% had cirrhosis at baseline, first-line use of tenofovir would be the most cost-effective

treatment for CHB if the NHS is willing to pay at least £8,743 per QALY gained. In this population, neither lamivudine then tenofovir nor lamivudine then BSC lay on the cost-effectiveness frontier since they were extendedly dominated by first-line use of tenofovir. Tenofovir then tenofovir+lamivudine was the most cost-effective strategy considered in the analysis at a £20,000 per QALY threshold and tenofovir then tenofovir+lamivudine then entecavir was optimal at a £30,000/QALY threshold.

Table 39: Subgroup analyses on patients with different degrees of liver disease at baseline. For clarity, only the four least effective treatments lying on/near the cost-effectiveness plane are shown.

	BSC	LAM-BSC	LAM-TDF	TDF-LAM
Mixed cohort of HBeAg positive and negative patients				
Total cost per patient	£11,907	£16,017	£34,150	£44,399
Total QALYs per patient	14.28	14.70	16.77	17.99
Cost/QALY vs. BSC		£9,592	£8,904	£8,743
Cost/QALY vs. LAM-BSC	*		£8,761	£8,633
Cost/QALY vs. LAM-TDF	*	*		£8,414
Cost/QALY vs. TDF-LAM	*	*	*	
HBeAg-positive active CHB				
Total cost per patient	£9,092	£12,603	£21,085	£28,346
Total QALYs per patient	17.20	17.72	19.08	19.76
Cost/QALY vs. BSC		£6,744	£6,373	£7,510
Cost/QALY vs. LAM-BSC	*		£6,231	£7,706
Cost/QALY vs. LAM-TDF	*	*		£10,648
Cost/QALY vs. TDF-LAM	*	*	*	
HBeAg-negative active CHB				
Total cost per patient	£14,016	£18,796	£46,385	£59,360
Total QALYs per patient	12.07	12.28	14.99	16.70
Cost/QALY vs. BSC		£22,272	£11,074	£9,800
Cost/QALY vs. LAM-BSC	*		£10,187	£9,194
Cost/QALY vs. LAM-TDF	*	*		£7,615
Cost/QALY vs. TDF-LAM	*	*	£7,615	
HBeAg-positive compensated cirrhosis				
Total cost per patient	£15,650	£17,562	£27,423	£34,593
Total QALYs per patient	10.62	12.73	15.15	16.63
Cost/QALY vs. BSC		£905	£2,600	£3,149
Cost/QALY vs. LAM-BSC	*		£4,080	£4,363
Cost/QALY vs. LAM-TDF	*	*		£4,823
Cost/QALY vs. TDF-LAM	*	*	*	
HBeAg-negative compensated cirrhosis				
Total cost per patient	£18,680	£26,969	£58,348	£77,077
Total QALYs per patient	5.95	6.61	9.65	11.37
Cost/QALY vs. BSC		£12,543	£10,723	£10,774
Cost/QALY vs. LAM-BSC	*		£10,328	£10,528
Cost/QALY vs. LAM-TDF	*	*		£10,883
Cost/QALY vs. TDF-LAM	*	*	*	

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

* Treatment is less costly and less effective than its comparator; see cost-effectiveness of comparator relative to this treatment

In patients who were HBeAg-positive and did not have cirrhosis at baseline, first-line tenofovir would be cost-effective if the NHS were willing to pay at least £10,648/QALY gained. In this population, lamivudine then BSC was not on the frontier. The most cost-effective strategy at a £20,000/QALY threshold would be tenofovir then tenofovir+lamivudine.

For patients who were HBeAg-negative and non-cirrhotic at baseline, tenofovir then lamivudine would be cost-effective at ceiling ratios of £7,615/QALY and above and extendedly dominated both lamivudine then BSC and lamivudine then tenofovir. The optimal strategy at a £20,000/QALY ceiling ratio was tenofovir then tenofovir+lamivudine.

As would be expected, patients who have compensated cirrhosis when they start treatment have substantially higher costs and lower life expectancy than those who are pre-cirrhotic at baseline. However, all ICERs were lower for HBeAg-positive patients with cirrhosis than for those without cirrhosis. Tenofovir would be the most cost-effective first-line antiviral at ceiling ratios of £4,823/QALY and above and tenofovir then tenofovir+lamivudine would be most cost-effective at a £20,000/QALY threshold.

For cirrhotic patients with HBeAg-negative CHB, ICERs were higher than the base case analysis, with first-line tenofovir showing extended dominance over lamivudine then BSC and being cost-effective at ceiling ratios of £10,883/QALY and above. In this population, tenofovir followed by tenofovir+lamivudine then entecavir was the most cost-effective strategy at a £20,000/QALY threshold.

Since the base case analysis assumed that all patients were nucleos(t)ide-naïve at the start of the period modelled, a further subgroup analysis evaluated outcomes in patients who were already lamivudine resistant. In this population, all treatment strategies involving use of lamivudine monotherapy were excluded. This analysis demonstrated that tenofovir is the most cost-effective second line-agent for patients who have already developed lamivudine resistance: both in HBeAg-positive (Table 40) and HBeAg-negative patients (Table 41). However, as discussed in Section 7.3.1, it is substantially more cost-effective to give tenofovir first-line than to wait until patients have already developed lamivudine resistance.

Table 40: Results for a population of HBeAg-positive patients who are resistant to lamivudine at baseline

Treatment strategy*	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs BSC	Cost/QALY vs next most effective strategy on frontier[¥]	NB £10,000 ceiling ratio	NB £20,000 ceiling ratio	NB £30,000 ceiling ratio
Strategies that would lie on the cost-effectiveness frontier[¥] if BSC is considered to be a relevant comparator							
BSC	16.78	£9,529	-	-	£158,235	£325,998	£493,762
TDF	19.07	£27,208	£7,707	£7,707	£163,493	£354,195	£544,896
TDF+LAM	19.30	£35,348	£10,242	£35,858	£157,623	£350,595	£543,566
TDF+LAM then ETV	19.30	£35,430	£10,270	£61,133	£157,555	£350,540	£543,524
Other strategies dominated by treatment pathways on the cost-effectiveness frontier[¥]							
TDF then ETV[§]	19.09	£28,870	£8,346	-	£162,067	£353,005	£543,942
ADV[∞]	18.17	£30,227	£14,810	-	£151,513	£333,252	£514,992
ADV then TDF[∞]	18.61	£33,446	£13,039	-	£152,661	£338,767	£524,874
ADV then TDF+LAM[∞]	18.66	£34,922	£13,486	-	£151,671	£338,263	£524,856
ETV[∞]	16.73	£36,164	Dominated	-	£131,100	£298,364	£465,628
ETV then TDF[∞]	18.04	£44,002	£27,261	-	£136,407	£316,817	£497,226
ADV+LAM[∞]	18.18	£48,162	£27,503	-	£133,648	£315,459	£497,269
ADV+LAM then TDF+LAM[∞]	18.21	£48,455	£27,118	-	£133,663	£315,780	£497,898

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

* Within this table, lamivudine is assumed to have been given before the start of the model; for brevity, this is not shown in the table.

∞ Second-line use of tenofovir (in lamivudine-resistant patients) followed by BSC shows strict dominance over this treatment strategy, since it is less costly and generates more QALYs.

‡ Second-line use of tenofovir (in lamivudine-resistant patients) shows extended dominance (208) over this treatment strategy, since it generates more QALYs and has a lower incremental cost-effectiveness ratio compared with LAM then BSC.

§ A more effective strategy involving second-line use of tenofovir shows extended dominance over this strategy

Table 41: Results for a population of HBeAg-negative patients who are resistant to lamivudine at baseline

Treatment strategy*	Total QALYs/ patient	Total cost/ patient	Cost/ QALY vs BSC	Cost/ QALY vs ETV	Cost/QALY vs next most effective strategy on frontier¥	NB £10,000 ceiling ratio	NB £20,000 ceiling ratio	NB £30,000 ceiling ratio
Strategies that would lie on the cost-effectiveness frontier¥ if BSC is considered to be a relevant comparator								
BSC	11.53	£14,641	-	£30,051	-	£100,666	£215,972	£331,279
TDF	15.02	£53,265	£11,078	£4,238	£11,078	£96,906	£247,077	£397,248
TDF then ETV	15.24	£57,873	£11,652	£5,551	£20,571	£94,538	£246,949	£399,360
TDF+LAM then ETV	15.87	£74,670	£13,841	£9,453	£26,811	£84,006	£242,682	£401,358
Other strategies dominated by treatment pathways on the cost-effectiveness frontier¥								
ETV‡	12.45	£42,405	£30,051	-	-	£82,141	£206,686	£331,232
ADV‡	12.78	£51,949	£29,760	£28,946	-	£75,894	£203,736	£331,579
ADV+LAM∞	14.49	£80,961	£22,384	£18,910	-	£63,974	£208,909	£353,844
ADV then TDF∞	13.94	£63,674	£20,310	£14,271	-	£75,775	£215,224	£354,672
ADV then TDF+LAM∞	14.17	£69,430	£20,741	£15,734	-	£72,292	£214,014	£355,735
ETV then TDF∞	14.70	£65,017	£15,910	£10,084	-	£81,953	£228,923	£375,893
ADV+LAM then TDF+LAM∞	14.58	£82,032	£22,109	£18,654	-	£63,756	£209,544	£355,332

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

* Within this table, lamivudine is assumed to have been given before the start of the model; for brevity, this is not shown in the table.

∞ Second-line use of tenofovir (in lamivudine-resistant patients) followed by BSC shows strict dominance over this treatment strategy, since it is less costly and generates more QALYs.

‡ Second-line use of tenofovir (in lamivudine-resistant patients) followed by BSC shows extended dominance (208) over this treatment strategy, since it generates more QALYs and has a lower incremental cost-effectiveness ratio compared with LAM then BSC.

§ A more effective strategy involving second-line use of tenofovir shows extended dominance over this strategy.

Conclusions of subgroup analyses

First-line tenofovir is the most cost-effective antiviral strategy for all four of the main patient subgroups:

- HBeAg-positive patients without cirrhosis
- HBeAg-negative patients without cirrhosis
- HBeAg-positive patients with compensated cirrhosis
- HBeAg-negative patients with compensated cirrhosis

Tenofovir is also the most cost-effective antiviral strategy for patients who have already developed lamivudine resistance:

- In HBeAg-positive patients, second-line use of tenofovir shows strict dominance over adefovir, entecavir and adefovir+entecavir, being less costly and generating more QALYs than these three strategies.
- In HBeAg-negative patients, second-line use of tenofovir shows extended dominance over entecavir or adefovir in patients who have already developed lamivudine resistance and shows strict dominance over adefovir plus lamivudine.

However, the analyses described in Section 7.3.1 demonstrate that it is more cost-effective to give tenofovir first-line rather than waiting until lamivudine resistance has already developed.

7.3.3. Sensitivity analysis (See Section 10.3 Addendum to Section 7.3.3.1.1, Probabilistic sensitivity analysis)

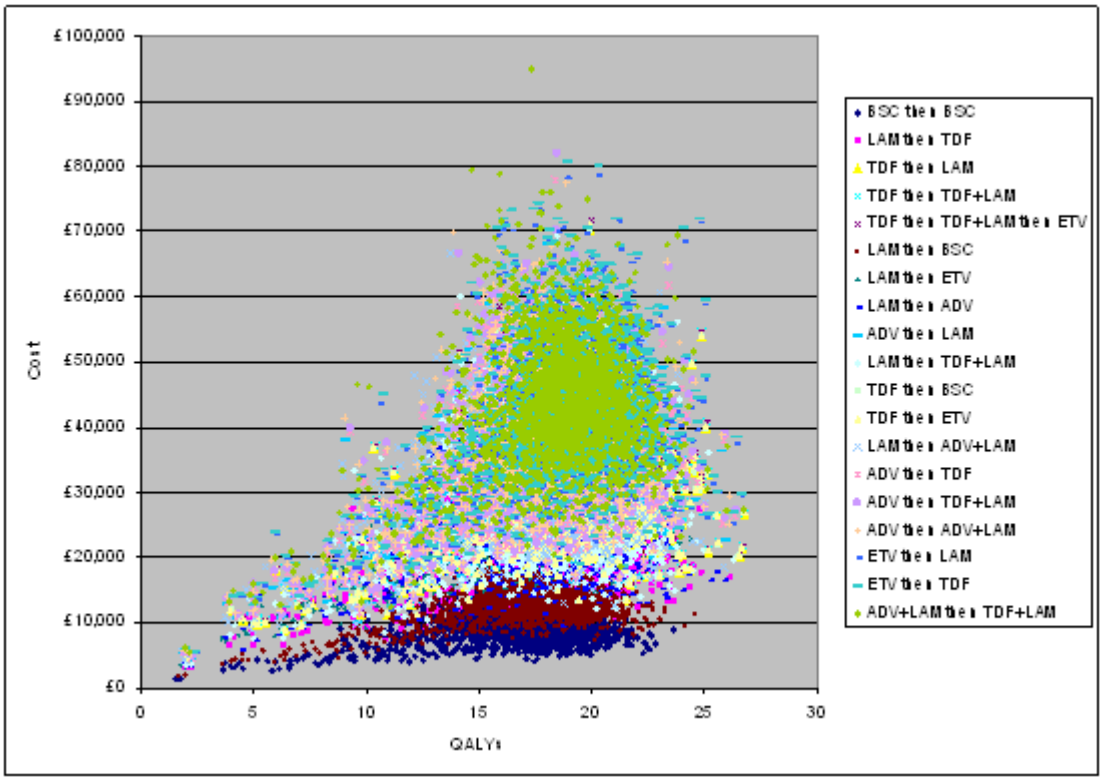
7.3.3.1. What were the main findings of the sensitivity analyses?

7.3.3.1.1. Probabilistic sensitivity analysis: HBeAg-positive patients

All parameters other than unit costs were varied simultaneously in probabilistic sensitivity analysis. All 20 strategies shown in Table 36 were subjected to PSA (Figure 9). It was not feasible to conduct PSA on all 211 treatment strategies listed in Appendix 11 due to the time taken to conduct the simulations; however, since the strategies included in PSA covered all of the main clusters lying on or near the frontier, restricting the number of strategies is unlikely to have any significant effect on the probability that first-line tenofovir is cost-effective.

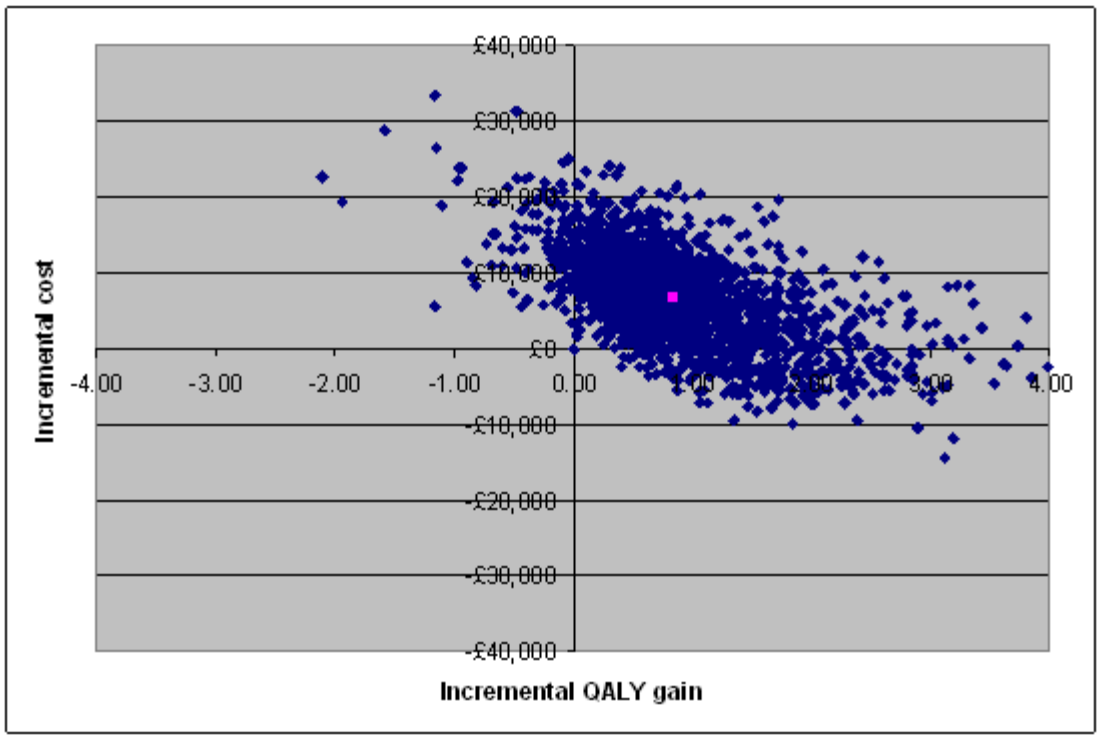
Only the main results of PSA are presented here. However, the spreadsheet model accompanying this submission enables PSA to be conducted on any plausible treatment strategy and allows generation of cost-effectiveness planes and curves for any pairwise or multiple-treatment comparisons.

Figure 9: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



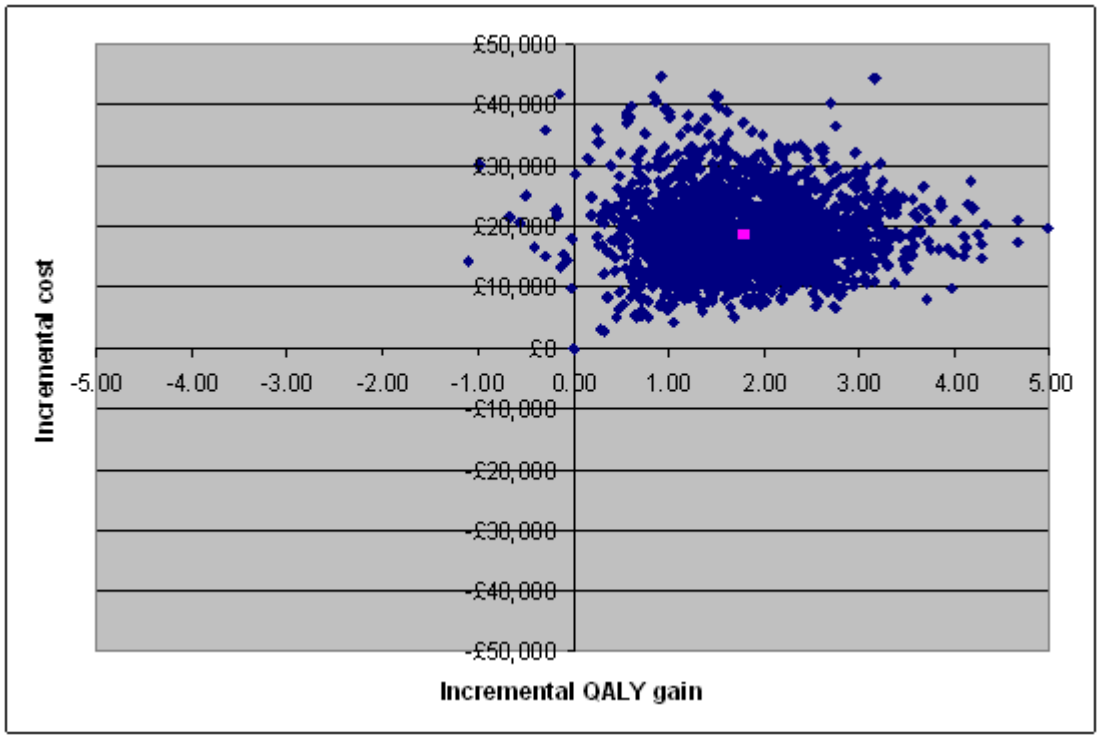
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 10: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs lamivudine then tenofovir for HBeAg-positive patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 11: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs lamivudine then BSC for HBeAg-positive patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

PSA confirmed the findings of the base case analysis, demonstrating that first-line use of tenofovir is the most cost-effective strategy if the NHS has a "threshold" cost/QALY of £20,000-£30,000/QALY gained. However, all cost-effectiveness ratios were slightly higher than those calculated in the deterministic base case analysis: for example, the ICER for tenofovir then lamivudine relative to lamivudine then BSC is £7,721 (95% CI: £3,909, £37,663) per QALY gained in the PSA, compared with £7,344/QALY in the base case analysis (Table 42).

Table 42: Mean ICERs and 95% CI and probability of each treatment strategy being cost-effective at different ceiling ratios: HBeAg-positive patients.

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean*	**Lower 95% CI†**	**Upper 95% CI†**	**£0**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
BSC then BSC	£16,339	£3,265	£43,572	99.60%	27.15%	6.20%	2.15%	0.75%
LAM then TDF	£21,316	#	#	0.00%	26.90%	21.30%	12.75%	5.10%
TDF then LAM	-	-	-	0.05%	25.15%	36.00%	28.40%	20.40%
TDF then TDF+LAM	£166,450	Dominant	£254,493	0.00%	1.25%	20.85%	32.15%	34.10%
TDF then TDF+LAM then ETV	£166,647	Dominant	£254,926	0.00%	0.00%	2.95%	10.30%	21.25%
LAM then BSC	£20,972	£4,164	£42,837	0.20%	10.65%	1.80%	0.45%	0.05%
LAM then ETV	£8,946	Dominant	£16,269	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then ADV	£26,201	#	#	0.00%	7.75%	6.05%	4.10%	2.55%
ADV then LAM	£3,468	#	#	0.00%	0.25%	0.75%	0.65%	0.20%
LAM then TDF+LAM	£1,500	Dominant	Dominated	0.00%	0.00%	0.85%	2.75%	5.05%
TDF then BSC	£19,396	#	#	0.10%	0.15%	0.15%	0.25%	0.20%
TDF then ETV	Dominant	Dominant	£245,920	0.05%	0.05%	0.05%	0.10%	0.10%
LAM then ADV+LAM	£3,834	Dominant	£38,121	0.00%	0.60%	0.65%	0.75%	0.35%
ADV then TDF	Dominant	#	#	0.00%	0.00%	0.25%	0.65%	0.45%
ADV then TDF+LAM	Dominant	#	#	0.00%	0.00%	0.00%	0.15%	0.40%
ADV then ADV+LAM	Dominant	Dominant	£320,384	0.00%	0.00%	0.00%	0.00%	0.25%
ETV then LAM	Dominant	#	#	0.00%	0.10%	1.25%	1.55%	2.25%
ETV then TDF	Dominant	#	#	0.00%	0.00%	0.65%	1.95%	5.00%
ADV+LAM then TDF+LAM	Dominant	Dominant	£131,867	0.00%	0.00%	0.25%	0.90%	1.45%
ETV+ADV then LAM	Dominant	Dominant	£3,806,724	0.00%	0.00%	0.00%	0.00%	0.10%
All first-line TDF strategies combined	-	-	-	**0.20%**	**26.60%**	**60.00%**	**71.20%**	**76.05%**
Cost-effectiveness frontier‡	-	-	-	**99.60%**	**10.65%**	**60.00%**	**71.20%**	**76.05%**

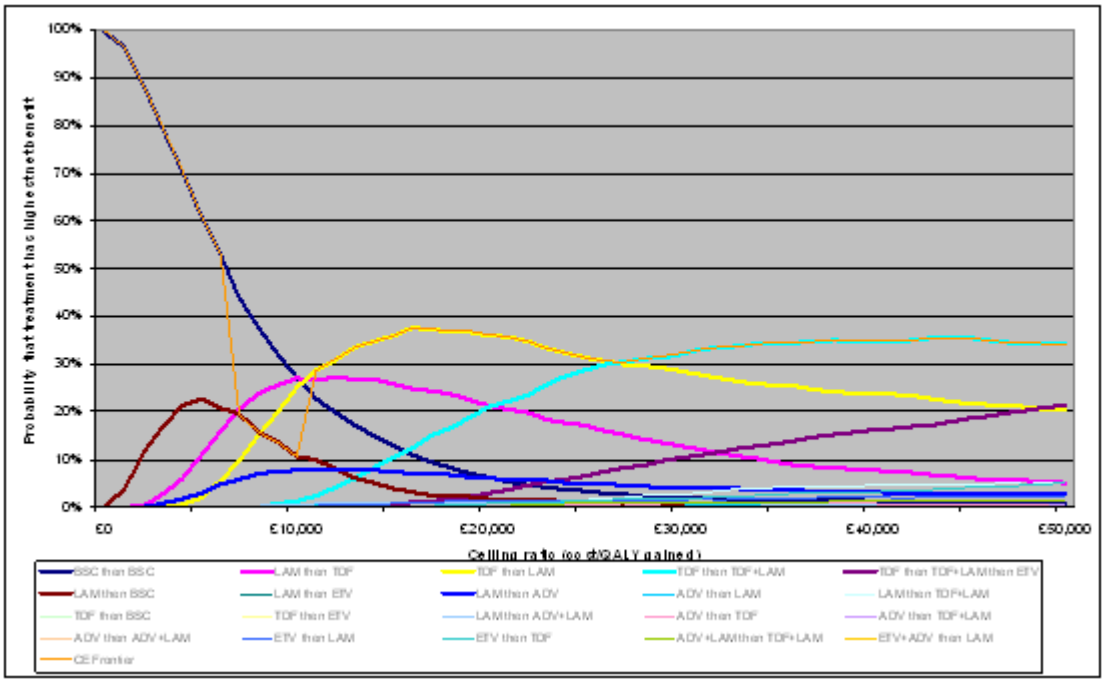
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.
Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.
* The "mean" ICER is the ratio of the mean incremental costs and mean incremental QALYs.
† 95% CI were calculated using the percentile method, assigning all ICERs falling in the north-west quadrant (in which treatment is dominated by its comparator, being more costly and less effective) an arbitrarily high ICER.
# The 95% CI was considered to be undefined as >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).
‡ The cost-effectiveness frontier represents the treatment with the highest expected net benefits at each ceiling ratio. The probabilities shown in this row represent the probability that the treatment with the highest expected net benefits is optimal. Error probabilities at any given threshold are equal to 1 minus the probabilities shown in this row.

For each of the 2,000 Monte Carlo simulations generated, the model calculated the net benefits for all 20 treatment strategies. These data were used to calculate the probability that (i.e. the proportion of simulations in which) each treatment is the most cost-effective treatment considered in the analysis at a range of different ceiling ratios showing possible values for our willingness to pay to gain one QALY (Figure 12 and Table 42).

This demonstrates that BSC is significantly less effective than all other treatment strategies considered in this analysis (p=0.004), in addition to having a >50% chance of being the optimal strategy at all ceiling ratios below £6,300.

Although it lies on the cost-effectiveness frontier in both the base case analysis and PSA, the probability that lamivudine then BSC is optimal never exceeds 23%. By contrast, lamivudine then tenofovir lies slightly above the cost-effectiveness frontier based on its mean costs and benefits within PSA (Table 42) but has a 27% probability of being optimal at a £10,000/QALY threshold.

Figure 12: Cost-effectiveness acceptability curves showing the probability that a particular treatment is the most cost-effective treatment considered in the analysis (i.e. has the highest net benefit) at a range of different threshold incremental cost-effectiveness ratios: HBeAg-positive patients.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

At a £20,000/QALY threshold, tenofovir followed by lamivudine had a 36% probability of being optimal, compared with 21% for lamivudine then tenofovir, 21% for tenofovir then tenofovir+lamivudine and 6% for lamivudine then adefovir. However, if the NHS were willing to pay £30,000 per QALY gained, tenofovir then tenofovir+lamivudine would have the highest probability of being cost-effective (32%). Tenofovir then lamivudine has the highest expected net benefits (and therefore lies on the cost-effectiveness frontier) at this threshold. The error probability at this threshold (one minus the probability that this treatment is optimal) is therefore 74%.

Pooling all strategies involving first-line use of tenofovir together demonstrates that we can be 60% confident that first-line use of tenofovir is the most cost-effective antiviral treatment for HBeAg-positive CHB if the NHS is willing to pay £20,000/QALY gained and 71% confident at a £30,000/QALY threshold.[II] Furthermore, there was a 59% probability that one of the first-line tenofovir strategies would be the most effective treatment considered in this analysis.

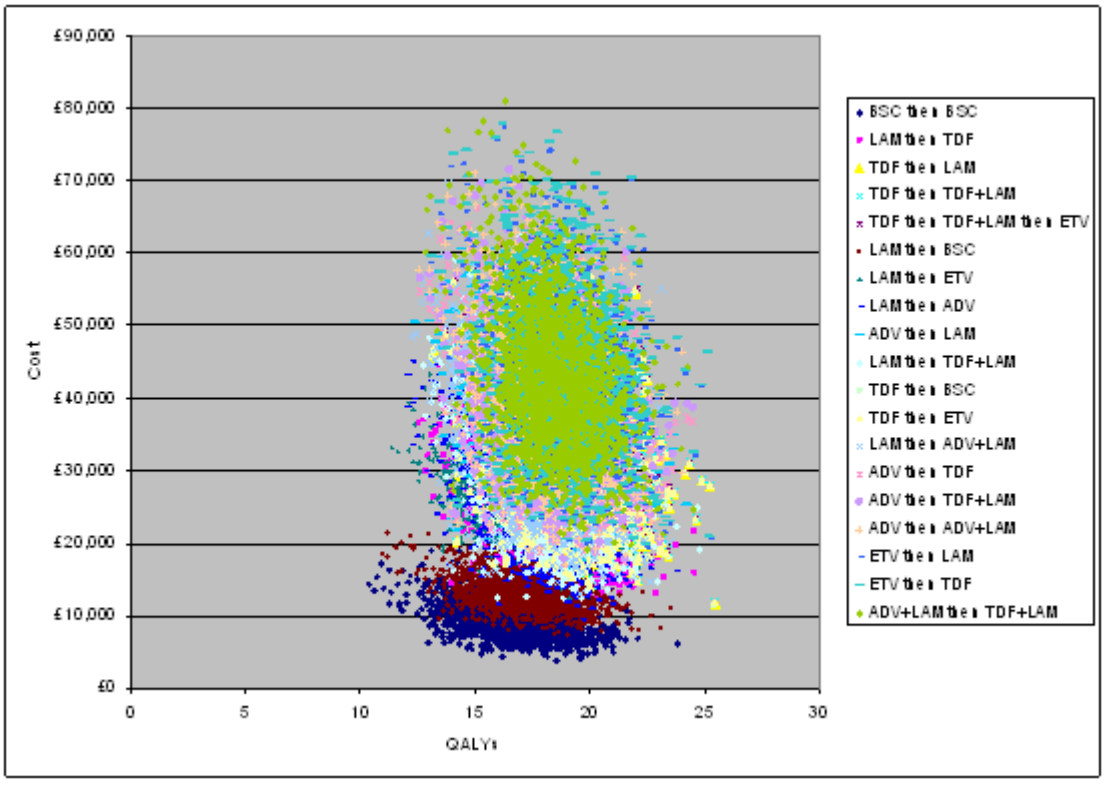
[II] If all first-line tenofovir strategies are treated as a single strategy, the error probability at a £20,000/QALY threshold is therefore 40%.

This analysis also demonstrated that the comparisons between different strategies including first-line tenofovir are extremely sensitive to model inputs: although at a £20,000/QALY ceiling ratio there is a 71% probability that lamivudine then BSC is cost-effective relative to BSC, a 66% probability that lamivudine then tenofovir is cost-effective relative to lamivudine then BSC and a 71% probability that tenofovir then lamivudine is cost-effective relative to lamivudine then tenofovir, the probability that tenofovir then tenofovir+lamivudine is cost-effective relative to tenofovir then lamivudine is just 44% and the probability that tenofovir then tenofovir+lamivudine then entecavir is cost-effective relative to tenofovir then tenofovir+lamivudine is only 5%.

7.3.3.1.2. Probabilistic sensitivity analysis: HBeAg-negative patients

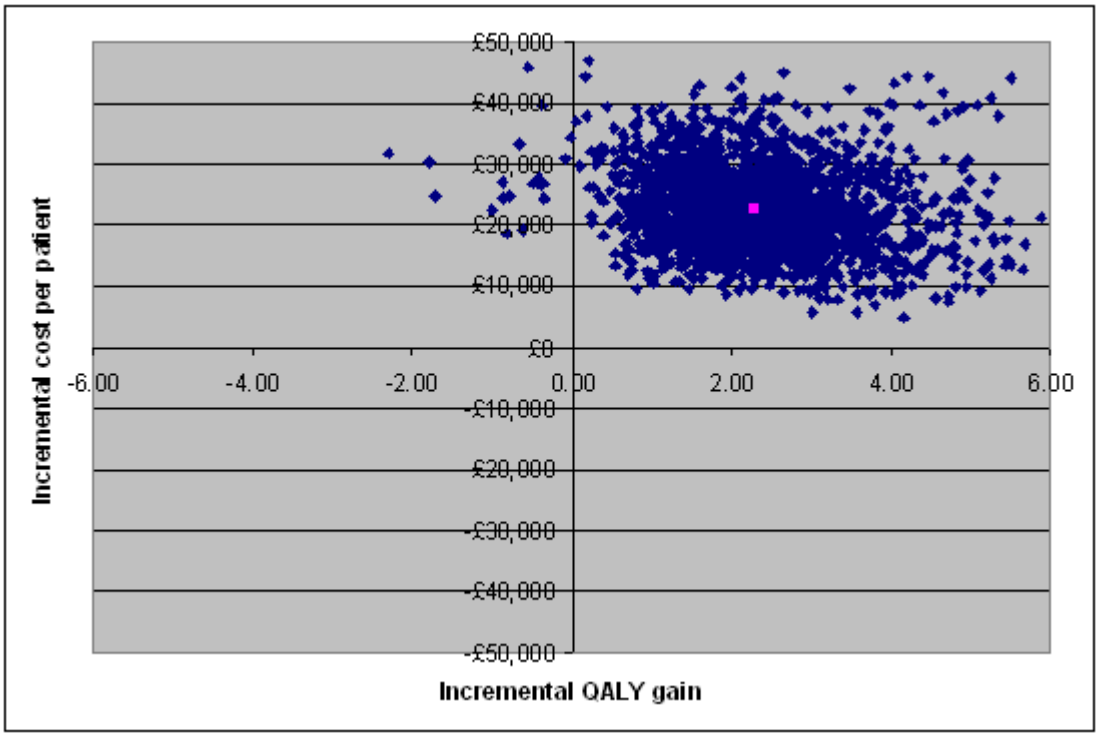
PSA was repeated for the HBeAg-negative population. The results for this population were strikingly similar to those for HBeAg-positive patients (Figure 12 and Figure 15).

Figure 13: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



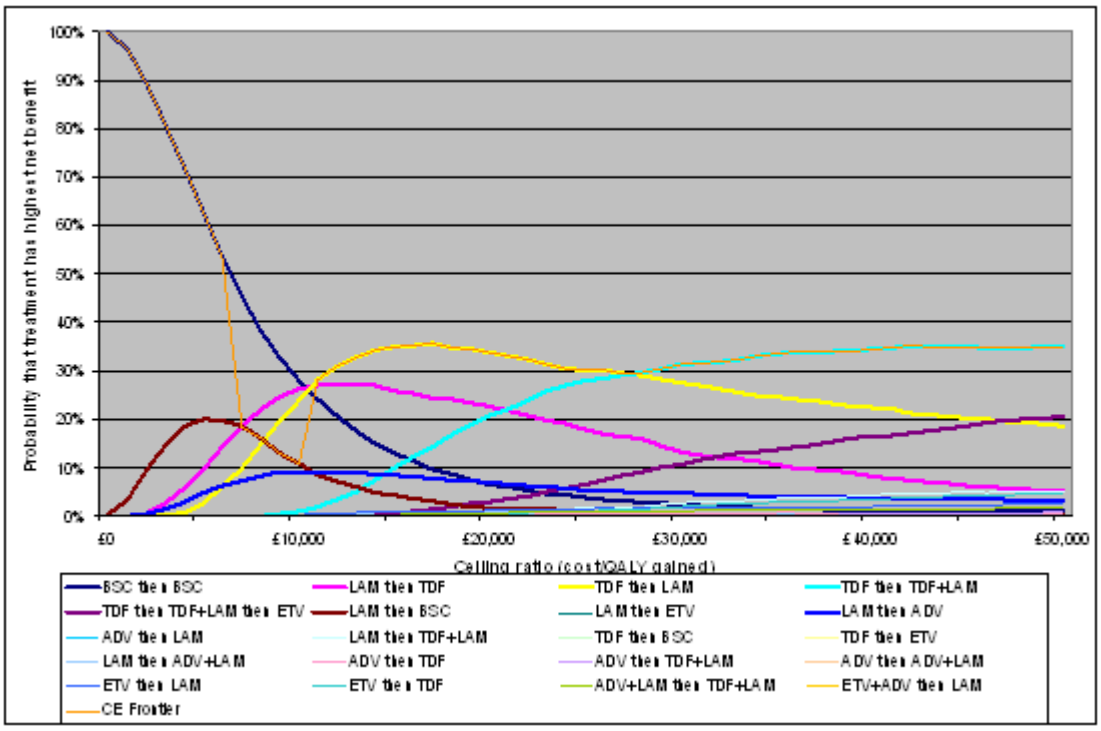
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 14: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs BSC for HBeAg-negative patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 15: Cost-effectiveness acceptability curves showing the probability that a particular treatment is the most cost-effective treatment considered in the analysis (i.e. has the highest net benefit) at a range of different threshold incremental cost-effectiveness ratios: HBeAg-negative patients.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

For HBeAg-negative patients, BSC had the highest probability of being cost-effective at all ceiling ratios below £10,300 and generated significantly fewer QALYs than any other treatment (p=0.0024).

At a £20,000/QALY threshold, tenofovir followed by lamivudine had a 34% probability of being optimal, compared with 23% for lamivudine then tenofovir, 21% for tenofovir then tenofovir+lamivudine and 7% for lamivudine then adefovir. However, if the NHS was willing to pay £30,000 per QALY gained, tenofovir then tenofovir+lamivudine would have the highest probability of being cost-effective (31%; Table 43).

Table 43: Mean ICERs and 95% CI and probability of each treatment strategy being cost-effective at different ceiling ratios: HBeAg-negative patients.

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean	Lower 95% CI	Upper 95% CI	£0	£10,000	£20,000	£30,000	£50,000
BSC then BSC	£21,789	£3,049	£51,475	99.76%	28.04%	6.52%	2.44%	0.96%
LAM then TDF	£6,211	#	#	0.00%	26.24%	22.56%	13.32%	5.00%
TDF then LAM	-	-	-	0.00%	23.96%	33.76%	27.36%	18.64%
TDF then TDF+LAM	Dominant	Dominant	£319,880	0.00%	0.92%	20.72%	31.28%	34.92%
TDF then TDF+LAM then ETV	Dominant	Dominant	£341,393	0.00%	0.04%	2.96%	10.64%	20.60%
LAM then BSC	£17,726	£3,986	£56,856	0.24%	10.92%	1.80%	0.44%	0.20%
LAM then ETV	£5,912	Dominant	£18,445	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then ADV	£5,961	#	#	0.00%	8.88%	6.92%	4.72%	3.32%
ADV then LAM	Dominant	#	#	0.00%	0.24%	0.64%	0.64%	0.44%
LAM then TDF+LAM	Dominant	Dominant	Dominated	0.00%	0.00%	0.72%	2.72%	5.16%
TDF then BSC	£19,075	#	#	0.00%	0.08%	0.08%	0.12%	0.00%
TDF then ETV	Dominant	Dominant	£225,902	0.00%	0.00%	0.00%	0.00%	0.08%
LAM then ADV+LAM	Dominant	Dominant	£40,598	0.00%	0.32%	0.84%	0.60%	0.40%
ADV then TDF	Dominant	#	#	0.00%	0.00%	0.12%	0.52%	0.40%
ADV then TDF+LAM	Dominant	#	#	0.00%	0.00%	0.08%	0.28%	0.68%
ADV then ADV+LAM	Dominant	Dominant	£122,462	0.00%	0.00%	0.00%	0.12%	0.28%
ETV then LAM	Dominant	#	#	0.00%	0.32%	1.24%	1.76%	2.32%
ETV then TDF	Dominant	#	#	0.00%	0.00%	0.48%	1.96%	4.88%
ADV+LAM then TDF+LAM	Dominant	Dominant	£231,941	0.00%	0.04%	0.56%	1.08%	1.72%
ETV+ADV then LAM	Dominant	Dominant	£5,625,798	0.00%	0.00%	0.00%	0.00%	0.00%
All first-line TDF strategies combined	**-**	**-**	**-**	**0.00%**	**25.00%**	**57.52%**	**69.40%**	**74.24%**
Cost-effectiveness frontier‡	-	-	-	**99.76%**	**10.92%**	**57.52%**	**69.40%**	**74.24%**

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.
Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.
* The "mean" ICER is the ratio of the mean incremental costs and mean incremental QALYs.
† 95% CI were calculated using the percentile method, assigning all ICERs falling in the north-west quadrant (in which treatment is dominated by its comparator, being more costly and less effective) an arbitrarily high ICER.
# The 95% CI was considered to be undefined as >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).
‡ The cost-effectiveness frontier represents the treatment with the highest expected net benefits at each ceiling ratio. The probabilities shown in this row represent the probability that the treatment with the highest expected net benefits is optimal. Error probabilities at any given threshold are equal to 1 minus the probabilities shown in this row.

We can be 58% confident that tenofovir is the most cost-effective antiviral strategy for managing HBeAg-negative CHB at a £20,000/QALY threshold (if all strategies involving first-line use of tenofovir are combined), which increases to 69% at a £30,000/QALY threshold. The error probability at a £20,000/QALY threshold is therefore 42% when all first-line tenofovir strategies are combined together. We can be 56% confident that one of the first-line tenofovir strategies would be the most effective treatment considered in this analysis.

As was the case for HBeAg-positive patients, the comparisons between different strategies including first-line tenofovir were extremely sensitive to model inputs: at a £20,000/QALY ceiling ratio there is a:

- 69% probability that lamivudine then BSC is cost-effective relative to BSC
- 67% probability that lamivudine then tenofovir is cost-effective relative to lamivudine then BSC
- 70% probability that tenofovir then lamivudine is cost-effective relative to lamivudine then tenofovir
- 44% probability that tenofovir then tenofovir+lamivudine is cost-effective relative to tenofovir then lamivudine
- 5% probability that tenofovir then tenofovir+lamivudine then entecavir is cost-effective relative to tenofovir then tenofovir+lamivudine.

7.3.3.1.3. Deterministic sensitivity analyses for HBeAg-positive patients

Choice of strategies evaluated in sensitivity analyses

Since the choice of treatments to use if/when resistance to tenofovir monotherapy develops has minimal impact on costs or benefits and as there is uncertainty about the costs and benefits of the treatments used after tenofovir, sensitivity analyses focused on the least effective first-line tenofovir strategy that lay on the cost-effectiveness frontier: tenofovir then lamivudine.

This treatment was compared against the next most effective non-dominated strategy that lay on the cost-effectiveness frontier (lamivudine then BSC), since this comprises the most appropriate reference point for calculating the cost-effectiveness of tenofovir then lamivudine in economic terms.

The comparison between tenofovir then lamivudine vs lamivudine then tenofovir was also evaluate as this comprises the most stringent test of the conclusion that first-line use of tenofovir is the most cost-effective antiviral strategy for managing CHB.

In addition, the comparison between lamivudine then tenofovir vs lamivudine then BSC was also evaluated to identify whether there are any situations in which it would be more cost-effective to reserve tenofovir until after lamivudine resistance has developed.

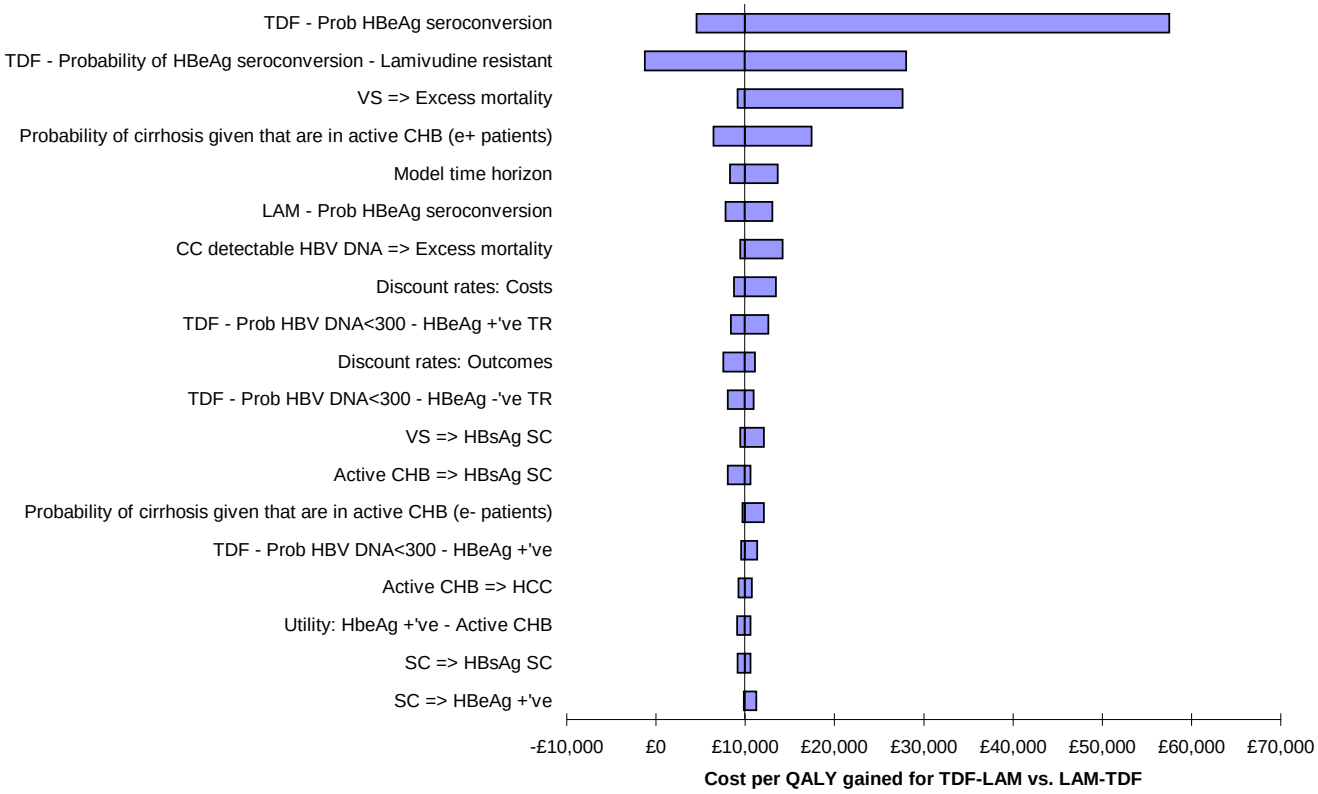
One-way sensitivity analyses for HBeAg-positive patients

One-way sensitivity analyses were conducted by varying all parameters not known with certainty between the minimum and maximum plausible values defined in Section 7.2.9 to produce tornado diagrams. For clarity, only the tornado diagrams for the comparisons lying on the cost-effectiveness frontier are shown below; tornado diagrams on the comparison between first-line tenofovir and BSC or lamivudine then BSC are shown in Appendix 11.

This showed that only three parameters could change the conclusion that first-line tenofovir is cost-effective relative to giving lamivudine first-line followed by tenofovir at a £20,000/QALY threshold: the probability of HBeAg seroconversion for antiviral-

naïve patients receiving tenofovir; the probability of HBeAg seroconversion for lamivudine-resistant patients receiving tenofovir; and the excess mortality associated with the viral suppression state (Figure 16).

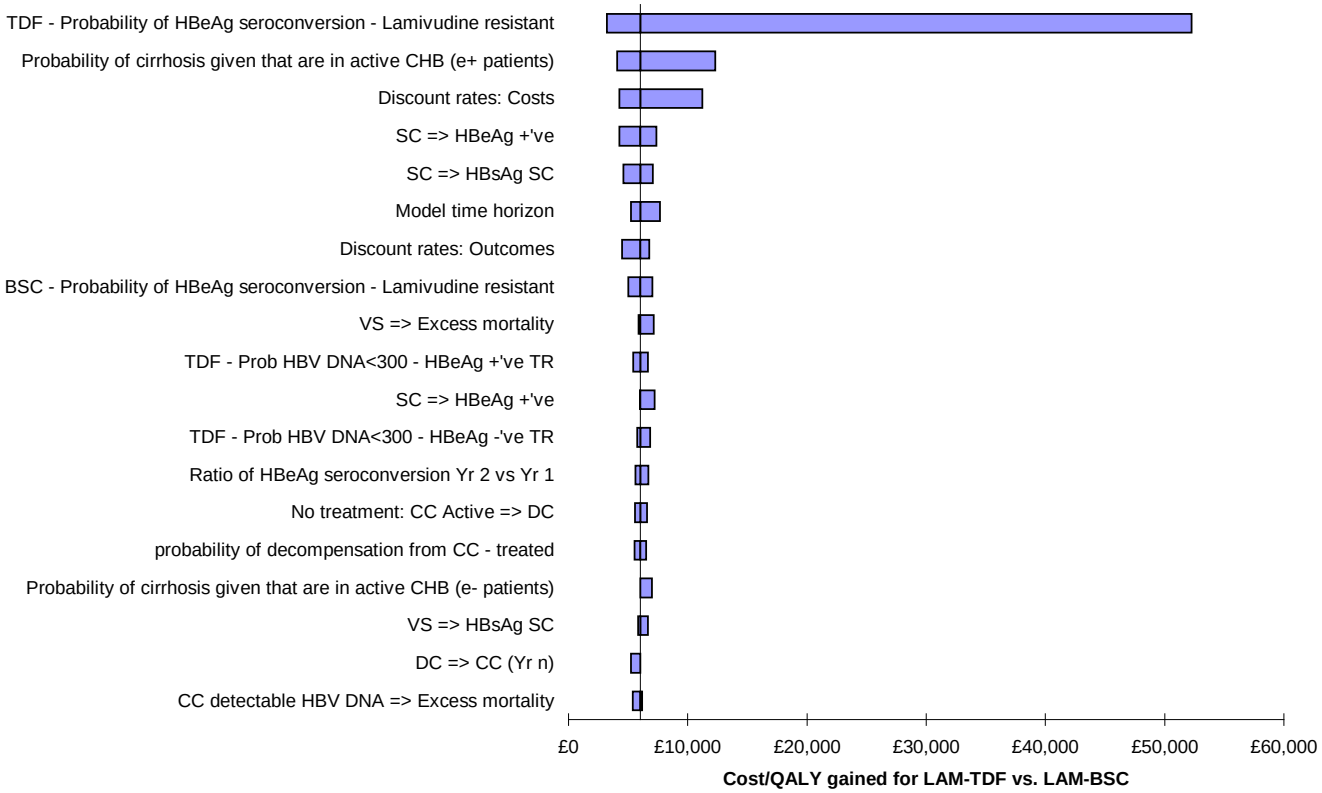
Figure 16: Tornado diagram showing the impact of different variables on the cost/QALY for the tenofovir then lamivudine then BSC strategy (first-line tenofovir) relative to lamivudine then tenofovir (second-line tenofovir) based on a 40-year horizon. Within the diagram, variables are ranked in descending order of importance. For clarity, only the 20 variables having most impact on the results are shown in this diagram. The vertical line shows the base case value of £9,940.



Abbreviations: <300, less than 300 copies/mL HBV DNA; =>, [probability of moving from state X] to [state Y]; BSC, best supportive care; CC, compensated cirrhosis; CHB, chronic hepatitis B; c/mL, copies per millilitre; DC; decompensated cirrhosis; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LT, liver transplant; prob, probability; prog, [disease] progression; pts, patients; SC, seroconverted; RR, relative risk; TDF, tenofovir; -'ve, negative; VS, viral suppression.

Furthermore, only one parameter could change the conclusion that second-line use of tenofovir was cost-effective relative to lamivudine then BSC at a £20,000/QALY threshold: the probability of HBeAg seroconversion for lamivudine-resistant patients receiving tenofovir (Figure 17).

Figure 17: Tornado diagram showing the impact of different variables on the cost/QALY for the lamivudine then tenofovir strategy (second-line tenofovir) relative to lamivudine then BSC based on a 40-year horizon. Within the diagram, variables are ranked in descending order of importance. For clarity, only the 20 variables having most impact on the results are shown in this diagram. The vertical line shows the base case value of £6,014.



Abbreviations: <300, less than 300 copies/mL HBV DNA; =>, [probability of moving from state X] to [state Y]; BSC, best supportive care; CC, compensated cirrhosis; CHB, chronic hepatitis B; c/mL, copies per millilitre; DC; decompensated cirrhosis; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LT, liver transplant; prob, probability; prog, [disease] progression; pts, patients; SC, seroconverted; RR, relative risk; TDF, tenofovir; -'ve, negative; VS, viral suppression.

Additional tornado diagrams (Appendix 11) showed that no parameters could change the conclusion that first-line tenofovir is cost-effective relative to lamivudine then BSC or BSC at a £20,000/QALY threshold when varied over the range of values that they could plausibly take.

Threshold analyses for HBeAg-positive patients

Threshold analyses were conducted to identify the threshold values for influential parameters that changed the conclusions of the analysis (Table 44). This analysis demonstrated that for most of the top 10 drivers, no logically-plausible value could change the conclusion that first-line tenofovir is the most cost-effective strategy at a £20,000/QALY threshold. For example, no discount rates between zero and 100% could cause any of these ICERs to reach this threshold. Although the analysis is sensitive to the probability of HBeAg seroconversion for tenofovir-treated patients, the probability of tenofovir-treated patients achieving these outcomes would need to be lower than the probability with lamivudine to change the conclusions of the analysis. Similarly, the excess mortality associated with viral suppression would need to be more than 6-fold higher than that for active CHB for tenofovir to cost more than £20,000/QALY gained.

Table 44: Threshold analysis around the 10 most influential variables. Threshold values lying within the plausible range for the parameter in question are shown in blue typeface. All results are based on a 40-year time horizon.

Variable	Base case value (plausible range)	LAM-TDF vs LAM-BSC: Value where ICER=		TDF-LAM vs BSC: Value where ICER=		TDF-LAM vs LAM-BSC: Value where ICER=		TDF-LAM vs LAM-TDF	
		£20k	£30k	£20k	£30k	£20k	£30k	£20k	£30k
Probability of cirrhosis given that are in active CHB (e+ patients)	5.00% (0.40% to 14.00%)	NA	NA	NA	NA	NA	NA	NA	NA
TDF - Prob HBeAg seroconversion	26.74% (11.12% to 49.14%)	NA	NA	5.12%	2.90%	7.28%	4.84%	17.14%	14.04%
Discount rates: Costs	3.50% (0.00% to 6.00%)	NA	NA	NA	NA	NA	NA	NA	NA
VS => Excess mortality	0.35% (0.00% to 2.80%)	12.48%	14.50%	6.56%	7.70%	5.39%	6.38%	2.28%	2.91%
Model time horizon	41 (30 to 51)	11	9	13	10	15	11	21	14
Discount rates: Outcomes	3.50% (0.00% to 6.00%)	NA	NA	NA	NA	NA	NA	NA	NA
Probability of moving from HBeAg seroconverted to Active CHB	0.85% (0.00% to 17.00%)	NA	NA	NA	NA	NA	NA	NA	NA
Probability of moving from HBeAg seroconverted to HBsAg seroconverted	2.90% (0.00% to 9.76%)	NA	NA	NA	NA	NA	NA	NA	NA
LAM - Prob HBeAg seroconversion	23.54% (16.40% to 32.07%)	NA	NA	NA	NA	NA	NA	46.08%	59.46%
BSC - Probability of HBeAg seroconversion - Lamivudine resistant	10.69% (8.02% to 13.36%)	47.90%	80.84%	NA	NA	NA	NA	NA	NA

NA: No meaningful parameter value could be determined (excluding negative values for costs, discount rates and transition probabilities as well as values greater than one for transition probabilities and utility scores).

Scenario analyses for HBeAg-positive patients

In addition to the one-way sensitivity analyses described above, a number of scenario analyses were conducted to evaluate a range of different values of key parameters, assess cost-effectiveness in patient subgroups and vary two or more parameters simultaneously (Table 45).

Table 45: Scenario analyses for HBeAg-positive patients. All results are based on a 40-year time horizon unless otherwise specified. Values shown in red are above £30,000/QALY gained, while those in orange are between £20,000 and £30,000/QALY gained.

Scenario	Cost/QALY for LAM-TDF relative to:	Cost/QALY for TDF-LAM relative to:		
	LAM-BSC	BSC	LAM-BSC	LAM-TDF
Base case	**£6,014**	**£6,945**	**£7,344**	**£9,940**
Discounting				
No discounting	£8,356	£8,165	£8,978	£10,216
Costs discounted at 6%, benefits at 1.5%	£3,684	£4,919	£5,016	£7,640
Time horizon				
5 years	£47,496	£52,654	£65,056	£76,705
10 years	£17,279	£22,038	£25,594	£35,700
11 years	£16,366	£20,712	£23,995	£33,676
12 years	£14,150	£18,107	£20,794	£29,841
13 years	£13,794	£17,411	£19,975	£28,636
14 years	£12,151	£15,169	£17,267	£24,992
15 years	£12,151	£15,169	£17,267	£24,992
16 years	£10,973	£13,732	£15,516	£22,692
17 years	£11,011	£13,556	£15,323	£22,225
18 years	£10,059	£12,405	£13,921	£20,334
19 years	£10,160	£12,338	£13,855	£20,045
20 years	£9,357	£11,385	£12,691	£18,449
30 years	£7,218	£8,438	£9,127	£12,777
40 years	£6,014	£6,945	£7,344	£9,940
43 years	£5,831	£6,727	£7,088	£9,539
47 years	£5,509	£6,345	£6,644	£8,845
50 years	£5,234	£6,022	£6,271	£8,269
60 years	£4,702	£5,398	£5,566	£7,192
Resource use				
Cost of LAM based on HIV cost	£6,007	£6,944	£7,489	£10,382
Assuming that treated patients have 11 secondary care consultations per year as assumed by SHTAC (64)	£7,007	£8,320	£7,885	£9,599
Assuming that untreated patients have the same frequency and cost of monitoring as treated patients	£5,913	£6,803	£7,274	£9,928
Increasing all disease management costs by 25%	£6,028	£6,874	£7,298	£9,776
Decreasing all disease management costs by 25%	£5,999	£7,017	£7,390	£10,104
Excluding cost of HBIG	£5,994	£6,958	£7,348	£9,988
Applying the cost of antiviral therapy for 6 months after HBeAg seroconversion	£5,983	£6,595	£7,009	£9,010
Applying the cost of antiviral therapy for 6 months after HBsAg seroconversion	£6,015	£6,956	£7,354	£9,967
Ceasing the cost of antiviral therapy as soon as patients undergo HBeAg seroconversion	£5,940	£6,096	£6,530	£7,682
Assuming that patients receiving tenofovir have only quarterly renal monitoring in Yr 1 (in line with clinical practice), instead of every 4 weeks as assumed in the base case analysis	£6,014	£6,937	£7,333	£9,907
Assuming that additional renal monitoring with tenofovir is done during an outpatient consultation with a registrar/consultant plus 10 minutes with a nurse, instead of in primary care	£6,014	£7,179	£7,645	£10,826
Utilities				

Scenario	Cost/QALY for LAM-TDF relative to:	Cost/QALY for TDF-LAM relative to:		
	LAM-BSC	BSC	LAM-BSC	LAM-TDF
Base case	**£6,014**	**£6,945**	**£7,344**	**£9,940**
Alternative 1: using mild hepatitis C study utilities (38) for severe states*	£6,230	£7,161	£7,549	£10,065
Alternative 2: using utilities used in the SMC submission for adefovir (65)*	£5,437	£6,207	£6,542	£8,608
Alternative 3: assuming that mild states are based on utility decrement from full health based on Wong estimates (124)*	£6,235	£7,234	£7,607	£10,277
Alternative 4: based on SG utilities from non-infected patients (37)*	£6,273	£7,394	£7,679	£10,442
Alternative 5: based on VAS preferences values from infected patients (37)*	£5,387	£6,143	£6,542	£8,759
Alternative 6: based on SG utilities from infected patients for their current disease state (37)*	£6,236	£7,238	£7,608	£10,275
Transition probabilities				
Assuming that 5% of treated HBV DNA-negative cirrhotic patients show regression of cirrhosis and move back to viral suppression each year	£5,686	£6,635	£6,958	£9,440
Assuming that no decompensated patients revert to compensated cirrhosis	£6,082	£6,946	£7,346	£9,784
Assuming that the probability of moving from decompensated cirrhosis to compensated cirrhosis in the second or subsequent years of therapy is 10% of the chance in Year 1.	£5,880	£6,874	£7,260	£9,979
Assume that combination therapy is 5% more effective than monotherapy	£6,082	£6,946	£7,346	£9,784
Assuming that treatment reduces the mortality associated with HCC by 10%	£6,014	£6,945	£7,344	£9,940
Assuming that treatment reduces the mortality associated with DC by 10%	£6,032	£6,954	£7,354	£9,937
Assuming that all treatments increase the chance of HBsAg seroconversion by 50%	£5,540	£6,593	£7,005	£9,827
Assuming that the probability of liver transplantation is 5-fold higher than in the base case	£5,916	£6,862	£7,289	£10,017
Assuming that no patients will undergo liver transplantation	£6,049	£6,974	£7,366	£9,917
Resistance rates				
Tenofovir resistance rates assumed to be same as those for adefovir	£5,811	£6,831	£7,254	£10,309
Tenofovir resistance rates assumed to be same as those for entecavir	£5,216	£6,916	£7,318	£9,052
Resistance rate associated with tenofovir doubles each year: 0.23%, 0.46%, 0.93%, 1.85% and 3.0% in years 1-4 and Year 5/n, respectively in naïve patients and 0.76%, 1.53%, 3.05%, 6.11% and 12.21% in years 1-5 and year 5/n, respectively in LAM-resistant patients.	£5,343	£6,803	£7,210	£9,877
Patterns of care				
Assuming that resistance is picked up as soon as HBV DNA levels rise/become detectable	£5,956	£6,943	£7,297	£9,958
Assuming that resistance is picked up 3 months after HBV DNA levels rise/become detectable	£6,071	£6,948	£7,391	£9,928
Assuming that resistance is picked up 6 months after	£6,182	£6,953	£7,483	£9,921

Scenario	Cost/QALY for LAM-TDF relative to:	Cost/QALY for TDF-LAM relative to:		
	LAM-BSC	BSC	LAM-BSC	LAM-TDF
Base case	**£6,014**	**£6,945**	**£7,344**	**£9,940**
HBV DNA levels rise/become detectable				
Assuming that resistance is picked up 12 months after HBV DNA levels rise/become detectable	£6,385	£6,966	£7,667	£9,982
Assuming pts in the CC, DC, post-LT, LT or HCC states do not receive antivirals AND all patients assumed to have active CHB at baseline	£6,621	£7,509	£8,364	£11,674
Assuming pts in the CC state receive antivirals but those in DC, HCC, LT or post-LT states do not	£5,957	£6,953	£7,259	£9,800
Assuming pts with HCC do not receive antivirals, but those in the DC, LT, post-LT states do	£6,008	£6,946	£7,340	£9,938
Assuming that pts in the DC, LT, post-LT states do not receive antivirals but those with HCC do	£5,968	£6,953	£7,264	£9,795

Abbreviations: BC, base case; CC, compensated cirrhosis; DC, decompensated cirrhosis; GP, general practitioner; LAM, lamivudine; LT, liver transplantation; BSC, best supportive care; SG, standard gamble; UK, United Kingdom.
* The values used in this sensitivity analysis are shown in Appendix 11.
† Within this scenario (unlike in the base case analysis), first-line use of tenofovir (TDF-LAM) did not show extended dominance over second-line use of tenofovir (LAM-TDF).

This analysis demonstrated that only one set of scenarios evaluated changed the conclusion that first-line tenofovir is cost-effective: variations in the time horizon used in the analysis. At time horizons below 10 years, neither first nor second-line tenofovir would be cost-effective at a £20,000/QALY threshold. At time horizons between 11 and 19 years (inclusive), second-line use of tenofovir would be cost-effective at a £20,000/QALY threshold, but first-line tenofovir would not.

However, if the time horizon were 10 years or less, no treatments (including entecavir or adefovir) other than lamivudine followed by BSC would be cost-effective at a £20,000/QALY threshold. Furthermore, the analyses taking shorter time horizons exclude all costs and benefits occurring more than this number of years after the start of first-line treatment – including any years of life lost through deaths that occur during the time horizon.

These analyses may nonetheless indicate that lamivudine then BSC may be the most cost-effective treatment for HBeAg-positive antiviral-naïve patients who would have a life expectancy below 10 years even if they did not have cirrhosis or hepatitis B: e.g. patients who are elderly or have comorbid conditions, such as HIV coinfection or hepatitis C or are at particularly high risk of cancer or heart disease. Similarly, this analysis would suggest that lamivudine then tenofovir may be the most cost-effective treatment for patients likely to die of conditions other than CHB in the next 11 to 19 years.

However, elderly patients are unlikely to account for a significant proportion of patients with CHB: the cohort included in the audit of the London clinic included no patients over 72 years and only 5% (4/83) of the cohort were over the age of 60 (Appendix 7). Furthermore, patients co-infected with hepatitis C virus or HIV are excluded from the analysis and it should be also noted that the analysis does not take into account any impact of advanced age or comorbid conditions on disease progression. Consequently, this finding should be interpreted cautiously. As discussed in Section 7.3.4.6, it may also not be socially desirable to ration treatment on the basis of age.

Other than analyses varying the time horizon, no scenario analyses increased the ICER for first-line tenofovir to above £10,400 per QALY gained, which is well below the £20,000/QALY threshold generally used in the UK. In particular, changing the resistance rates for tenofovir had minimal impact on results. This demonstrates that the results are extremely robust. In particular, first-line use of tenofovir monotherapy would remain the most cost-effective option for managing CHB even if patients attended monthly outpatient consultations for renal monitoring (instead of receiving monitoring in primary care) or if combination therapy was assumed to have the same resistance rate as the best component in the combination[mm].

In particular, analyses using different stopping rules demonstrated that first-line use of tenofovir is cost-effective regardless of which of these severe states treatment is given in. In particular, assuming that patients discontinue treatment when they develop decompensated cirrhosis had negligible impact on ICERs and, indeed almost all ICERs were slightly lower than in the base case analysis. This demonstrates that taking a strict definition of the licensing recommendation that tenofovir is licensed only for patients with compensated disease (Appendix 1) would have no impact on the conclusions and would have implied that tenofovir was slightly more cost-effective than was found in the base case analysis.

Furthermore, it was found to be cost-effective to continue treatment after compensated cirrhosis develops (since [for the tenofovir then lamivudine strategy] this costs £5,459/QALY vs discontinuing treatment when compensated cirrhosis develops). Continuing treatment after hepatic decompensation (but not after development of HCC) cost £24,622/QALY compared with stopping treatment at this point but treating patients with compensated cirrhosis, although the true ICER is likely to be lower than this, since the model does not take account of the rapid deterioration in liver function that may arise from discontinuing antiviral therapy (or switching to adefovir or lamivudine) in a patient with decompensated cirrhosis.

Whether or not patients with HCC were treated had negligible impact on costs or QALYs due to the low incidence and high mortality associated with HCC and the highly conservative assumption that treatment had no impact on mortality in HCC.

These analyses demonstrate that the most cost-effective stopping rule for tenofovir (at a £20,000/QALY threshold) is to continue treatment until HCC, seroconversion, death or drug resistance develop. Since there is currently a shortage of evidence on the risks, benefits and cost-effectiveness of continuing tenofovir after hepatic decompensation, treatment decisions in this patient group should be made by a clinician specialised in this field, although these preliminary analyses suggest that continuing treatment may be cost-effective at a £20,000-£30,000/QALY ceiling ratio.

7.3.3.1.4. Deterministic sensitivity analyses for HBeAg-negative patients

Choice of strategies evaluated in sensitivity analyses

The three strategies evaluated in deterministic sensitivity analyses on HBeAg-positive patients were also used for HBeAg-negative patients: although neither lamivudine then BSC nor lamivudine then tenofovir lay on the cost-effectiveness

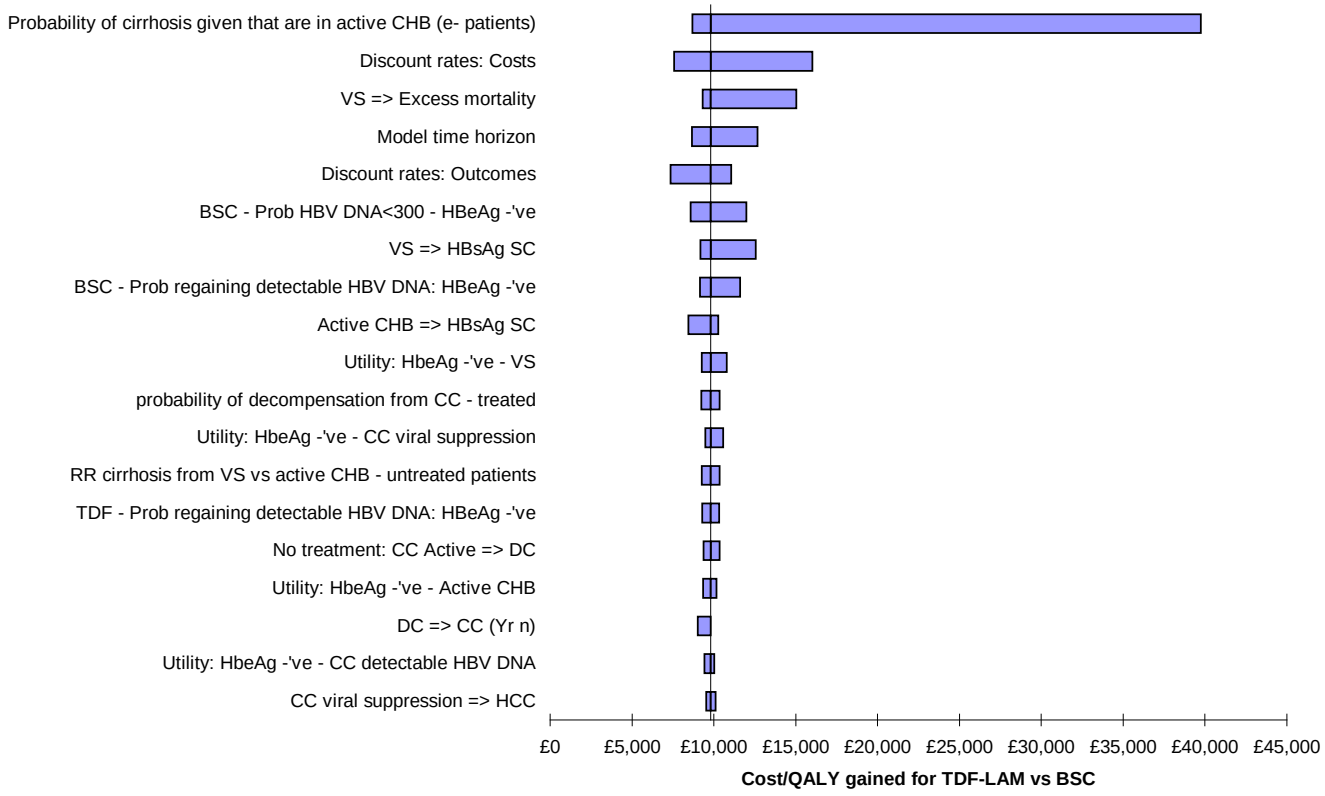
[mm] When the risk of resistance with each combination therapy was assumed to be equal to the risk for the best component in the combination, each combination therapy regimen generated the same number of QALYs as the best monotherapy component but at higher cost: for example, TDF+LAM then BSC generated the same number of QALYs as TDF then BSC when the risk of resistance for TDF+LAM was assumed to be the same as for TDF monotherapy. In HIV, combination therapy has been shown to reduce the risk of virologic resistance below that of the best treatment in the combination, although there is as yet no RCT evidence to support this assumption in patients with CHB. Results of this scenario analysis are not shown in the above table, but are available on request.

frontier in this population, they were nonetheless close to the frontier and could become cost-effective in some sensitivity analyses. A fourth comparison (tenofovir then lamivudine vs BSC) was also included for HBeAg-negative patients since this comprises the most appropriate reference point for calculating the cost-effectiveness of tenofovir then lamivudine in economic terms as it is the next most effective non-dominated strategy.

One-way sensitivity analyses for HBeAg-negative patients

One-way sensitivity analysis demonstrated that only one parameter could affect the conclusion that first-line tenofovir was cost-effective compared with BSC at a £20,000/QALY threshold: the probability that an untreated patient in the HBeAg-negative active CHB state would develop cirrhosis in any given year (Figure 18).

Figure 18: Tornado diagram showing the impact of different variables on the cost/QALY for the tenofovir then lamivudine strategy (first-line tenofovir) relative to BSC based on a 40-year horizon. Within the diagram, variables are ranked in descending order of importance. For clarity, only the 20 variables having most impact on the results are shown in this diagram. The vertical line shows the base case value of £9,811.



Abbreviations: <300, less than 300 copies/mL HBV DNA; =>, [probability of moving from state X] to [state Y]; BSC, best supportive care; CC, compensated cirrhosis; CHB, chronic hepatitis B; c/mL, copies per millilitre; DC; decompensated cirrhosis; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LT, liver transplant; prob, probability; prog, [disease] progression; pts, patients; SC, seroconverted; RR, relative risk; TDF, tenofovir; -'ve, negative; VS, viral suppression.

Additional tornado diagrams (Appendix 11) showed that the same parameter could also affect the conclusion that tenofovir then lamivudine costs less than £20,000/QALY compared with lamivudine then BSC or lamivudine then tenofovir or that lamivudine then tenofovir costs less than £20,000/QALY compared with

lamivudine then BSC. However, no other parameters affected any of these three conclusions when varied over the range of values that they could plausibly take.

Threshold analyses for HBeAg-negative patients

Threshold analysis showed that the probability of cirrhosis for untreated HBeAg-negative patients would need to be reduced to below 2% to change the conclusion that first-line tenofovir is cost-effective at a £20,000/QALY threshold.

Table 46: Threshold analysis around the 10 most influential variables. Threshold values lying within the plausible range for the parameter in question are shown in blue typeface. All results are based on a 40-year time horizon.

Variable	Base case value (plausible range)	LAM-TDF vs LAM-BSC: Value where ICER=		TDF-LAM vs BSC: Value where ICER=		TDF-LAM vs LAM-BSC: Value where ICER=		TDF-LAM vs LAM-TDF	
		£20k	£30k	£20k	£30k	£20k	£30k	£20k	£30k
Probability of cirrhosis in active CHB e-patients	9.00% (0.40% to 20.00%)	1.90%	0.86%	1.95%	0.86%	1.67%	0.71%	1.28%	0.45%
Discount rates: Costs	3.50% (0.00% to 6.00%)	NA	NA	NA	NA	NA	NA	NA	NA
VS => Excess mortality	0.35% (0.00% to 2.80%)	5.67%	8.01%	3.99%	5.24%	4.20%	5.39%	3.15%	3.67%
Model time horizon	40 (30 to 51)	21	15	19	12	19	15	18	14
Discount rates: Outcomes	3.50% (0.00% to 6.00%)	NA	NA	NA	NA	NA	NA	NA	NA
BSC - Prob HBV DNA<300 - HBeAg -'ve	6.21% (1.37% to 15.26%)	NA	NA	NA	NA	NA	NA	NA	NA
VS => HBsAg SC	1.75% (0.00% to 2.30%)	NA	NA	NA	NA	NA	NA	NA	NA
BSC - Prob regaining detectable HBV DNA: HBeAg -'ve	12.50% (0.00% to 28.71%)	NA	NA	NA	NA	NA	NA	NA	NA
Active CHB => HBsAg SC	1.75% (0.00% to 2.30%)	27.42%	46.39%	11.64%	18.53%	12.42%	19.65%	9.17%	12.54%
Utility: HbeAg -'ve - VS	0.77 (0.71 to 0.81)	0.34	0.19	0.37	0.21	0.42	0.32	0.49	0.43

NA: No meaningful parameter value could be determined (excluding negative values for costs, discount rates and transition probabilities as well as values greater than one for transition probabilities and utility scores).

Abbreviations: <300, less than 300 copies/mL HBV DNA; =>, [probability of moving from state X] to [state Y]; BSC, best supportive care; CC, compensated cirrhosis; CHB, chronic hepatitis B; c/mL, copies per millilitre; DC; decompensated cirrhosis; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LT, liver transplant; prob, probability; prog, [disease] progression; pts, patients; SC, seroconverted; RR, relative risk; TDF, tenofovir; -'ve, negative; VS, viral suppression.

Scenario analyses for HBeAg-negative patients

As for HBeAg-positive patients, variations in time horizon were the only scenario analysis that affected the conclusion that first-line tenofovir was the most cost-effective antiviral treatment for CHB (Table 47).

First-line use of tenofovir extendedly dominated lamivudine then tenofovir at all time horizons evaluated. However, no treatments other than lamivudine then BSC were found to be cost-effective at a £20,000/QALY threshold if a time horizon of 17 years or less was used. However, first-line use of tenofovir continued to be cost-effective at

a £30,000/QALY threshold at time horizons of 13 years or more. As discussed above, this may suggest that lamivudine then BSC is the most cost-effective antiviral strategy for patients likely to die of conditions other than CHB in the next 17 years, although this finding is uncertain and may be contrary to equity objectives.

Table 47: Scenario analyses for HBeAg-negative patients. All results are based on a 40-year time horizon unless otherwise specified. Values shown in red are above £30,000/QALY gained, while those in orange are between £20,000 and £30,000/QALY gained.

Scenario	Cost/QALY for LAM-TDF relative to:	Cost/QALY for TDF-LAM relative to:		
	LAM-BSC	BSC	LAM-BSC	LAM-TDF
Base case	**£10,202**	**£9,811**	**£9,260**	**£7,762**
Discounting				
No discounting	£13,244	£12,007	£11,616	£9,017
Costs discounted at 6%, benefits at 1.5%	£6,383	£6,556	£6,028	£5,460
Time horizon				
5 years	£174,139	£114,715	£140,385	£124,142
10 years	£45,262	£38,175	£41,749	£37,817
11 years	£41,922	£35,585	£38,517	£34,475
12 years	£34,120	£30,003	£31,779	£28,747
13 years	£32,591	£28,707	£30,194	£26,977
14 years	£26,697	£24,160	£24,837	£22,117
15 years	£26,697	£24,160	£24,837	£22,117
16 years	£22,999	£21,281	£21,538	£19,303
17 years	£22,718	£20,970	£21,171	£18,775
18 years	£19,956	£18,748	£18,681	£16,640
19 years	£19,891	£18,629	£18,542	£16,368
20 years	£17,752	£16,858	£16,594	£14,687
30 years	£12,307	£11,901	£11,354	£9,753
40 years	£10,202	£9,811	£9,260	£7,762
43 years	£9,934	£9,533	£8,987	£7,498
47 years	£9,485	£9,060	£8,524	£7,051
50 years	£9,128	£8,675	£8,149	£6,686
60 years	£8,490	£7,966	£7,464	£6,009
Resource use				
Cost of LAM based on HIV cost	£10,202	£9,809	£9,341	£7,972
Assuming that treated patients have 11 secondary care consultations per year as assumed by SHTAC (64)	£11,319	£11,237	£10,139	£8,260
Assuming that untreated patients have the same frequency and cost of monitoring as treated patients	£10,124	£9,715	£9,207	£7,748
Increasing all disease management costs by 25%	£10,516	£9,994	£9,416	£7,665
Decreasing all disease management costs by 25%	£9,889	£9,628	£9,105	£7,858
Excluding cost of HBIG	£10,146	£9,793	£9,243	£7,807
Applying the cost of antiviral therapy for 6 months after HBsAg seroconversion	£10,203	£9,815	£9,263	£7,768
Applying the cost of antiviral therapy for 6 months after HBeAg seroconversion	£10,202	£9,811	£9,260	£7,762
Ceasing the cost of antiviral therapy as soon as patients undergo HBeAg seroconversion	£10,202	£9,811	£9,260	£7,762
Assuming that patients receiving tenofovir have only quarterly renal monitoring in Yr 1 (in line with clinical practice), instead of every 4 weeks as assumed in the base case analysis	£10,202	£9,806	£9,255	£7,748

Scenario	Cost/QALY for LAM-TDF relative to:	Cost/QALY for TDF-LAM relative to:		
	LAM-BSC	BSC	LAM-BSC	LAM-TDF
Base case	**£10,202**	**£9,811**	**£9,260**	**£7,762**
Assuming that additional renal monitoring with tenofovir is done during an outpatient consultation with a registrar/consultant plus 10 minutes with a nurse, instead of in primary care	£10,202	£9,950	£9,407	£8,141
Utilities				
Alternative 1: using mild hepatitis C study utilities (38) for severe states*	£11,288	£10,454	£9,851	£7,780
Alternative 2: using utilities used in the SMC submission for adefovir (65)*	£10,304	£9,296	£8,749	£6,649
Alternative 3: assuming that mild states are based on utility decrement from full health based on Wong estimates (124)*	£10,213	£9,825	£9,273	£7,777
Alternative 4: based on SG utilities from non-infected patients (37)*	£9,349	£9,136	£8,627	£7,428
Alternative 5: based on VAS preferences values from infected patients (37)*	£9,844	£9,272	£8,744	£7,088
Alternative 6: based on SG utilities from infected patients for their current disease state (37)*	£10,202	£9,811	£9,260	£7,762
Transition probabilities				
Assuming that 5% of treated HBV DNA-negative cirrhotic patients show regression of cirrhosis and move back to viral suppression each year	£8,666	£8,699	£8,078	£7,074
Assuming that no decompensated patients revert to compensated cirrhosis	£10,250	£9,813	£9,262	£7,697
Assuming that the probability of moving from decompensated cirrhosis to compensated cirrhosis in the second or subsequent years of therapy is 10% of the chance in Year 1.	£9,993	£9,679	£9,129	£7,745
Assume that combination therapy is 5% more effective than monotherapy	£10,202	£9,811	£9,260	£7,762
Assuming that treatment reduces the mortality associated with HCC by 10%	£10,297	£9,879	£9,327	£7,772
Assuming that treatment reduces the mortality associated with DC by 10%	£10,224	£9,825	£9,275	£7,762
Assuming that all treatments increase the chance of HBsAg seroconversion by 50%	£9,943	£9,478	£8,966	£7,441
Assuming that the probability of liver transplantation is 5-fold higher than in the base case	£10,001	£9,682	£9,138	£7,726
Assuming that no patients will undergo liver transplantation	£10,282	£9,860	£9,307	£7,772
Resistance rates				
Tenofovir resistance rates assumed to be same as those for adefovir	£10,562	£10,337	£9,621	£7,720
Tenofovir resistance rates assumed to be same as those for entecavir	£12,576	£9,895	£9,314	£8,221
Resistance rate associated with tenofovir doubles each year: 0.23%, 0.46%, 0.93%, 1.85% and 3.0% in years 1-4 and Year 5/n, respectively in naïve patients and 0.76%, 1.53%, 3.05%, 6.11% and 12.21% in years 1-5 and year 5/n, respectively in LAM-resistant patients.	£11,493	£10,259	£9,560	£8,004
Patterns of care				

Scenario	Cost/QALY for LAM-TDF relative to:	Cost/QALY for TDF-LAM relative to:		
	LAM-BSC	BSC	LAM-BSC	LAM-TDF
Base case	**£10,202**	**£9,811**	**£9,260**	**£7,762**
Assuming that resistance is picked up as soon as HBV DNA levels rise/become detectable	£10,152	£9,807	£9,281	£7,869
Assuming that resistance is picked up 3 months after HBV DNA levels rise/become detectable	£10,253	£9,815	£9,240	£7,657
Assuming that resistance is picked up 6 months after HBV DNA levels rise/become detectable	£10,357	£9,823	£9,202	£7,456
Assuming that resistance is picked up 12 months after HBV DNA levels rise/become detectable	£10,567	£9,840	£9,133	£7,089
Assuming pts in the CC, DC, post-LT, LT or HCC states do not receive antivirals AND all patients assumed to have active CHB at baseline	£10,111	£9,782	£9,572	£8,705
Assuming pts in the CC state receive antivirals but those in DC, HCC, LT or post-LT states do not	£10,223	£9,824	£9,212	£7,578
Assuming pts with HCC do not receive antivirals, but those in the DC, LT, post-LT states do	£10,202	£9,811	£9,259	£7,759
Assuming that pts in the DC, LT, post-LT states do not receive antivirals but those with HCC do	£10,224	£9,823	£9,213	£7,579

Abbreviations: BC, base case; CC, compensated cirrhosis; DC, decompensated cirrhosis; GP, general practitioner; LAM, lamivudine; LT, liver transplantation; BSC, best supportive care; SG, standard gamble; UK, United Kingdom.
* The values used in this sensitivity analysis are shown in Appendix 11.
† Within this scenario (unlike in the base case analysis), first-line use of tenofovir (TDF-LAM) did not show extended dominance over second-line use of tenofovir (LAM-TDF).

However, no other scenario analyses changed the conclusion that first-line tenofovir is cost-effective compared with BSC, lamivudine then BSC and lamivudine then tenofovir. In particular, variations in resistance rates for tenofovir had minimal impact and first-line tenofovir remained cost-effective regardless of whether patients were assumed to continue treatment after decompensation. Tenofovir monotherapy remained the most cost-effective first-line strategy when the resistance rates for combination therapy were assumed to be equal to those for the best drug in the combination[nn].

Additional analyses demonstrated that it was also cost-effective to continue treatment after cirrhosis develops in this patient subgroup, since continuing treatment in patients with compensated cirrhosis but not treating patients in the decompensated cirrhosis, HCC, liver transplant or post-liver transplant states cost £6,840/QALY compared with treating only pre-cirrhotic patients. As was the case in HBeAg-positive patients, the ICER for continuing treatment after hepatic decompensation was close to the threshold ICER used in the UK: continuing treatment after hepatic decompensation (but not after development of HCC) cost £22,966/QALY compared with stopping treatment at this point but treating patients with compensated cirrhosis, although this finding should be interpreted cautiously as discussed above. As for HBeAg-positive patients, continuing treatment after HCC developed had negligible impact, since it was conservatively assumed that this did not affect outcomes. This demonstrates that the most cost-effective stopping rule for tenofovir is to continue treatment until HCC, seroconversion, death or drug resistance develop, while treatment decisions regarding patients with decompensated cirrhosis should be made by experienced specialists on a case-by-case basis.

[nn] Results of this scenario analysis are not shown in the above table, but are available on request.

Conclusions of sensitivity analyses

We can be 60% confident that first-line tenofovir monotherapy is the most cost-effective antiviral strategy for HBeAg-positive patients at a £20,000/QALY threshold (increasing to 71% if society is willing to pay £30,000/QALY gained).

There is a 58% probability that first-line tenofovir monotherapy is the most cost-effective antiviral strategy for HBeAg-negative patients based on a £20,000/QALY ceiling ratio (69% at a £30,000/QALY threshold).

By contrast, probability that first-line entecavir is the most cost-effective was less than 2% in both subgroups.

Deterministic sensitivity analyses demonstrated that the results are extremely robust, but highlighted five parameters that could affect the conclusions (Section 7.3.3.2).

7.3.3.2. What are the key drivers of the cost effectiveness results?

Only three parameters could affect the conclusion that first-line tenofovir is cost-effective for HBeAg-positive patients when varied over their 95% CI or the range of values that they could plausibly take:

- the probability of HBeAg seroconversion for antiviral-naïve patients receiving tenofovir
- the probability of HBeAg seroconversion for lamivudine-resistant patients receiving tenofovir; and
- the excess mortality associated with the viral suppression state

Variations in only one parameter could affect the finding that first-line tenofovir is cost-effective in HBeAg-negative patients, namely the probability that an untreated patient in the HBeAg-negative active CHB state would develop cirrhosis in any given year.

However, larger changes in time horizon could also affect the conclusions for both subgroups: if all costs and benefits occurring more than 17-19 years after the start of treatment were excluded, only lamivudine then BSC would be cost-effective at a £20,000/QALY threshold. Although this may suggest that this is the only cost-effective strategy for patients with a short life expectancy for reasons other than CHB, this finding must be interpreted cautiously due to the equity implications and as the impact of age or comorbidity on the risk of disease progression was not considered in the analysis. Advanced age and comorbidities are also likely to be associated with an increased risk of cirrhosis or a lower risk of seroconversion, although data on the magnitude of such variation is not available at present and is an important area for future research. The impact of age on these factors has (to our knowledge) not been considered in other economic evaluations published previously. Consequently, the finding that no treatments other than lamivudine then BSC are cost-effective at short time horizons may not necessarily translate into a lack of cost-effectiveness for older patients.

7.3.4. Interpretation of economic evidence

7.3.4.1. Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

This analysis confirms the findings of the previous Gilead submission to NICE (63). The ICERs for LAM-ADV vs LAM-BSC that were calculated within the current analysis (£11,216/QALY for HBeAg-positive patients vs £23,853 for HBeAg-negative) are very similar to that estimated within the NICE submission for adefovir (£23,020/QALY (63)), which used a patient-level model and which differed in some of the data inputs and assumptions used. However, the current analysis found LAM-NT to be less cost-effective than suggested previously (LAM-NT vs BSC: £5,549/QALY for HBeAg-positive and £19,897 for HBeAg-negative, c.f. £4,875/QALY in the previous NICE submission) and found first-line use of adefovir (ADV-LAM) to be substantially more cost-effective than calculated previously (ADV-LAM vs LAM-ADV (£17,849/QALY for HBeAg-positive patients and £10,308 for HBeAg-negative, c.f. £63,297/QALY in the previous analysis). The main reason for these differences is likely to be the more accurate modelling of resistance within the current analysis, in addition to differences in the data inputs used.[oo]

The previous two analyses evaluating tenofovir (147, 148) found first-line tenofovir to be strictly dominant over entecavir, adefovir and lamivudine, being less costly and more effective. Our analysis also found first-line use of tenofovir to be strictly dominant over entecavir. We also found that first-line tenofovir showed strict dominance over all first-line adefovir strategies in HBeAg-positive patients and a subset of first-line adefovir strategies in HBeAg-negative patients (147, 148), but showed only extended dominance over adefovir then lamivudine in HBeAg-negative patients. However, unlike Deniz et al (147, 148), we did not find tenofovir to be cost-saving relative to strategies involving first-line use of lamivudine. However, in common with this previous analysis, we found tenofovir to be the most cost-effective strategy for managing CHB. The differences between the studies may reflect differences in relative drug prices between the UK and Spain, France and Italy, variations in the resources used to manage CHB or differences in the assumptions used. Although it is difficult to critically appraise the study by Deniz et al from the brief details given in the abstracts or podium presentations, we can be confident that the current analysis will be more relevant to a UK setting.

The ICERs for first-line use of entecavir calculated in this analysis were also similar to those presented by BMS: we estimate first-line entecavir (followed by lamivudine) to cost £11,101/QALY compared with lamivudine then BSC in HBeAg-positive patients and £14,765/QALY in HBeAg-negative patients, while BMS estimated ICERs of £14,329/QALY in HBeAg-positive patients and £13,208/QALY for HBeAg-negative patients (209). However, unlike BMS, we found that entecavir was not a cost-effective treatment for lamivudine-resistant patients: whereas BMS found entecavir to dominate lamivudine+adefovir in this population (209), we found entecavir to be less costly and less effective than lamivudine+adefovir, with the combination costing less than £20,000/QALY gained compared with entecavir. Furthermore, our analysis adds to this previous research by demonstrating that tenofovir is less costly and more effective than entecavir and has lower ICERs compared with lamivudine.[pp]

[oo] The main differences in data inputs comprise: (a) long-term follow up data on the risk of resistance to adefovir; (b) use of transition probabilities from the meta-analysis instead of values taken directly from the individual arms of clinical trials; and (c) updated utilities and costs for mild disease states.
pp We found tenofovir to cost £9,940/QALY compared with the next most effective treatment on the frontier (lamivudine then tenofovir) in HBeAg-positive patients and £9,811/QALY in HBeAg-negative

7.3.4.2. Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Subgroup analyses demonstrated that tenofovir is cost-effective in all main subgroups evaluated, including in:

- HBeAg-positive patients without cirrhosis
- HBeAg-negative patients without cirrhosis
- HBeAg-positive patients with compensated cirrhosis
- HBeAg-negative patients with compensated cirrhosis
- Patients who have already developed lamivudine resistance:

There is currently insufficient evidence on the benefits of giving any antiviral medication in patients with HCC to accurately assess the cost-effectiveness of treating this populaton, although some studies do suggest that treatment confers some benefits that were excluded by this analysis (188, 189).

Furthermore, discontinuing tenofovir or entecavir or switching from these potent drugs to adefovir or lamivudine in patients with decompensated cirrhosis could result in hepatic flares that could trigger rapid deterioration or even death. Although a sensitivity analysis suggests that continuing therapy after hepatic decompensation costs £23,000-25,000/QALY compared with discontinuing therapy at this point, this analysis excludes these risks of discontinuing treatment, which means that the true benefits of continuing therapy are likely to be substantially greater. Decisions about continuing treatment after hepatic decompensation should be made by an experienced clinician specialised in this field, taking account of the likely risks, benefits and costs of continued treatment.

In general, it is likely that the conclusions of this analysis are applicable to all clinics across England and Wales. Although the age, sex and starting state distributions of the patients considered in the analysis were based on a cohort from London who were predominantly ethnically Chinese (Appendix 7), sensitivity analyses demonstrate that tenofovir would remain cost-effective in all patient sub-groups other than those who would be expected to die of conditions unrelated to CHB in the next 17-19 years. In particular, tenofovir was cost-effective in both HBeAg-positive and negative patients, although ICERs were lower for HBeAg-positive patients. Although the distribution of HBV genotypes may differ between clinics based on variations in ethnic mix, no relationship has been seen between genotype and response rates for adefovir (137, 138), which is closely related to tenofovir.

The unit costs and resource use data used in the analysis were estimated by clinicians working in England or Scotland or taken from a patient-level costing study involving patients with CHC attending one of three UK clinics (Section 7.2.9). Although clinicians vary in the frequency with which they see patients and the tests and investigations conducted alongside viral load quantification (Appendix 10), varying disease management costs by ±25% had minimal impact on the results (Tables 30 and 32). The prices for most healthcare resources were taken from UK tariffs, although the costs for the main HBV-related tests were based on those charged in Glasgow, which are applicable to around two-thirds of Scotland, but are likely to be similar to those charged in England and Wales.

Although most clinicians advocate quarterly monitoring with viral load quantification and other tests and generally add in adefovir when lamivudine resistance develops,

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patients. These ICERs are substantially lower than the ICERs for entecavir compared with lamivudine that are presented above.

expert interviews did highlight some variations in the frequency of monitoring, the duration of treatment after HBeAg or HBsAg seroconversion and the alternative second-line agents used (Appendices 6 and 10). This means that the cost of each disease state and the average delay before treatment is switched/added after drug resistance develops may differ between clinics. However, sensitivity analyses suggested that variations in these parameters would have minimal impact on the conclusions (Tables 30 and 32).

Similarly, the UK data on utilities and drug costs are likely to apply to all clinics, although there is some evidence that health state valuations vary between cultures (36) and the discounts received on different medications may differ between hospitals.

Although the transition probabilities used in the model were based on epidemiological studies and clinical trials conducted around the world, natural history is unlikely to differ substantially between countries and it is also likely that the results of clinical trials will be applicable to routine clinical use in England and Wales, since the inclusion criteria of the pivotal trials closely match the proposed licensed indication and current clinical guidelines for patient selection. While the probability of liver transplantation may differ between time periods and hospitals, sensitivity analyses demonstrated that this has minimal impact on cost-effectiveness.

7.3.4.3. What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Like all model-based economic evaluations, this analysis is limited by the quality of data available and the assumptions that were necessary to simplify the analysis. However, where possible, assumptions were based on peer-reviewed journal articles and were validated by clinical experts. In particular, lack of data necessitated assumptions about the potency and risk of resistance associated with combination therapy and for second-line use of tenofovir.

The risk that treatment-naïve patients would develop resistance while on combination therapies was assumed to be 10% of the risk for the treatment in the combination with the *highest* resistance rate, based on a small RCT comparing lamivudine with adefovir+lamivudine (92) (Section 7.2.7.2.2). This assumption may underestimate the advantages of first-line combination therapy, since the drug combination may continue to provide effective viral suppression even after patients become resistant to one component – particularly when a potent agent, such as tenofovir, forms part of the combination therapy regimen. However, sensitivity analyses demonstrated that first-line use of tenofovir monotherapy would remain the most cost-effective strategy even if combination therapies were assumed to have the same risk of resistance as the best treatment in the combination. In HIV, combination therapy has been shown to reduce the risk of virologic resistance below that of the best treatment in the combination, although there is as yet no RCT evidence to support this assumption in patients with CHB.

The efficacy of tenofovir in nucleos(t)ide-resistant patients was also based on a meta-analysis that included trials on HIV-co-infected patients, since no RCTs evaluating tenofovir specifically in this indication have yet been published. Furthermore, as no cases of virologic HBV resistance to tenofovir have yet been identified, the resistance rates used in the model were based on the highest incidence rates possible, conservatively underestimating the potential benefits associated with tenofovir.

The life expectancy and mortality data used in the model were based on Scottish life tables; since life expectancy is higher in England and Wales, this assumption will have slightly biased the analysis against tenofovir.

Furthermore, due to a shortage of data on patients who are resistant to nucleos(t)ides other than lamivudine, the transition probabilities and resistance rates for lamivudine-resistant patients were applied to patients who were resistant to adefovir, tenofovir and/or entecavir as well as those resistant to lamivudine. Since adefovir and tenofovir are chemically similar and as overlapping sets of mutations confer resistance to entecavir and lamivudine (14), this may mean that the model underestimates the efficacy of entecavir in tenofovir-resistant patients and overestimates the efficacy of tenofovir in adefovir-resistant patients. However, transition probabilities and resistant rates for second-line use of entecavir are also based on trials using 1 mg/day entecavir (whereas costs are based on 0.5 mg/day), which may bias the analysis slightly in favour of second-line use of entecavir.

In almost all cases where there was uncertainty about the true value for any given parameter, conservative assumptions were made that will bias the analysis slightly against tenofovir, such as assuming that treatment did not increase the probability of HBsAg seroconversion or basing outcomes in patients with severe liver disease on trials on adefovir or lamivudine.

Furthermore, the impact of these assumptions was evaluated in extensive sensitivity analyses, which demonstrated that the conclusions are only sensitive to changes in discount rates, time horizon and five transition probabilities: the probability of cirrhosis for HBeAg-negative patients with active CHB; the probability of HBeAg seroconversion for lamivudine-resistant or nucleos(t)ide-naïve patients receiving tenofovir; the excess mortality associated with the viral suppression state; and the probability of HBsAg seroconversion from the viral suppression state.

7.3.4.4. What further analyses could be undertaken to enhance the robustness/completeness of the results?

This analysis focused on comparing the costs and benefits of nucleos(t)ides and did not assess the cost-effectiveness of nucleos(t)ides relative to (peg)interferon-alpha. Interferons were not included in the analysis as they are generally used only as an initial treatment for a specific subset of patients who are willing and able to tolerate the side-effects of treatment and have the highest probability of response, while nucleos(t)ides provide long-term viral suppression and are well tolerated in those patients who are unsuitable for, do not respond to, or do not tolerate interferon therapy. Consequently, interferons are not appropriate alternatives for most patients indicated for nucleos(t)ides. Previous economic evaluations comparing nucleos(t)ides with interferons have reported conflicting results (46, 64, 177, 194). Furthermore, only one study (to be presented in November 2008) has yet assessed the cost-effectiveness of tenofovir compared with interferons, which found tenofovir to be cost-effective relative to peginterferon in a Spanish setting at a €30,000/QALY ceiling ratio (210). Unlike other nucleos(t)ides, there is evidence to suggest that tenofovir significantly increases the likelihood of HBsAg loss and seroconversion: in study 0103, 3.2% (5/158) of patients randomised to tenofovir lost HBsAg by Week 48, compared with 0% (0/82) of patients in the adefovir group (26); furthermore, by week 96, a total of 4.2%% (6/142) of patients initially randomised to tenofovir underwent HBsAg seroconversion (18). This percentage is similar to the proportion of HBeAg-positive patients undergoing HBsAg seroconversion with peginterferon-alpha,

between 0% and 6% underwent HBsAg seroconversion 0-26 weeks after the end of a one-year course of treatment (80, 211-214)[qq].

Additionally, the current analysis excluded telbivudine, which is rarely used in England and Wales and is not recommended by NICE (56). However, since tenofovir is less costly (202), more potent (32) and has a lower risk of resistance (39, 43) (Appendix 4) than telbivudine, the inclusion of telbivudine would not have changed the conclusion that first-line tenofovir is the most cost-effective nucleos(t)ide strategy for CHB as telbivudine would be dominated by tenofovir.

Further clinical trials on use of nucleos(t)ide combinations, second-line use of tenofovir and use of newer nucleos(t)ides in patients with more severe liver disease are required to inform future economic evaluations and to produce more accurate estimates of cost-effectiveness. Additionally, the cost-effectiveness of nucleos(t)ides in patients co-infected with HIV, hepatitis C virus and/or hepatitis D virus has not yet been assessed; although this lies outside the decision problem for the current analysis, it remains an important topic for future research.

7.3.4.5. Equity implications raised by the results

In addition to the equity issues described in Section 5, sensitivity analyses suggest that it may not be cost-effective to give any treatment other than lamivudine followed by BSC to those patients who have a low life expectancy (below 17-19 years) due to advanced age or comorbid conditions. In addition to the uncertainty around this finding, equity considerations mean that it may not be appropriate to deny patients treatment based on their age or the average life expectancy in their region or social group, which may be low through poverty. Furthermore, society may be willing to pay more to reduce morbidity and increase life expectancy in patients who have also been afflicted with other conditions (based on double-jeopardy arguments) or those in poorer communities.

7.3.4.6. Recap of conclusions and discussion on interpretation of results

This economic evaluation demonstrates that first-line use of tenofovir is the most cost-effective strategy for managing CHB with nucleos(t)ides in all the main patient subgroups if society is willing to pay £20,000-£30,000 per QALY gained. Furthermore, first-line tenofovir was also more effective and less costly than first-line entecavir and was cost-effective (or even dominant) over strategies reserving adefovir, tenofovir or combination therapy until after lamivudine resistance develops.

Tenofovir also generated the greatest net benefits of all treatments that may be considered for patients who have already developed lamivudine resistance. Tenofovir was cost-effective at a £20,000-£30,000/QALY threshold in all subgroups investigated (including both HBeAg-positive and HBeAg-negative patients with or without cirrhosis or pre-existing lamivudine resistance).

[qq] Additional details on the studies evaluating peginterferon in HBeAg-positive patients that were used to define this range are given below. Flink et al found that 6% (16/266) of patients underwent HBsAg within 26 weeks of the end of treatment (213). Lau et al found that 3% (8/271) of patients receiving peginterferon monotherapy underwent HBsAg seroconversion by week 72 (80). Based on the systematic review by Hui et al (212), 0% of patients in the one-year study by Chan et al seroconverted (211), compared with 5% of the patients in the study by Janssen et al (215).

In addition to these trials on HBeAg-positive patients, a long-term study by Brunetto et al found that 9% of HBeAg-negative patients had cleared HBsAg and 4% had HBsAg seroconverted within three years of the end of peginterferon therapy (216).

Expert interviews (Section 7.2.7.5 and Appendix 6) suggested that combination therapy is currently widely used to treat CHB in order to minimise the risk of drug resistance developing. In particular, clinicians frequently add adefovir to ongoing lamivudine in patients who develop lamivudine resistance (rather than switching therapy) and commonly give combination therapy with adefovir+lamivudine first-line to cirrhotic patients in order to minimise the risk of hepatic decompensation associated with lamivudine resistance. The model suggested that first-line use of adefovir+lamivudine is more costly and less effective than first-line use of tenofovir – both in HBeAg-positive and HBeAg-negative patients. However, adding in adefovir to ongoing lamivudine after patients become resistant to first-line lamivudine was found to be cost-effective relative to lamivudine followed by a switch to adefovir for HBeAg-negative patients (£16,409/QALY), but not in HBeAg-positive patients (£144,995/QALY), but was dominated by both first and second-line use of tenofovir.

The conclusions remained robust across a wide range of different sensitivity analyses. PSA demonstrated that we can be at least 60% confident that tenofovir is the most cost-effective first-line treatment for HBeAg-positive patients and 58% confident that it is the most cost-effective treatment for HBeAg-negative patients.

However, all analyses were extremely sensitive to the time horizon taken, with no treatments other than lamivudine followed by BSC being cost-effective at a £20,000/QALY threshold if all benefits occurring more than 17-19 years in the future were excluded from the analysis. This may suggest that giving lamivudine followed by BSC is the most cost-effective treatment for patients who have a very low life expectancy due to co-morbid conditions. However, as described above this finding should be interpreted cautiously since relatively few people with CHB will be elderly (Appendix 7), patients co-infected with hepatitis C virus or HIV are excluded from the analysis and the analysis does not allow for the impact of advanced age or co-morbid conditions on disease progression.

The base case analysis included all logically-plausible nucleos(t)ide treatment strategies for managing CHB and demonstrated that first-line use of tenofovir is the most cost-effective strategy of all those considered, generating highest net benefits at a £20,000-£30,000/QALY threshold.

Although BSC and lamivudine followed by BSC may be the most cost-effective strategies for societies with low healthcare budgets, these treatment strategies are now rarely used in the UK as they are clinically inferior to other strategies. However, first-line use of tenofovir remains the most cost-effective strategy at a £20,000-£30,000/QALY threshold regardless of whether first or second-line use of BSC is considered in the analysis.

It should be noted that although no cases of virologic resistance to tenofovir have yet been reported, the model uses a conservatively high estimate of the risk of developing tenofovir resistance (Section 5.7.3 and Appendix 4). Subsequently, the analysis may underestimate the true benefits of tenofovir.

8. Assessment of factors relevant to the NHS and other parties

8.1. What is the estimated annual budget impact for the NHS in England and Wales?

This section provides a summary of the findings of the budget impact analysis. The methods and assumptions used to calculate patient numbers and costs are outlined in later sections.

The total net budget impact for England and Wales was calculated for three distinct patient groups:

- First-line use of tenofovir in treatment-naïve patients who would otherwise have received other nucleos(t)ides: 243 patients per year in England and Wales (10% of the 2,428 patients currently receiving nucleos(t)ides).
- Second-line use of tenofovir in patients who have already become resistant to their current nucleos(t)ide therapy: 296 patients per year in England and Wales (12.2% of the 2,428 patients currently receiving nucleos(t)ides). Since most of these patients will be resistant only to lamivudine, it is assumed that these patients would otherwise have received entecavir, adefovir or adefovir+lamivudine.
- First-line use of tenofovir in treatment-naïve patients who would otherwise have received no treatment: in the absence of data on the likely increase in the total nucleos(t)ide market, it was assumed that 400 patients would receive tenofovir in place of best supportive care. Most of these patients would have previously remained undiagnosed.

It is difficult to predict how the incidence and prevalence of CHB and the market shares of the different medications will change over the next few years as the market is extremely dynamic, while the epidemiology will be affected by changes in screening and immigration. Due to these uncertainties, budget impact calculations were based on an extremely conservative assumption that the market share for entecavir will remain at the level seen in 2007 and that a high proportion of suitable patients will receive tenofovir. In reality, it is likely that entecavir would increase its market share in the absence of tenofovir; if this is the case, the true budget impact associated with tenofovir would be substantially lower than the values presented in Table 48 as tenofovir is substantially less costly than entecavir.

Table 48: Total budget impact associated with the introduction of tenofovir in England and Wales over the next five years

		2009	2010	2011	2012	2013	TOTAL
First-line use of tenofovir in place of other nucleos(t)ides (243 patients per year)							
Patients starting tenofovir this year		243	243	243	243	243	1214
Patients already on tenofovir		0	243	486	728	971	-
Total patients in this population		243	486	728	971	1214	3642 pt-yrs
50% uptake	No. pts likely to receive tenofovir	121	243	364	486	607	1821 pt-yrs
	Drug cost for current practice	£393,235	£786,471	£1,179,706	£1,572,942	£1,966,177	£5,898,531
	Drug cost for tenofovir	£442,998	£885,842	£1,328,686	£1,771,530	£2,214,374	£6,643,430
	Incremental cost	**£49,763**	**£99,371**	**£148,980**	**£198,588**	**£248,197**	**£744,899**
100% uptake	No. pts receiving tenofovir	243	486	728	971	1214	3642 pt-yrs
	Drug cost for current practice	£786,471	£1,572,942	£2,359,412	£3,145,883	£3,932,354	£11,797,062
	Drug cost for tenofovir	£885,842	£1,771,530	£2,657,218	£3,542,905	£4,428,593	£13,286,088
	Incremental cost	**£99,371**	**£198,588**	**£297,805**	**£397,022**	**£496,239**	**£1,489,026**
Second-line use of tenofovir (296 patients per year)							
Patients starting tenofovir this year		296	296	296	296	296	1481
Patients already on tenofovir		0	296	592	889	1185	-
Total patients in this population		296	592	889	1185	1481	4443 pt-yrs
50% uptake	No. pts likely to receive tenofovir	148	296	444	592	741	2222 pt-yrs
	Drug cost for current practice	£479,747	£959,494	£1,439,242	£1,918,989	£2,398,736	£7,196,208
	Drug cost for tenofovir	£540,424	£1,080,693	£1,620,963	£2,161,232	£2,701,502	£8,104,815
	Incremental cost	**£60,677**	**£121,199**	**£181,721**	**£242,244**	**£302,766**	**£908,607**
100% uptake	No. pts likely to receive tenofovir	296	592	889	1185	1481	4443 pt-yrs
	Drug cost for current practice	£959,494	£1,918,989	£2,878,483	£3,837,977	£4,797,472	£14,392,415
	Drug cost for tenofovir	£1,080,693	£2,161,232	£3,241,771	£4,322,310	£5,402,849	£16,208,857
	Incremental cost	**£121,199**	**£242,244**	**£363,288**	**£484,333**	**£605,378**	**£1,816,442**
Use of tenofovir in patients who would otherwise have received no nucleos(t)ide therapy (400 patients per year)							
Patients starting tenofovir this year		400	400	400	400	400	2000
Patients already on tenofovir		0	400	800	1200	1600	-
Total patients in this population		400	800	1200	1600	2000	6000 pt-yrs
50% uptake	No. pts likely to receive tenofovir	200	400	600	800	1000	3000 pt-yrs
	Drug cost for current practice	£0	£0	£0	£0	£0	£0
	Drug cost for tenofovir	£729,741	£1,459,328	£2,188,915	£2,918,502	£3,648,089	£10,944,575
	Incremental cost	**£729,741**	**£1,459,328**	**£2,188,915**	**£2,918,502**	**£3,648,089**	**£10,944,575**
100% uptake	No. pts likely to receive tenofovir	400	800	1200	1600	2000	6000 pt-yrs
	Drug cost for current practice	£0	£0	£0	£0	£0	£0
	Drug cost for tenofovir	£1,459,328	£2,918,502	£4,377,676	£5,836,849	£7,296,023	£21,888,378
	Incremental cost	**£1,459,328**	**£2,918,502**	**£4,377,676**	**£5,836,849**	**£7,296,023**	**£21,888,378**

Base case budget impact calculation
Based on this analysis, the total net budget impact associated with using tenofovir first-line in patients who would otherwise have received other nucleos(t)ides is £744,899 over the next five years, if 50% of newly diagnosed patients receive tenofovir.

The total cost of using tenofovir second-line in 50% of the 296 patients developing resistance to currently-available nucleos(t)ides each year is £908,607 over the next five years.

If tenofovir is used in 50% of patients who would otherwise have received other nucleos(t)ides, the total anticipated budget impact is £1,653,506 over the next five years.

As described above, this budget impact estimate is likely to be extremely conservative since some of these patients are already receiving tenofovir and as the market share for entecavir is likely to continue to rise over the next five years. For example, if the market share of entecavir increased to 50% by 2009 and remained at that level for the next five years, the budget impact of using tenofovir in 50% of all suitable patients would be just £8,418,987 over the next five years.

Sensitivity analyses around budget impact calculations
If 200 additional patients who do not currently receive any nucleos(t)ide therapy start treatment with tenofovir each year, the total cost would be £10,944,575 over the next five years.

The combined budget impact of all three of these scenarios would be £12,598,081 over the next five years if 50% of suitable patients receive tenofovir. The maximum budget impact would be £25.19 million over the next five years, which would arise if 100% of the 939 patients potentially suitable for treatment received tenofovir.

Impact on health
However, use of tenofovir will also increase patients' life expectancy and improve quality of life relative to standard practice. Since first-line use of tenofovir (followed by lamivudine) will gain around 4.4 QALYs and 5.6 life-years per patient treated[rr] relative to lamivudine, treating 939 patients could gain up to 3,870 QALYs and 4,919 life-years over the cohort's lifetime.

This treatment strategy will also reduce the number of liver transplants needed for CHB. In addition to the substantial financial savings from avoiding transplant operations, which are included in the net cost, avoiding transplantation will enable more patients to receive this life-saving treatment for other indications.

[rr] Values shown are undiscounted and are based on a mixed cohort of whom 2.7% enter the model with HBeAg-positive compensated cirrhosis and detectable HBV DNA, 2.7% enter the model with HBeAg-negative compensated cirrhosis and detectable HBV DNA, 42.1% have HBeAg-positive active CHB and the remaining 52.6% have HBeAg-negative active CHB.

8.2. What number of patients were assumed to be eligible? How was this figure derived?

The incidence and prevalence of chronic hepatitis B (CHB) was estimated using data from the Department of Health (217) and the study by Hahne et al (59). The prevalence of CHB is estimated to be 0.3% in the UK (217). It is therefore likely that there will be around 161,186 patients with CHB in England and Wales (0.3% of the population of England and Wales, 53,728,800 (218)). Between 1995 and 2000 the incidence of CHB in England and Wales was 0.0074% per year (59). This equates to around 3,976 cases diagnosed each year in England and Wales (0.0074% of the population of England and Wales, 53,728,800 (218)).

It is important to note that the majority of new chronic infections in the UK are due to immigration of established HBV carriers. The estimated patient numbers may therefore vary considerably depending on future immigration patterns. Based on the economic model described in Section 7, around 2.2% of patients treated with lamivudine then lamivudine+adefovir[ss] died in each of the first five years covered by the model, while 1.5% of patients underwent HBsAg seroconversion each year, which is effectively equivalent to resolving the infection. We assumed that the population of England and Wales, mortality, incidence and the chance of HBsAg seroconversion remained constant during the next five years. A half-cycle correction was applied such that incident cases had half the chance of dying or undergoing HBsAg seroconversion as prevalent cases.

Table 49: Patient numbers in each of the first five years after introduction.

Year		Year 1	Year 2	Year 3	Year 4	Year 5
Number of prevalent cases		161,186	161,186	161,186	161,186	161,186
Number of incident cases		3,976	3,976	3,976	3,976	3,976
Number of deaths	Among prevalent pts	3,546	3,546	3,546	3,546	3,546
	Among incident pts	44	44	44	44	44
Number of HBsAg seroconversions		2,448	2,448	2,448	2,448	2,448
Net number of patients		165,162	165,162	165,162	165,162	165,162

8.3. What assumption(s) were made about current treatment options and uptake of technologies?

The economic evaluation described in Section 7 demonstrates that tenofovir is dominant over adefovir, entecavir and adefovir+lamivudine and is cost-effective relative to lamivudine and best supportive care, regardless of whether tenofovir is used first-line or following lamivudine resistance. However, the analysis demonstrated that it was more cost-effective to give tenofovir first-line than to wait until after lamivudine resistance has already developed.

Although the current evidence base suggests that tenofovir is more potent than telbivudine (Appendix 4) and is likely to have a lower risk of resistance (Appendix 5), in addition to being less costly (1), it was conservatively assumed that no patients would switch from telbivudine to tenofovir as this comparison was not evaluated in the economic evaluation.

[ss] The lamivudine then lamivudine+adefovir arm was used to obtain these figures in preference to the other arms since expert interviews (Section 7.2.7.5 and Appendix 6) suggest that this is currently the most commonly used treatment strategy in the UK.

Tenofovir is most likely to be used by new patients who have recently been diagnosed, those patients who have only recently developed active CHB with compensated liver disease and signs of liver inflammation that warrant treatment and patients developing resistance to current agents.

The incidence of new cases of *active* CHB in England and Wales is unknown and is difficult to calculate since it depends on a wide range of factors including immigration, disease progression and local strategies for diagnosis and monitoring. For simplicity, it was assumed that the number of treatment-naïve patients starting nucleos(t)ide therapy each year is approximately 10% of the number currently receiving therapy. This would suggest that around 243 patients in England and Wales start nucleos(t)ide therapy each year. It was assumed that an average of 12.2% of treated patients will develop resistance to current nucleos(t)ides each year, based on the weighted average of the resistance rates for each drug (Table 51). This would equate to 296 patients requiring second-line nucleos(t)ide therapy in England and Wales each year.

Therefore a total of 539 patients in England and Wales who would otherwise have received other nucleos(t)ides may be eligible to start treatment with tenofovir each year. However, in practice, not all suitable patients will receive tenofovir. It was assumed that 50% of the 539 patients starting/switching between nucleos(t)ides each year would receive tenofovir, although a scenario analysis was also conducted to calculate the total budget impact if all suitable patients received tenofovir.

Since tenofovir is also cost-effective relative to best supportive care and comprises the most cost-effective nucleos(t)ide treatment currently used in England and Wales, there is also the potential for tenofovir to be used in patients who would otherwise have received no treatment, such as those who have not been referred to specialist clinics. A sensitivity analysis estimated the additional budget impact of initiating tenofovir therapy in 400 patients per year who would otherwise have received no treatment.

8.4. What assumption(s) were made about market share (where relevant)?

[redacted] (Table 50). [redacted] expert interviews suggest that adefovir plus lamivudine is currently the main combination therapy regimen used widely at present[tt], [redacted] Given that around 88.7% of people in the UK live in England and Wales (218), [redacted].

[tt] However, it should be noted that one clinician used tenofovir+lamivudine first-line.

Table 50: Number of patients currently receiving nucleos(t)ides in England and Wales. This analysis makes the following assumptions: (1) it was assumed, based on expert opinion, that no patients currently receive off-label nucleos(t)ide therapy or any combinations other than adefovir plus lamivudine; (2) it was assumed that the number of patients receiving each medication is equal to the number of packets sold in November 2007, since all nucleos(t)ides are sold in packs lasting 28-30 days; (3) it was assumed that only around 100 patients receive adefovir monotherapy (Gilead, data on file); (4) since 88.7% (53,728,800 divided by 60,587,300 (218)) of people in the UK live in England and Wales, it was assumed that this also represents the proportion of UK nucleos(t)ide prescribing that occurs in England and Wales.

Treatment	Market share by packets sold (153)	No. patients in UK receiving therapy	Market share by patients	No. patients in England and Wales receiving nucleos(t)ides
LAM – monotherapy and combination combined				
ADV – monotherapy and combination combined				
ADV monotherapy				
ADV+LAM				
LAM monotherapy				
Entecavir				
Telbivudine				
TOTAL nucleos(t)ides				

* Gilead, data on file
† Number of patients receiving adefovir (1,152) minus number of patients receiving adefovir monotherapy (100).
‡ Number of patients receiving lamivudine (2,513), minus number of patients receiving adefovir plus lamivudine (1,052).

In addition to those patients receiving nucleos(t)ides, UK hepatologists estimate that around 5-20% of patients receive interferon-alpha or peginterferon at some point during their lifetime (Section 7.2.7.5 and Appendix 6). The number of patients receiving interferon has not been quantified due to the uncertainty about how many patients are referred to specialist centres and as it is currently unlikely that tenofovir will be used as an alternative to interferon (Section 7.2.3).

Nonetheless, this sales data would suggest that even though clinicians treat almost all patients indicated for treatment who present to specialist clinics, up to 98% of the 161,186 HBsAg-positive patients in England and Wales do not currently receive nucleos(t)ide treatment. This suggests that a large proportion of patients remain undiagnosed or have not been referred to specialist clinics with the relevant expertise to properly manage their condition.

The above sales data from 2007 will be used in the budget impact calculations. This may mean that the budget impact of more widespread use of tenofovir is overestimated for two reasons. Secondly, expert interviews suggest that the market share of entecavir has increased following publication of the NICE guidance and it is highly likely that its market share would increase further in the future if tenofovir were not available; since increased use of entecavir will increase the average cost of current medications, underestimating the entecavir market share will mean that the calculations presented in this section will overestimate the budget impact associated with tenofovir.

8.5. What unit costs were assumed? How were these calculated?

The cost of the alternative nucleos(t)ides is shown in Table 51; the drug costs presented in this section include VAT (17.5%). For simplicity, the weighted average cost of current nucleos(t)ides was based on the overall weighted average cost of the nucleos(t)ides used at present (£3,240.98 per patient-year; Table 51). Since most patients receive first-line therapy with lamivudine and have second-line treatment with the more costly agents, this means that the budget impact calculations may underestimate the incremental cost of first-line tenofovir and overestimate the incremental cost of second-line tenofovir; however, this will have no impact on the total cost across these two scenarios.

The 0.14% of patients who receive telbivudine was excluded from these calculations since it would equate to less than one telbivudine-treated patient in England and Wales. For simplicity, it was assumed that the number of new patients starting treatment and the number of patients developing resistance to other drugs each year would be constant over time. Similarly, it was assumed that no patients would die, develop tenofovir resistance or undergo HBeAg or HBsAg seroconversion during this five-year period.

Tenofovir is more costly than lamivudine, but is substantially less expensive than adefovir, entecavir or telbivudine. Excluding telbivudine, the weighted average cost of the current mix of nucleos(t)ide agents is £8.87 per patient-day or £3,239.28 per patient-year, compared with a cost of £9.99 per patient-day and £3,647.93 per patient-year for tenofovir.

Table 51: The costs of nucleos(t)ides licensed for CHB (including VAT).

Treatment		Mean dose	Mean daily cost (1)*	Mean annual cost (1)*	% patients receiving therapy (153)	Annual risk of resistance (Appendix 5)
Lamivudine (Epivir®)		100 mg/day	£3.28	£1,197.38	[redacted]	37.53%
Adefovir (Hepsera®)		10 mg/day	£12.34	£4,506.27	[redacted]	1.39%
Adefovir (Hepsera®) + lamivudine (Epivir®)		10 mg/day+ 100 mg/day	£15.62	£5,703.65	[redacted]	0.41%
Entecavir (Baraclude®) - for naïve patients		0.5 mg/day	£14.81	£5,407.53	[redacted]	0.43%
Entecavir (Baraclude®) – for lamivudine resistant patients		1 mg/day	£14.81	£5,407.53		
Telbivudine (Sebivo®)		600 mg/day	£12.18	£4,450.48	[redacted]	4.10%
Weighted average of non-tenofovir (Viread®) treatments	Inc Tel	-	£8.87	£3,240.98	[redacted]	20.3%
	Exc Tel	-	£8.87	£3,239.28	[redacted]	20.3%
Tenofovir (Viread®)		245 mg/day	£9.99	£3,647.93	[redacted]	0.22%*

Resistance rates are across all years and were calculated by adding up the total number of people who developed (or are assumed to develop) resistance by the number of people exposed to the treatment. The adjustment for zero counts was used: for example, since clinical trials have included 908 patient-years of experience with tenofovir without any cases of virologic resistance developing (Appendix 5), 1 additional patient was added to this exposure time in each year who was assumed to have developed virologic resistance, to give a total assumed risk of resistance of 0.002% (2/1000). With the exception of adefovir plus lamivudine, all resistance rates are based on the risk of resistance in lamivudine-naive patients.

* Drug costs include VAT at 17.5% per annum.

8.6. In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

In addition to the drug acquisition cost, patients need to be monitored for adverse events (such as nephrotoxicity), drug resistance and treatment efficacy. However, expert interviews suggested that all nucleos(t)ide-treated patients would undergo routine monitoring of ALT, viral load and urea and electrolytes every three months. Patients receiving tenofovir may receive more frequent testing of renal parameters (U&E), since they should be monitored for changes in serum creatinine and phosphorous levels every four weeks in Year 1 and once every three months thereafter (Appendix 1). The cost of 10 additional U&E tests conducted in a practice

nurse consultation (£15.44 per test [Appendix 10]) was added to the cost of tenofovir within the budget impact calculations.

8.7. Were there any estimates of resource savings? If so, what were they?

Based on the market shares shown in Table 50, the mix of nucleos(t)ides currently used in England and Wales costs an average of £3,239.28 per patient-year (excluding telbivudine). Using tenofovir in place of other nucleos(t)ides will therefore produce savings of £3,239.28 per patient-year, which will offset the cost of tenofovir.

The net cost of using tenofovir in place of the nucleos(t)ide mix currently used in England and Wales is therefore £408.65 per year for each patient who receives tenofovir instead of an alternative nucleos(t)ide (this reflects the current high use of lamivudine). However, giving a patient tenofovir rather than adefovir or entecavir will save £858.34-£1,759.60 per year.

8.8. Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

By concentrating on direct costs and savings, this budget impact analysis excludes many of the savings associated with treatment, since use of tenofovir will avoid the risk of additional consultations associated with managing resistance and reduce the incidence of serious liver disease, thereby reducing the cost of managing HCC, hepatic decompensation and liver transplantation. Furthermore, since there is some evidence that tenofovir may be associated with a higher incidence of HBeAg seroconversion (Appendix 4) and HBsAg seroconversion (18, 26), increased use of tenofovir treatment is likely to enable a higher proportion of patients to improve to the extent that they no longer need treatment and can be monitored less frequently.

[redacted]

Subsequently, the true savings associated with use of tenofovir are likely to be substantially higher than suggested by this analysis.

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10. Post submission addendum

The following addendum is added in response to questions asked regarding the submission by the evidence review group (ERG) commissioned to review the submission by NICE.

10.1. Addendum to section 7.3.1

There was a discrepancy between the model and the described methodology, in that the model assumed that 0% of patients could move from the HBeAg seroconverted state to compensated cirrhosis. We have corrected this error and rerun the base case results, which are shown in Table 3 and Table 4 below. Correcting this error has no effect on the conclusions and has only a small impact on ICERs for HBeAg-positive patients. Furthermore, it has no impact on outcomes for HBeAg-negative patients as they cannot enter the HBeAg seroconverted disease state. The model now assumes that patients who experience disease reactivation after HBeAg seroconversion may move to one of four states:

- HBeAg-positive active CHB
- HBeAg-negative active CHB
- HBeAg-positive compensated cirrhosis with detectable HBV DNA
- HBeAg-negative compensated cirrhosis with detectable HBV DNA

This assumption matches the data inputs presented in Appendix 9 and the assumptions/model outline described in Section 7.2.6.

Due to the Markovian assumption, it is not possible to track the history of patients through the model without using tunnel states; subsequently, all patients in the HBeAg seroconversion state are assumed to be identical, regardless of whether or not they had previously had cirrhosis. The probability of making one of these four transitions is therefore the same for patients who were cirrhotic when they underwent HBeAg-seroconversion as for patients who have not yet developed cirrhosis. However, this simplification will have little/no effect on the total costs or benefits for a large cohort of patients of whom only a minority will have seroconverted from the cirrhotic state.

Table 3: Disaggregated base case results for HBeAg-positive patients with amended transition between HBeAg seroconverted state to compensated cirrhosis state. Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	Drug cost Rx1 (Disc)	Other drug cost (Disc)	Disease management cost (Disc)	Total cost/pt		Life years/ pt	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£9,995	£9,995	£15,249	24.76	16.33	20.02
LAM then BSC	£3,139	£0	£10,426	£13,565	£19,511	25.53	16.90	20.75
LAM then TDF	£3,139	£9,082	£10,913	£23,134	£37,548	27.95	18.39	22.75
LAM then ADV	£3,139	£9,910	£10,973	£24,023	£37,527	26.95	17.78	21.92
LAM then ETV	£3,139	£11,913	£11,112	£26,164	£37,144	25.70	16.90	20.75
LAM then TDF+LAM	£3,139	£13,510	£11,137	£27,786	£46,890	28.26	18.56	22.98
TDF then BSC	£18,477	£0	£12,440	£30,917	£48,360	29.11	19.15	23.75
TDF then LAM	£18,477	£34	£12,446	£30,958	£48,444	29.12	19.16	23.77
TDF then ETV	£18,477	£262	£12,459	£31,199	£48,885	29.12	19.16	23.76
TDF then TDF+LAM	£18,477	£365	£12,479	£31,321	£49,284	29.17	19.19	23.80
TDF then TDF+LAM then ETV	£18,477	£366	£12,479	£31,322	£49,287	29.17	19.19	23.80
ADV then LAM	£20,216	£348	£13,030	£33,594	£49,129	27.78	18.32	22.63
LAM then ADV+LAM	£3,139	£18,897	£11,880	£33,916	£55,574	27.37	17.91	22.11
ADV then TDF	£20,216	£2,505	£13,344	£36,064	£54,646	28.23	18.56	22.97
ADV then TDF+LAM	£20,216	£3,733	£13,421	£37,371	£57,644	28.32	18.60	23.03
ADV then ADV+LAM	£20,216	£4,745	£13,521	£38,482	£59,525	28.11	18.47	22.84
ETV then LAM	£27,141	£104	£13,689	£40,935	£62,354	28.85	18.97	23.52
ADV+LAM then TDF+LAM	£24,051	£2,932	£14,440	£41,424	£63,672	28.12	18.52	22.91
ETV then TDF	£27,141	£750	£13,778	£41,670	£64,053	28.98	19.05	23.62
ETV+ADV then LAM	£50,914	£43	£17,126	£68,083	£103,434	28.97	19.04	23.61

Table 4: Disaggregated base case results for HBeAg-negative patients with amended transition between HBeAg seroconverted state to compensated cirrhosis state. Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	1st line drug cost	2nd/3rd line drug cost	Disease management cost	Total cost/pt		Life years/pt (Undisc)	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£14,331	£14,331	£21,573	18.39	11.75	13.90
LAM then BSC	£4,283	£0	£14,852	£19,135	£27,218	18.77	11.99	14.18
LAM then TDF	£4,283	£24,481	£18,073	£46,837	£75,643	23.78	14.70	17.84
LAM then ADV	£4,283	£23,294	£17,597	£45,173	£68,555	20.90	13.08	15.62
LAM then ETV	£4,283	£17,945	£15,750	£37,978	£52,853	20.18	12.80	15.23
LAM then TDF+LAM	£4,283	£38,287	£19,005	£61,575	£103,675	24.97	15.30	18.67
TDF then BSC	£42,557	£0	£17,390	£59,948	£96,041	26.59	16.39	20.10
TDF then LAM	£42,557	£99	£17,423	£60,079	£96,295	26.63	16.41	20.13
TDF then ETV	£42,557	£680	£17,446	£60,683	£97,387	26.66	16.42	20.15
TDF then TDF+LAM	£42,557	£1,340	£17,558	£61,455	£99,278	26.83	16.51	20.27
TDF then TDF+LAM then ETV	£42,557	£1,345	£17,558	£61,460	£99,291	26.83	16.51	20.27
ADV then LAM	£38,739	£942	£17,355	£57,037	£83,536	22.81	14.23	17.16
LAM then ADV+LAM	£4,283	£41,955	£19,406	£65,644	£108,567	23.31	14.33	17.33
ADV then TDF	£38,739	£8,494	£18,559	£65,792	£101,661	24.40	15.04	18.28
ADV then TDF+LAM	£38,739	£13,112	£18,892	£70,743	£112,246	24.79	15.23	18.55
ADV then ADV+LAM	£38,739	£14,419	£18,980	£72,138	£114,395	24.23	14.91	18.10
ETV then LAM	£59,224	£299	£17,411	£76,933	£119,660	25.88	15.99	19.55
ADV+LAM then TDF+LAM	£51,400	£10,145	£19,315	£80,860	£125,610	24.16	14.83	18.02
ETV then TDF	£59,224	£2,619	£17,746	£79,589	£125,450	26.36	16.23	19.89
ETV+ADV then LAM	£113,307	£128	£17,995	£131,431	£204,248	26.30	16.20	19.85

10.2. Addendum to Section 7.3.1.1.2, Table 37

The strategies listed in the first column of Table 37 in the submission are in the wrong order. The amended Table 37 is shown below.

Amended Table 37: Disaggregated base case results for HBeAg-negative patients (based on deterministic base case). Unless otherwise specified, all costs and benefits are discounted at 3.5% per annum.

Treatment strategy	1st line drug cost	2nd/3rd line drug cost	Disease manage-ment cost	Total cost/pt		Life years/pt (Undisc)	Total QALYs/ pt	
				Disc	Undisc		Disc	Undisc
BSC	£0	£0	£14,331	£14,331	£21,573	18.39	11.75	13.9
LAM then BSC	£4,283	£0	£14,852	£19,135	£27,218	18.77	11.99	14.18
LAM then TDF	£4,283	£24,481	£18,073	£46,837	£75,643	23.78	14.7	17.84
LAM then ADV	£4,283	£23,294	£17,597	£45,173	£68,555	20.9	13.08	15.62
LAM then ETV	£4,283	£17,945	£15,750	£37,978	£52,853	20.18	12.8	15.23
LAM then TDF+LAM	£4,283	£38,287	£19,005	£61,575	£103,675	24.97	15.3	18.67
TDF then BSC	£42,557	£0	£17,390	£59,948	£96,041	26.59	16.39	20.1
TDF then LAM	£42,557	£99	£17,423	£60,079	£96,295	26.63	16.41	20.13
TDF then ETV	£42,557	£680	£17,446	£60,683	£97,387	26.66	16.42	20.15
TDF then TDF+LAM	£42,557	£1,340	£17,558	£61,455	£99,278	26.83	16.51	20.27
TDF then TDF+LAM then ETV	£42,557	£1,345	£17,558	£61,460	£99,291	26.83	16.51	20.27
ADV then LAM	£38,739	£942	£17,355	£57,037	£83,536	22.81	14.23	17.16
LAM then ADV+LAM	£4,283	£41,955	£19,406	£65,644	£108,567	23.31	14.33	17.33
ADV then TDF	£38,739	£8,494	£18,559	£65,792	£101,661	24.4	15.04	18.28
ADV then TDF+LAM	£38,739	£13,112	£18,892	£70,743	£112,246	24.79	15.23	18.55
ADV then ADV+LAM	£38,739	£14,419	£18,980	£72,138	£114,395	24.23	14.91	18.1
ETV then LAM	£59,224	£299	£17,411	£76,933	£119,660	25.88	15.99	19.55
ADV+LAM then TDF+LAM	£51,400	£10,145	£19,315	£80,860	£125,610	24.16	14.83	18.02
ETV then TDF	£59,224	£2,619	£17,746	£79,589	£125,450	26.36	16.23	19.89
ETV+ADV then LAM	£113,307	£128	£17,995	£131,431	£204,248	26.3	16.2	19.85

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

10.3. Addendum to Section 7.3.3.1.1 Probabilistic sensitivity analysis

Due to the complex nature and scale of the model, several versions of the model were generated to produce the required results. We had a deterministic version, a probabilistic version, a version for tornado diagrams and a version for threshold analysis. Minor modifications were required to each version to generate results for the two patient subgroups (HBeAg positive and HBeAg negative).

Upon review we discovereed that the model used to generate the PSA for the submission contained a minor error relating to two cells. This occurred in the probabilistic version only. It appears that in converting the model to consider HBeAg negative patients from HBeAg positive patients the PSA range defining the HBeAg positive patients was not correctly updated (cells I233 and H233 on the Data & References sheet). This resulted in some simulations generating a negative value in the starting state page (cell E16) which in turn resulted in the incorrect CEACs and cost effectiveness acceptability frontier submitted in the submission.

The amended probabilistic sensitivity analysis is described below.

It should be noted that the error only affected the probabilistic sensitivity analysis and would not result in any differences to the deterministic results or the other sensitivity analysis results presented. It should also be noted that the updated probabilistic results still show first line tenofovir is cost-effective.

7.3.3. Sensitivity analysis

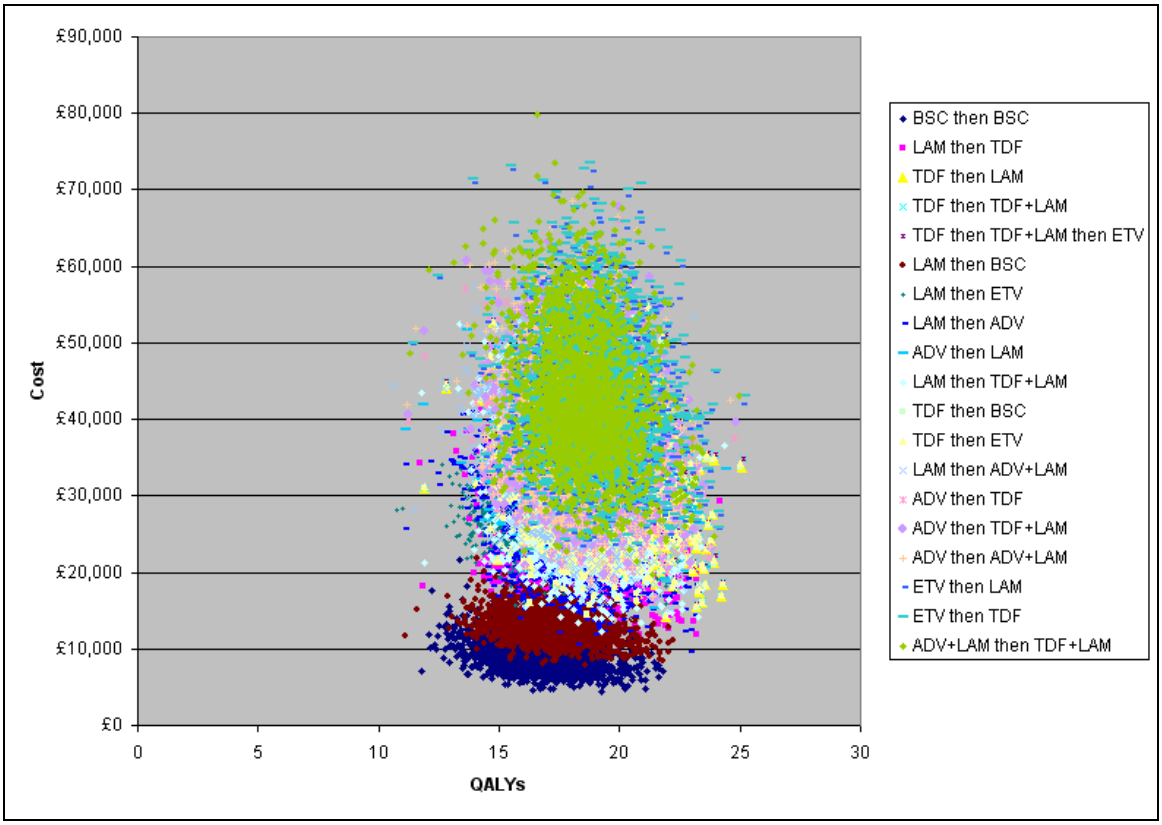
7.3.3.1. What were the main findings of the sensitivity analyses?

7.3.3.1.1. Probabilistic sensitivity analysis: HBeAg-positive patients

All parameters other than unit costs were varied simultaneously in probabilistic sensitivity analysis. All 20 strategies shown in Table 36 were subjected to PSA (Figure 9). It was not feasible to conduct PSA on all 211 treatment strategies listed in Appendix 11 due to the time taken to conduct the simulations; however, since the strategies included in PSA covered all of the main clusters lying on or near the frontier, restricting the number of strategies is unlikely to have any significant effect on the probability that first-line tenofovir is cost-effective.

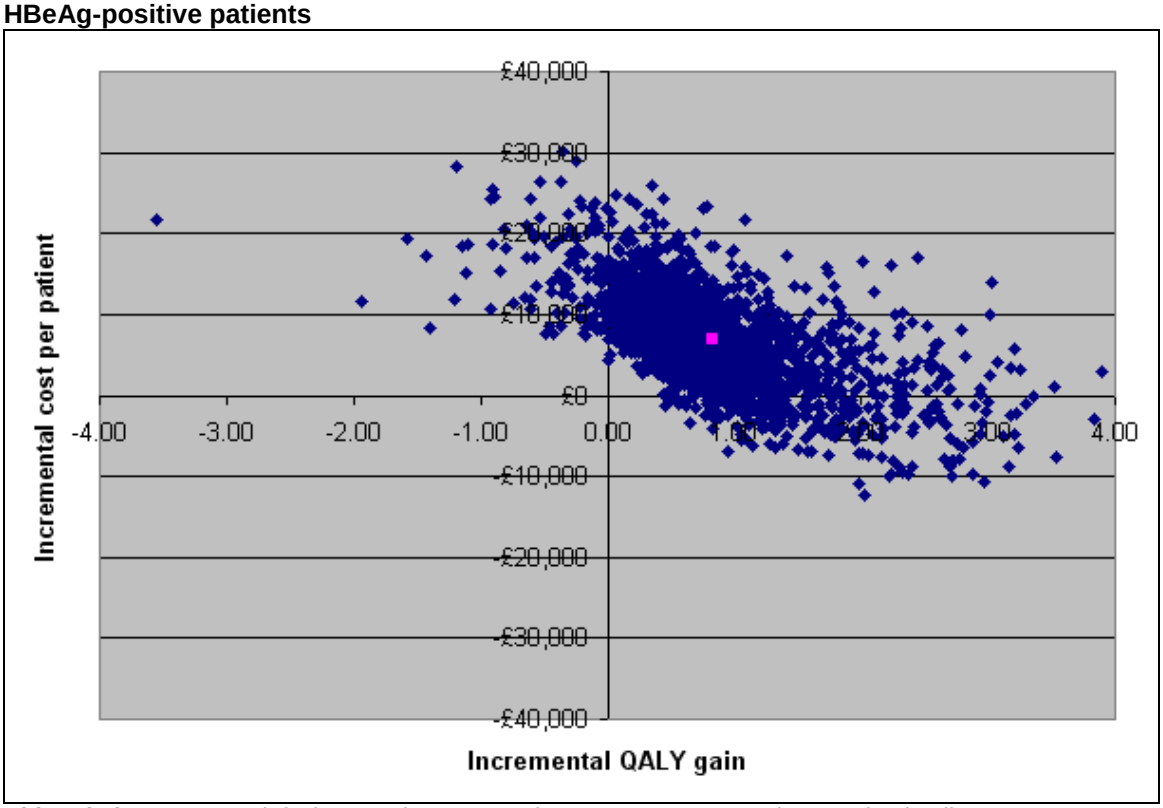
Only the main results of PSA are presented here. However, the spreadsheet model accompanying this submission enables PSA to be conducted on any plausible treatment strategy and allows generation of cost-effectiveness planes and curves for any pairwise or multiple-treatment comparisons.

Figure 9: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



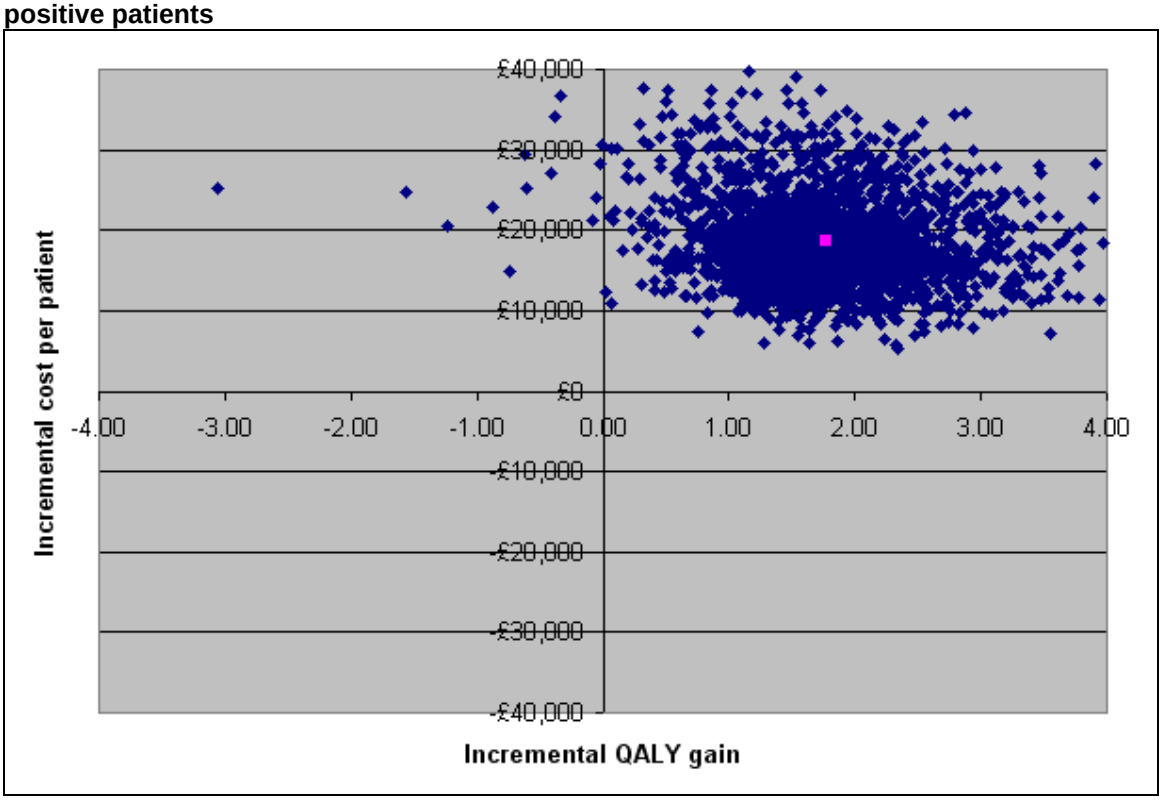
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 10: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs lamivudine then tenofovir for HBeAg-positive patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 11: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs lamivudine then BSC for HBeAg-positive patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

PSA confirmed the findings of the base case analysis, demonstrating that first-line use of tenofovir is the most cost-effective strategy if the NHS has a "threshold" cost/QALY of £20,000-£30,000/QALY gained. However, all cost-effectiveness ratios were slightly higher than those calculated in the deterministic base case analysis: for example, the ICER for tenofovir then lamivudine relative to lamivudine then BSC is £10,577 (95% CI: £3,994, £50,251) per QALY gained in the PSA, compared with £7,344/QALY in the base case analysis (Table 42).

Table 42: Mean ICERs and 95% CI and probability of each treatment strategy being cost-effective at different ceiling ratios: HBeAg-positive patients.

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean*	Lower 95% CI†	Upper 95% CI†	£0	£10,000	£20,000	£30,000	£50,000
BSC then BSC	£9,622	£3,124	£59,830	99.75%	29.25%	6.55%	2.75%	1.05%
LAM then TDF	£8,403	#	#	0.00%	26.65%	21.00%	11.85%	4.65%
TDF then LAM	-	-	-	0.00%	23.65%	35.90%	27.60%	18.40%
TDF then TDF+LAM	£26,074	#	£238,196	0.00%	1.05%	20.40%	33.10%	34.25%
TDF then TDF+LAM then ETV	£26,165	#	£240,042	0.00%	0.00%	3.30%	10.00%	21.95%
LAM then BSC	£10,577	£3,994	£50,251	0.25%	10.80%	2.05%	0.65%	0.05%
LAM then ETV	£3,048	#	£17,590	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then ADV	£3,480	#	#	0.00%	7.85%	5.85%	4.35%	2.95%
ADV then LAM	Dominant	#	#	0.00%	0.25%	0.80%	0.65%	0.45%
LAM then TDF+LAM	£1,806	#	#	0.00%	0.00%	0.95%	3.05%	5.30%
TDF then BSC	£4,305	£885	£15,871	0.00%	0.30%	0.15%	0.10%	0.20%
TDF then ETV	Dominant	#	£243,155	0.00%	0.00%	0.10%	0.00%	0.05%

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean*	**Lower 95% CI†**	**Upper 95% CI†**	**£0**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
LAM then ADV+LAM	Dominant	#	£34,278	0.00%	0.05%	0.20%	0.25%	0.25%
ADV then TDF	Dominant	#	#	0.00%	0.00%	0.45%	0.80%	0.45%
ADV then TDF+LAM	Dominant	#	#	0.00%	0.00%	0.05%	0.20%	0.50%
ADV then ADV+LAM	Dominant	#	£141,944	0.00%	0.00%	0.00%	0.05%	0.05%
ETV then LAM	Dominant	#	£1,296,267	0.00%	0.05%	1.00%	1.85%	2.45%
ETV then TDF	Dominant	#	£1,261,105	0.00%	0.05%	0.60%	1.75%	5.20%
ADV+LAM then TDF+LAM	Dominant	#	£129,924	0.00%	0.05%	0.65%	1.00%	1.75%
ETV+ADV then LAM	Dominant	#	£3,098,753	0.00%	0.00%	0.00%	0.00%	0.05%
All first-line TDF strategies combined	-	-	-	0.00%	24.70%	59.60%	70.70%	74.60%
Cost-effectiveness frontier‡	-	-	-	99.75%	10.80%	35.90%	33.10%	34.25%

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.

* The "mean" ICER is the ratio of the mean incremental costs and mean incremental QALYs.

† 95% CI were calculated using the percentile method, assigning all ICERs falling in the north-west quadrant (in which treatment is dominated by its comparator, being more costly and less effective) an arbitrarily high ICER.

The 95% CI was considered to be undefined as >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).

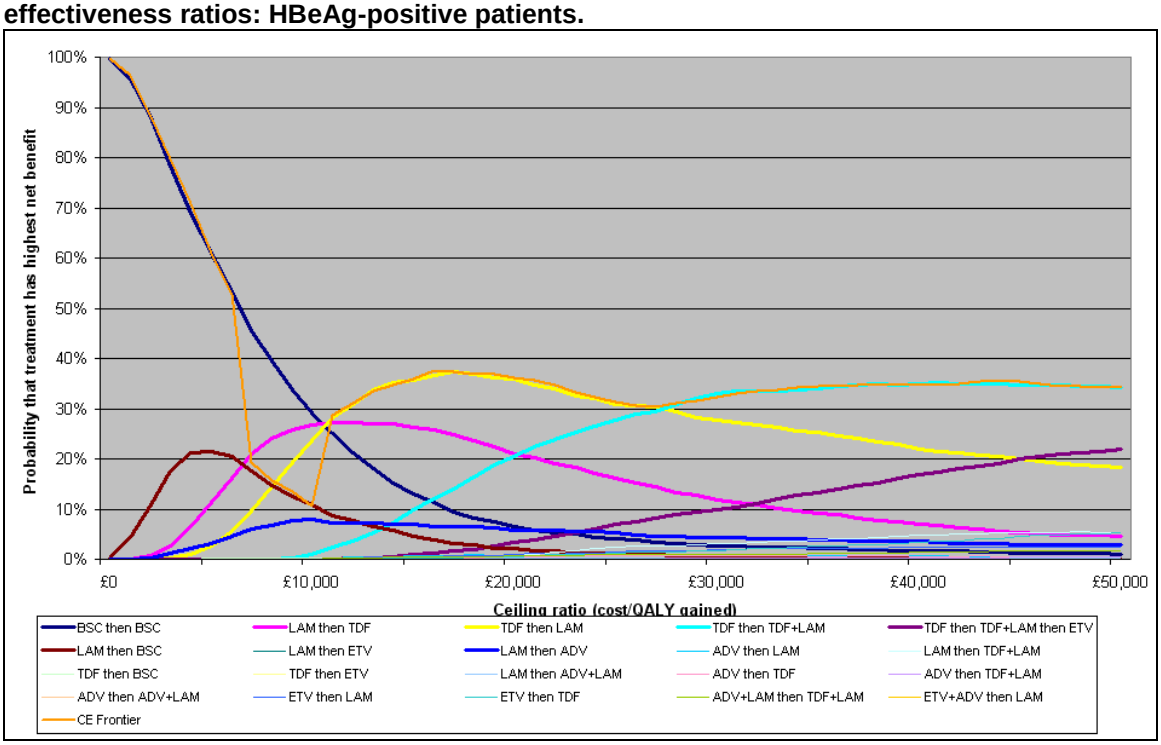
‡ The cost-effectiveness frontier represents the treatment with the highest expected net benefits at each ceiling ratio. The probabilities shown in this row represent the probability that the treatment with the highest expected net benefits is optimal. Error probabilities at any given threshold are equal to 1 minus the probabilities shown in this row.

For each of the 2,000 Monte Carlo simulations generated, the model calculated the net benefits for all 20 treatment strategies. These data were used to calculate the probability that (i.e. the proportion of simulations in which) each treatment is the most cost-effective treatment considered in the analysis at a range of different ceiling ratios showing possible values for our willingness to pay to gain one QALY (Figure 12 and Table 42).

This demonstrates that BSC is significantly less effective than all other treatment strategies considered in this analysis (p=0.004), in addition to having a >50% chance of being the optimal strategy at all ceiling ratios below £6,404.

Although it lies on the cost-effectiveness frontier in both the base case analysis and PSA, the probability that lamivudine then BSC is optimal never exceeds 21%. By contrast, lamivudine then tenofovir lies slightly above the cost-effectiveness frontier based on its mean costs and benefits within PSA (Table 42) but has a 27% probability of being optimal at a £10,000/QALY threshold.

Figure 12: Cost-effectiveness acceptability curves showing the probability that a particular treatment is the most cost-effective treatment considered in the analysis (i.e. has the highest net benefit) at a range of different threshold incremental cost-effectiveness ratios: HBeAg-positive patients.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

At a £20,000/QALY threshold, tenofovir followed by lamivudine had a 36% probability of being optimal, compared with 21% for lamivudine then tenofovir, 20% for tenofovir then tenofovir+lamivudine and 6% for lamivudine then adefovir. However, if the NHS were willing to pay £30,000 per QALY gained, tenofovir then tenofovir+lamivudine would have the highest probability of being cost-effective (33%). Tenofovir then lamivudine has the highest expected net benefits (and therefore lies on the cost-effectiveness frontier) at this threshold. The error probability at this threshold (one minus the probability that this treatment is optimal) is therefore 77%.

Pooling all strategies involving first-line use of tenofovir together demonstrates that we can be 60% confident that first-line use of tenofovir is the most cost-effective antiviral treatment for HBeAg-positive CHB if the NHS is willing to pay £20,000/QALY gained and 71% confident at a £30,000/QALY threshold.[uu] Furthermore, there was a 57% probability that one of the first-line tenofovir strategies would be the most effective treatment considered in this analysis.

This analysis also demonstrated that the comparisons between different strategies including first-line tenofovir are extremely sensitive to model inputs: although at a £20,000/QALY ceiling ratio there is a 69% probability that lamivudine then BSC is cost-effective relative to BSC, a 68% probability that lamivudine then tenofovir is cost-effective relative to lamivudine then BSC and a 71% probability that tenofovir then lamivudine is cost-effective relative to lamivudine then tenofovir, the probability that tenofovir then tenofovir+lamivudine is cost-effective relative to tenofovir then lamivudine is just 44% and the probability that tenofovir then tenofovir+lamivudine

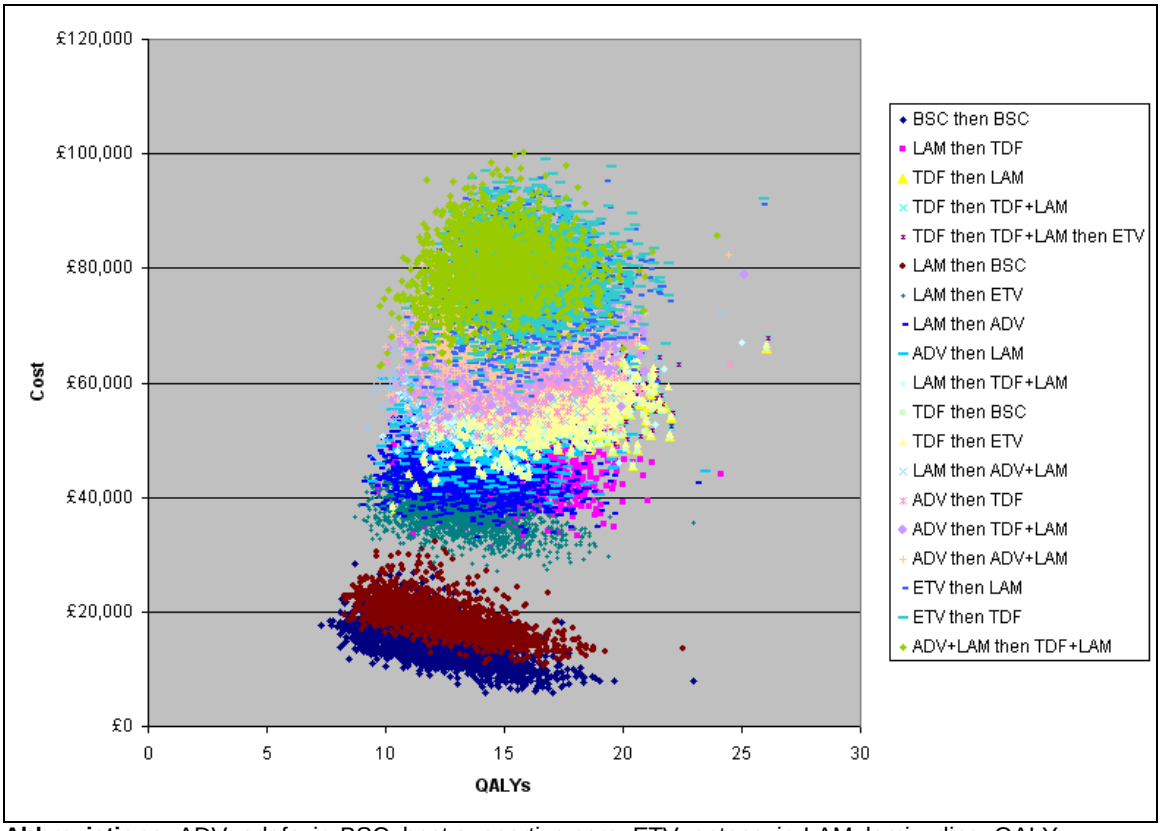
[uu] If all first-line tenofovir strategies are treated as a single strategy, the error probability at a £20,000/QALY threshold is therefore 40%.

then entecavir is cost-effective relative to tenofovir then tenofovir+lamivudine is only 5%.

7.3.3.1.2. Probabilistic sensitivity analysis: HBeAg-negative patients

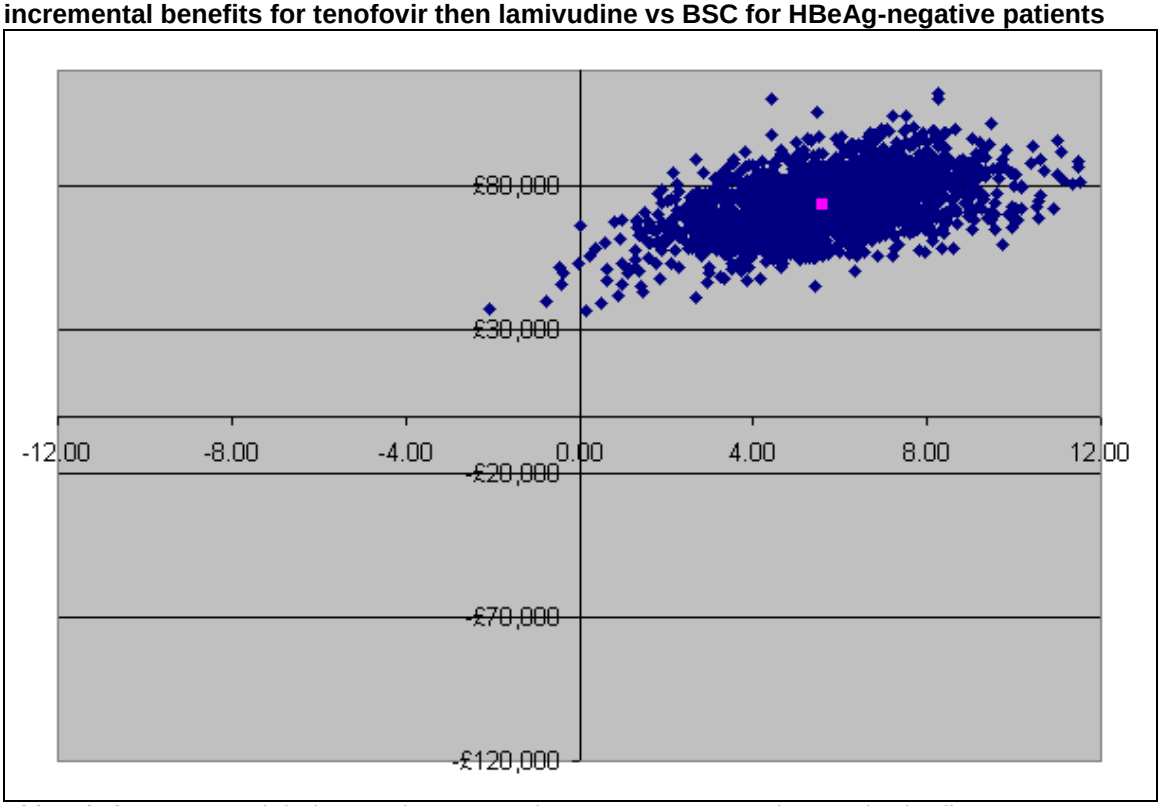
PSA was repeated for the HBeAg-negative population. The results for this population were strikingly similar to those for HBeAg-positive patients (Figure 12 and Figure 15).

Figure 13: Scattergraph/cost-effectiveness plane plotting the total lifetime cost per patient against the total number of QALYs per patient for each of the 20 treatments considered in PSA



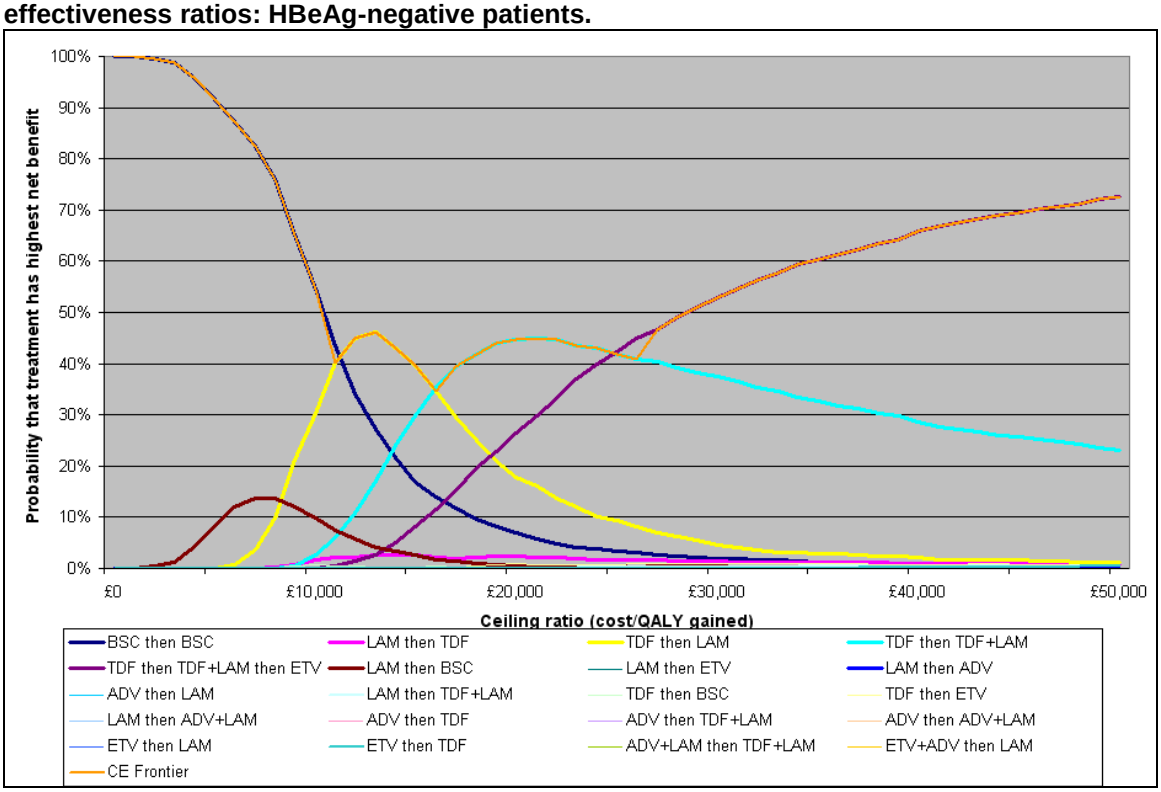
Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 14: Cost-effectiveness plane plotting the incremental costs against the incremental benefits for tenofovir then lamivudine vs BSC for HBeAg-negative patients



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Figure 15: Cost-effectiveness acceptability curves showing the probability that a particular treatment is the most cost-effective treatment considered in the analysis (i.e. has the highest net benefit) at a range of different threshold incremental cost-effectiveness ratios: HBeAg-negative patients.



Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

For HBeAg-negative patients, BSC had the highest probability of being cost-effective at all ceiling ratios below £11,200 and generated significantly fewer QALYs than any other treatment.

At a £20,000/QALY threshold, tenofovir then tenofovir+lamivudine had a 45% probability of being optimal, compared with 27% for tenofovir then tenofovir+lamivudine then entecavir, 18% for tenofovir followed by lamivudine, 7% for BSC and 2.3% for lamivudine then tenofovir. However, if the NHS was willing to pay £30,000 per QALY gained, tenofovir then tenofovir+lamivudine then entecavir would have the highest probability of being cost-effective (53%; Table 43).

Table 43: Mean ICERs and 95% CI and probability of each treatment strategy being cost-effective at different ceiling ratios: HBeAg-negative patients.

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean	Lower 95% CI	Upper 95% CI	£0	£10,000	£20,000	£30,000	£50,000
BSC then BSC	£10,888	£6,432	£30,144	100.00%	54.60%	6.95%	2.00%	0.65%
LAM then TDF	£8,085	£3,872	£34,827	0.00%	1.70%	2.35%	1.40%	0.65%
TDF then LAM	-	-	-	0.00%	30.30%	17.80%	4.50%	1.20%
TDF then TDF+LAM	£16,083	£9,819	£47,066	0.00%	2.70%	44.70%	37.60%	23.10%
TDF then TDF+LAM then ETV	£16,108	£9,821	£47,176	0.00%	0.10%	26.55%	52.90%	72.65%
LAM then BSC	£10,232	£6,462	£26,272	0.00%	9.80%	0.65%	0.40%	0.10%
LAM then ETV	£6,506	£3,780	£17,737	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then ADV	£4,822	£2,414	£12,907	0.00%	0.00%	0.00%	0.00%	0.05%

	ICER TDF-LAM vs. treatment X			Probability of being most cost-effective (i.e. having highest net benefit)				
	Mean	**Lower 95% CI**	**Upper 95% CI**	**£0**	**£10,000**	**£20,000**	**£30,000**	**£50,000**
ADV then LAM	£907	#	£6,822	0.00%	0.00%	0.00%	0.00%	0.00%
LAM then TDF+LAM	Dominant	#	£3,925	0.00%	0.00%	0.00%	0.25%	0.55%
TDF then BSC	£7,184	£4,532	£18,712	0.00%	0.80%	0.15%	0.00%	0.00%
TDF then ETV	£51,490	#	£577,408	0.00%	0.00%	0.85%	0.95%	0.55%
LAM then ADV+LAM	Dominant	#	£1,221	0.00%	0.00%	0.00%	0.00%	0.00%
ADV then TDF	Dominant	#	£34	0.00%	0.00%	0.00%	0.00%	0.00%
ADV then TDF+LAM	Dominant	#	Dominant	0.00%	0.00%	0.00%	0.00%	0.00%
ADV then ADV+LAM	Dominant	#	Dominant	0.00%	0.00%	0.00%	0.00%	0.00%
ETV then LAM	Dominant	#	£515,164	0.00%	0.00%	0.00%	0.00%	0.00%
ETV then TDF	Dominant	#	£1,378,639	0.00%	0.00%	0.00%	0.00%	0.50%
ADV+LAM then TDF+LAM	Dominant	#	Dominant	0.00%	0.00%	0.00%	0.00%	0.00%
ETV+ADV then LAM	Dominant	#	£3,037,118	0.00%	0.00%	0.00%	0.00%	0.00%
All first-line TDF strategies combined	-	-	-	**0.00%**	**33.10%**	**89.05%**	**95.00%**	**96.95%**
Cost-effectiveness frontier‡	-	-	-	**100.00%**	**54.60%**	**44.70%**	**52.90%**	**72.65%**

Abbreviations: ADV, adefovir; BSC, best supportive care; ETV, entecavir; LAM, lamivudine; QALY, quality-adjusted life-year; TDF, tenofovir.

Values shown in blue typeface indicate that the treatment(s) in question has/have the highest probability of being cost-effective at this threshold.
* The "mean" ICER is the ratio of the mean incremental costs and mean incremental QALYs.
† 95% CI were calculated using the percentile method, assigning all ICERs falling in the north-west quadrant (in which treatment is dominated by its comparator, being more costly and less effective) an arbitrarily high ICER.
# The 95% CI was considered to be undefined as >2.5% of simulations lay in the south-west quadrant (in which treatment is less costly and less effective than its comparator) AND >2.5% lay in the north-east quadrant (in which treatment is more costly and more effective than its comparator).
‡ The cost-effectiveness frontier represents the treatment with the highest expected net benefits at each ceiling ratio. The probabilities shown in this row represent the probability that the treatment with the highest expected net benefits is optimal. Error probabilities at any given threshold are equal to 1 minus the probabilities shown in this row.

We can be 89% confident that tenofovir is the most cost-effective antiviral strategy for managing HBeAg-negative CHB at a £20,000/QALY threshold (if all strategies involving first-line use of tenofovir are combined), which increases to 95% at a £30,000/QALY threshold. The error probability at a £20,000/QALY threshold is therefore 5% when all first-line tenofovir strategies are combined together. We can be 83% confident that one of the first-line tenofovir strategies would be the most effective treatment considered in this analysis.

As was the case for HBeAg-positive patients, the comparisons between different strategies including first-line tenofovir were extremely sensitive to model inputs: at a £20,000/QALY ceiling ratio there is a:

- 49% probability that lamivudine then BSC is cost-effective relative to BSC
- 91% probability that lamivudine then tenofovir is cost-effective relative to lamivudine then BSC
- 94% probability that tenofovir then lamivudine is cost-effective relative to lamivudine then tenofovir
- 73% probability that tenofovir then tenofovir+lamivudine is cost-effective relative to tenofovir then lamivudine
- 29% probability that tenofovir then tenofovir+lamivudine then entecavir is cost-effective relative to tenofovir then tenofovir+lamivudine.