National Clinical Guideline Centre

.

# Hepatitis B (chronic)

## Appendices A - D

*Hepatitis B Guideline*

*Appendices*

*June 2013*

*Final*

*Commissioned by the National Institute for Health and Care Excellence*

Royal College of Physicians
Setting higher medical standards
Royal College of Nursing
RCGP Royal College of General Practitioners
The Royal College of Surgeons of England
NICE accredited
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**Disclaimer**
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.



**Funding**
National Institute for Health and Care Excellence

# Contents

# Appendices

# Appendix A: Scope

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Centre for Clinical Practice

## SCOPE

**Clinical guideline title:** Hepatitis B (chronic): diagnosis and management of chronic hepatitis B in children, young people and adults

**Quality standard title:** Hepatitis B (chronic)

## 1 Introduction

### *1.1 Clinical guidelines*

Clinical guidelines are recommendations by NICE on the appropriate treatment and care of people with specific diseases and conditions within the NHS. They are based on the best available evidence.

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

### *1.2 Quality standards*

Quality standards are a set of specific, concise quality statements and measures that act as markers of high-quality, cost-effective patient care, covering the treatment and prevention of different diseases and conditions.

For this topic a NICE quality standard will be produced based on the guideline recommendations. The clinical guideline and the quality standard will be published at the same time.

This scope defines the areas of care for which specific quality statements and measures will (and will not) be developed.

The guideline and quality standard development processes are described in detail on the NICE website (see section 8).

# 2 Need for guidance

## *2.1 Epidemiology*

a) Chronic hepatitis B is usually defined as hepatitis B infection that continues for longer than 6 months. It is usually indicated by persisting positivity for hepatitis B surface antigen (HBsAG). However, people who have recovered following hepatitis B virus infection may, if immunosuppressed, become HBsAg positive again. Chronic hepatitis B virus infection is a major healthcare problem in the UK, with an estimated prevalence of 0.3%. Approximately 180,000 people in the UK have the condition. Its prevalence is considerably higher among high-risk groups such as first generation migrants from areas where hepatitis B is endemic; people who have multiple sexual partners; and injecting drug users. The incidence of hepatitis B has risen sharply, from 435 new cases in 1990 to 1151 in 2003.

b) Currently, there are approximately 600 to 800 new cases of symptomatic (jaundiced) acute hepatitis B infection in the UK each year. In 50% of cases there is no obvious risk factor; 20% of cases relate to intravenous drug use; and 25% are sexually acquired (80% of these in men who have sex with men). In the remaining cases the infection is thought to have been transmitted from people with chronic hepatitis B who are asymptomatic.

c) The risk of an acute infection progressing to a chronic infection is closely related to age at acquisition, and varies from 5% in adulthood to more than 90% in perinatal infection.

d) Chronic hepatitis B most commonly follows childhood infection, and thus people often present to health services after many years of asymptomatic infection (often unknown to the patient).

e) Treatment is needed for those at highest risk of progressive liver disease and its complications. It aims to primarily reduce viral loads and bring about HBsAg loss. Multiple studies have shown that therapeutic reduction in viral loads leads to a marked reduction in hepatic inflammation, fibrosis progression and risk of cirrhosis. Among people who already have cirrhosis the risk of liver complications, including hepatocellular carcinoma, is also reduced.

f) Currently, no long-term studies of the clinical outcome for the most recently approved nucleoside or nucleotide analogue treatments are available. However, early studies (that have been running for up to 5 years) suggest that these treatments have the most potent effect on viral loads and liver histology, and are likely to have the greatest impact on complications associated with hepatitis B infection.

## *2.2 Current practice*

a) Diagnosing chronic hepatitis B infection includes the use of immunoassays for HBsAg, hepatitis B ‘e’ antigen (HBeAg), and antibodies to hepatitis B ‘e’ antigen (HBeAb). People with hepatitis B may be either HBeAg positive or negative. Chronic hepatitis B infection may also be diagnosed using quantitative and qualitative hepatitis B virus DNA assays. Co-infections with hepatitis C, hepatitis D and HIV are identified by serological assay.

b) To assess the phase of chronic hepatitis B, routine liver function tests are performed. Serological assays are used to detect HBeAg and HBeAb. Molecular assays to measure hepatitis B virus DNA are also undertaken.

c) Two classes of drug are currently used to treat chronic hepatitis B infection: pegylated interferon and nucleoside or nucleotide analogues. Four nucleoside or nucleotide analogues are currently recommended by NICE and are in widespread clinical use.

d) Pegylated interferon suppresses the virus in a smaller proportion of patients than nucleoside or nucleotide analogues (especially entecavir and tenofovir) but is given for a fixed duration of 48 weeks. In contrast, nucleoside or nucleotide analogues often need to be used as long-term treatment.

e) If needed, nucleoside or nucleotide analogue therapy may be given after pegylated interferon.

f) Combination nucleoside or nucleotide analogue treatment may be necessary to reduce the risk of, or to treat, any type of established resistance to treatment.

g) The earliest licensed nucleoside or nucleotide analogues (lamivudine and adefovir) appear to be less effective than the more recently approved agents (entecavir and tenofovir), judged according to patient seroconversion rates, rates of resistance, and the proportion of patients achieving undetectable viral loads.

h) Telbivudine is licensed for treating hepatitis B but is not recommended by NICE (NICE technology appraisal guidance 154).

i) Tenofovir in combination with emtricitabine is used in some people with chronic hepatitis B, but is licensed at present only for HIV infection.

j) 'Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B' (NICE technology appraisal guidance 96), compares interferon, lamivudine, and adefovir, but otherwise NICE guidance considers each drug for hepatitis separately.

k) Patient information and counselling offered to family members and/or sexual partners by healthcare professionals should include treatment options, the risk of other family members and/or sexual partners being infected, and the benefits of vaccination against the hepatitis B virus.

l) Several audits have shown significant variation in practice. For example, a recent audit in London showed that only two-thirds of people with chronic hepatitis B infection diagnosed in primary care were referred for assessment. There is also strong anecdotal evidence of wide variation in prescribing practice with regard to initial choice of agents and duration of therapy, particularly after HBeAg or HBeAb seroconversion. This guideline is needed to reduce variation in practice and improve the care of people with chronic hepatitis B.

# 3 Clinical guideline

## *3.1 Population*

### 3.1.1 Groups that will be covered

a) Children, young people and adults with chronic hepatitis B virus infection including:

- people co-infected with hepatitis C or hepatitis delta (D) virus
- immunocompromised people (such as those undergoing cancer treatments) who are carriers or have been previously infected, for whom prophylactic treatment might be beneficial
- pregnant and lactating women
- people with cirrhosis, including those with liver decompensation.

### 3.1.2 Groups that will not be covered

a) People who have had a liver transplant.

b) People with acute hepatitis B.

c) People co-infected with HIV.

## *3.2 Healthcare settings*

a) Primary, secondary, tertiary and community NHS settings.

## *3.3 Diagnosis and management*

### 3.3.1 Key issues that will be covered

**Identification and assessment of chronic hepatitis B**

a) Healthcare setting for pre-therapeutic tests in people found to be hepatitis B antigen positive (HBeAg, HBeAb, quantitative HBsAg, and hepatitis B virus DNA), for example in primary or secondary care.

b) Criteria for referral to specialist services.

c) Laboratory tests to determine severity of necro-inflammatory activity, fibrosis (grade/stage) and whether or not treatment needs to be started:

- liver biopsy
- non-invasive methods of assessing liver fibrosis (for example, serum fibrosis markers, elastography, aspartate aminotransferase/platelet ratio index [APRI]).

d) Diagnosis of concomitant infections, hepatitis C and hepatitis delta (D) virus.

**Pharmacological treatment**

e) Sequential and combination drug therapy for specified subgroups:

- adefovir
- emtricitabine (in combination with tenofovir)
- entecavir
- lamivudine
- pegylated alpha-interferon

- telbivudine
- tenofovir.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

**Monitoring stages of the condition**

f) Surveillance timing, and frequency of:

- quantitative DNA assays and resistance genotyping
- adverse events, for example renal toxicity
- hepatitis B markers (HBeAg, hepatitis B virus DNA, HBsAg) as stopping points for treatment
- quantitative HBsAg by serology
- case finding for hepatocellular carcinoma.

g) Patient information

### 3.3.2 Key issues that will not be covered

a) Primary prevention of hepatitis B, including vaccination.

b) Case finding.

c) Signs and symptoms of advanced hepatitis B with cirrhosis.

d) Non-pharmacological management of chronic hepatitis B.

e) Co-infection of chronic hepatitis B with HIV or hepatitis viruses A or E.

f) Guidance on working practices for infected healthcare workers.

g) Liver transplantation.

h) Acute hepatitis B.

## *3.4 Main outcomes*

a) Reduction of serum hepatitis B DNA, tested by the most sensitive available quantitative assay

b) Clearance of HBeAg and seroconversion forHBeAb.

c) Clearance of HBsAg and seroconversion forHBsAb.

d) Regression of hepatic inflammation and fibrosis grade/stage.

e) Frequency of liver decompensation

f) Incidence of hepatocellular carcinoma.

g) Quality of life, tested using a validated general instrument or a validated liver disease-specific instrument.

h) Mortality.

i) Adverse effects.

j) Rates of vertical transmission from mother to infant for pregnant and lactating women.

k) Resistance

## *3.5 Economic aspects*

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see section 8).

# 4 Quality standard

Information on the NICE quality standards development process is available on the NICE website, see section 8.

## *4.1 Areas of care*

The areas of care of a patient's journey that will inform the development of the quality statements are set out below (see 4.1.1). The content of the final quality standard statements may differ before and after consultation with stakeholders.

### 4.1.1 Areas of care that will be considered

**Identification and assessment of chronic hepatitis B**

a) Case finding strategies (from Hepatitis B and C: ways to promote and offer testing. NICE public health guidance. Publication expected December 2012)

b) Healthcare setting for pre-therapeutic tests in people found to be hepatitis B antigen positive (HBeAg, HBeAb, quantitative HBsAg, and hepatitis B virus DNA).

c) Criteria for referral to specialist services

d) Laboratory tests to determine severity of necro-inflammatory activity, fibrosis (grade/stage) and whether or not treatment needs to be started

e) Diagnosis of concomitant infections, heptatitis C and hepatitis delta (D) virus.

**Pharmacological treatment**

f) Pharmacological treatment for management of chronic hepatitis B including sequential and combination therapies for specific subgroups.

**Monitoring stages of the condition**

g) Monitoring of chronic hepatitis B including timing and frequency of tests on and off treatment

h) Patient information.

### 4.1.2 Areas of care that will not be considered

a) Primary prevention of hepatitis B including vaccination

b) Signs and symptoms of hepatitis B.

c) Non-pharmacological management of chronic hepatitis B.

d) Co-infection of chronic hepatitis B with HIV or hepatitis viruses A or E.

e) Guidance on working practices for infected healthcare workers.

f) Liver transplantation.

g) Acute hepatitis B.

## *4.2 Economic aspects*

Developers will take into account both clinical and cost effectiveness when prioritising the quality statements to be included in the quality standard. The economic evidence will be considered, and the cost and commissioning impact of implementing the quality standard will be assessed.

# 5 Status

## *5.1 Scope*

This is the final scope.

## *5.2 Timings*

The development of the guideline recommendations and the quality standard will begin in September 2011.

# 6 Related NICE guidance

### 6.1.1 NICE guidance that will be incorporated in or updated by the clinical guideline

This guideline will incorporate the following NICE guidance:

- Tenofovir disoproxil for the treatment of chronic hepatitis B. NICE technology appraisal guidance 173 (2009). Available from www.nice.org.uk/guidance/TA173
- Telbivudine for the treatment of chronic hepatitis B. NICE technology appraisal guidance 154 (2008). Available from www.nice.org.uk/guidance/TA154
- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance 153 (2008). Available from www.nice.org.uk/guidance/TA153
- 1.1 of Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/guidance/TA96

This guideline will update the following NICE guidance:

- 1.2 - 1.4 of Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B. NICE technology appraisal guidance 96 (2006). Available from www.nice.org.uk/guidance/TA96

### *6.2 Related NICE guidance*

**Published**

- Increasing the uptake of HIV testing among men who have sex with men. NICE public health guidance 34 (2011). Available from: www.nice.org.uk/guidance/PH34
- Increasing the uptake of HIV testing among black Africans in England. NICE public health guidance 33 (2011). Available from: www.nice.org.uk/guidance/PH33
- Alcohol-use disorders. NICE clinical guideline 115 (2011). Available from www.nice.org.uk/guidance/CG115
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Obesity NICE clinical guideline 43 (2006). Available from www.nice.org.uk/guidance/CG43

**NICE guidance under development**

NICE is currently developing the following related guidance (details available from the NICE website):

- Patient experience in generic terms. NICE clinical guideline. Publication expected October 2011.
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance. Publication expected December 2012.

# 7 Further information

Information on the guideline development process is provided in:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’
- ‘The guidelines manual’
- ‘Developing NICE quality standards: interim process guide'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual and www.nice.org.uk/aboutnice/qualitystandards). Information on the progress of the guideline and quality standards is also available from the NICE website (www.nice.org.uk).

# Appendix B: Declarations of interest

## B.1 Ala, Aftab

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting 26th September 2011 | No interests to declare. | |
| Second GDG Meeting 1st November 2011 | No interests to declare. | |
| Third GDG Meeting 29th November 2011 | Non personal pecuniary interest:<br>• Received research grants from Roche and BMS for a hypothesis driven clinical research project looking at the prevalence and knowledge of viral hepatitis (b and c) in the Surrey asian population. It specifically involves the use of dry blood spot testing in the setting of mosques. The research grant has been used to support a part time nurse and dry blood spot testing kits<br><br>Personal pecuniary interest:<br>• Received support for travel expenses to AASLD meeting from Gilead and Roche. | No action taken.<br><br>No action taken |
| Fourth GDG Meeting 17th January 2012 | Did not attend. | |
| Fifth GDG Meeting 28th February 2012 | No change in declaration. | No action taken. |
| Sixth GDG Meeting 3rd April 2012 | No change in declaration. | No action taken. |
| Seventh GDG Meeting 8th May 2012 | Did not attend. | |
| Eighth GDG Meeting 19th June 2012 | Did not attend. | |
| Ninth GDG Meeting | No change in declaration. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 24th July 2012 | | |
| Tenth GDG Meeting 4th September 2012 | Non personal pecuniary interest:<br>• Awarded Gilead fellowship. Chief investigator considering prevalence of hepatitis b and c | No action taken. |
| Eleventh GDG Meeting 10th October 2012 | No change in declaration. | No action taken. |
| Twelfth GDG Meeting 20th November 2012 | No change in declaration. | No action taken. |
| Thirteenth GDG Meeting 26th March 2013 | No change in declaration | No action taken |

## B.2 Boxall, Elizabeth

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting 26th September 2011 | Personal pecuniary interest:<br>• Involved in a consulting arrangement with Sanofi Pasteur with regard to Hepatitis B vaccine in babies<br>• Paid to attend a focus group on antiviral drugs led by Gilead which consisted of presentations on epidemiology, current pathways and EASL guidelines. The meeting discussion centred on the impact of Health Service re-organisation and commissioning. | No action taken. |
| Second GDG Meeting 1st November 2011 | No change in declaration. | No action taken. |
| Third GDG Meeting 29th November 2011 | No change in declaration. | No action taken. |
| Fourth GDG Meeting 17th January 2012 | No change in declaration. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| Fifth GDG Meeting<br>28th February 2012 | No change in declaration. | No action taken. |
| Sixth GDG Meeting<br>3rd April 2012 | No change in declaration. | No action taken. |
| Seventh GDG Meeting<br>8th May 2012 | personal pecuniary interest:<br>• Asked to sit on advisory group for Sanofi-Pasteur MSD on best practice delivery of Hepatitis B vaccine to babies at risk in June 2012 | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | Personal pecuniary interest:<br>• Received a fee for talking about the epidemiology of hepatitis b at a meeting of hepatitis nurses. The meeting was sponsored by BMS. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October 2012 | No change in declaration. | No action taken. |
| Twelfth GDG Meeting<br>20th November 2012 | No change in declaration. | No action taken. |
| Thirteenth GDG Meeting<br>26th March 2013 | No change in declaration. | No action taken. |

## B.3 Bradley, Steven

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | No interests to declare. | |
| Second GDG Meeting<br>1st November 2011 | No interests to declare. | |
| Third GDG Meeting<br>29th November 2011 | No interests to declare. | |
| Fourth GDG Meeting<br>17th January 2012 | No interests to declare. | |
| | Resigned from GDG Jan 2012 | |

## B.4 Brown, Ashley (Co-optee member)

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | Did not attend. | |
| Second GDG Meeting<br>1st November 2011 | Did not attend. | |
| Third GDG Meeting<br>29th November 2011 | Personal pecuniary interest:<br>• Sat on advisory boards and received honoraria from Roche, Merck, Sharpe and Dome, BMS, Novartis, Gilead, Jansen and Sanofi-Pasteur.<br>• Received support for attendance at conferences and clinical research from Roche, MSD, BMS, Novartis, Gilead, Jansen and Sanofi-Pasteur | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| Fourth GDG Meeting<br>17th January 2012 | Did not attend. | |
| Fifth GDG Meeting<br>28th February 2012 | Did not attend. | |
| Sixth GDG Meeting<br>3rd April 2012 | Did not attend. | |
| Seventh GDG Meeting<br>8th May 2012 | Did not attend. | |
| Eighth GDG Meeting<br>19th June 2012 | Did not attend. | |
| Ninth GDG Meeting<br>24th July 2012 | Did not attend. | |
| Tenth GDG Meeting<br>4th September 2012 | Did not attend. | |
| Eleventh GDG Meeting<br>10th October 2012 | Did not attend. | |
| Twelfth GDG Meeting<br>20th November 2012 | Did not attend. | |
| Thirteenth GDG Meeting<br>26th March 2013 | Did not attend. | |

## B.5 Das, Joyeta (Co-optee member)

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | Did not attend. | |
| Second GDG Meeting<br>1st November 2011 | Did not attend. | |
| Third GDG Meeting<br>29th November 2011 | Did not attend. | |
| Fourth GDG Meeting<br>17th January 2012 | Did not attend. | |
| Fifth GDG Meeting<br>28th February 2012 | No interests to declare. | No action taken. |
| Sixth GDG Meeting<br>3rd April 2012 | No interests to declare. | No action taken. |
| Seventh GDG Meeting<br>8th May 2012 | Did not attend. | |
| Eighth GDG Meeting<br>19th June 2012 | No interests to declare. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | No interests to declare. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | Did not attend. | |
| Eleventh GDG Meeting | Did not attend. | |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 10th October 2012 | | |
| Twelfth GDG Meeting<br>20th November 2012 | Did not attend. | |
| Thirteenth GDG Meeting<br>26th March 2013 | Did not attend. | |

## B.6 Dusheiko, Geoffrey

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | Personal pecuniary interest:<br>• Served as an advisor to and received consulting fees from Abbott, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Human Genome Sciences, Novartis, Pharmasset, Pfizer, Roche/Genentech, Schering-Plough/merck, Tibotec, Vertex Pharmaceuticals and Zymogenetics.<br>• Received travel support from Gilead Science and Schering-Plough/Merck and grant support from Gilead Sciences, Novartis, Pharmasset, Roche/Genentech, Schering-Plough/Merck, Tibotex and Vertex Pharmaceuticals<br>Personal family interest<br>• Shares held in MSD stock, these have been held since 2000 and no trading in these shares has occurred. | No action taken. |
| Second GDG Meeting<br>1st November 2011 | No changes in declarations. | withdrew from recommendation making discussions. |
| Third GDG Meeting<br>29th November 2011 | No changes in declarations. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| Fourth GDG Meeting<br>17th January 2012 | No changes in declarations. | withdrew from recommendation making discussions for the cirrhosis and liver decompensation clinical question. |
| Fifth GDG Meeting<br>28th February 2012 | No change in declaration. | No action taken. |
| Sixth GDG Meeting<br>3rd April 2012 | No change in declaration. | No action taken. |
| Seventh GDG Meeting<br>8th May 2012 | No change in declaration. | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | Did not attend. | |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October 2012 | Did not attend. | |
| Twelfth GDG Meeting<br>20th November 2012 | No change in declaration. | Withdrew from discussions for the antiviral drugs recommendations. |
| Thirteenth GDG Meeting<br>26th March 2013 | Did not attend. | |

## B.7 Kennedy, Patrick

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| | Joined at GDG 7 | |
| Seventh GDG Meeting<br>8th May 2012 | Non personal pecuniary interest:<br>• Department received an educational grant from Gilead Sciences, Roche and BMS all supporting the set up and delivery of the young adult clinic at Barts and the Royal London Hospital. The grant was to aid the initial set up followed by support for the experimental work looking at the drivers of immune mediated damage in young patients (2010- 2011) | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | No change in declaration. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October 2012 | No change in declaration. | No action taken. |
| Twelfth GDG Meeting<br>20th November 2012 | Lecturing and consultancy for BMS, Roche and Gilead | Withdrew from discussions for antiviral drugs recommendations. |
| Thirteenth GDG Meeting<br>26th March 2013 | No change in declaration. | No action taken. |

## B.8 Lam, Emily

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting | Personal non-pecuniary interest | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 26th September 2011 | • She has been a community member on the NICE Hepatitis B and C testing programme development group since March 2011 | |
| Second GDG Meeting<br>1st November 2011 | No change in declaration. | No action taken. |
| Third GDG Meeting<br>29th November 2011 | No change in declaration. | No action taken. |
| Fourth GDG Meeting<br>17th January 2012 | No change in declaration. | No action taken. |
| Fifth GDG Meeting<br>28th February 2012 | No change in declaration. | No action taken. |
| Sixth GDG Meeting<br>3rd April 2012 | No change in declaration. | No action taken. |
| Seventh GDG Meeting<br>8th May 2012 | No change in declaration. | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | Personal non-pecuniary interest:<br>• Is a patient member on a Gilead funded HBV testing project in Manchester. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October | No change in declaration. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 2012 | | |
| Twelfth GDG Meeting<br>20th November 2012 | No change in declaration. | No action taken. |
| Thirteenth GDG Meeting<br>26th March 2013 | No change in declaration. | No action taken. |

## B.9 Mitchell, Alan

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | Did not attend. | |
| Second GDG Meeting<br>1st November 2011 | No interests to declare. | |
| Third GDG Meeting<br>29th November 2011 | No interests to declare. | |
| Fourth GDG Meeting<br>17th January 2012 | No interests to declare. | |
| Fifth GDG Meeting<br>28th February 2012 | No interests to declare. | |
| Sixth GDG Meeting<br>3rd April 2012 | No interests to declare. | |
| Seventh GDG Meeting | Did not attend. | |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 8th May 2012 | | |
| Eighth GDG Meeting<br>19th June 2012 | No interests to declare. | |
| Ninth GDG Meeting<br>24th July 2012 | No interests to declare. | |
| Tenth GDG Meeting<br>4th September 2012 | No interests to declare. | |
| Eleventh GDG Meeting<br>10th October 2012 | No interests to declare. | |
| Twelfth GDG Meeting<br>20th November 2012 | No interests to declare. | |
| Thirteenth GDG Meeting<br>26th March 2013 | No interests to declare. | |

## B.10 Narbey, Angela

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | No interests to declare. | |
| Second GDG Meeting<br>1st November 2011 | Did not attend. | |
| Third GDG Meeting | Did not attend. | |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 29th November 2011 | | |
| Fourth GDG Meeting<br>17th January 2012 | No interests to declare. | |
| Fifth GDG Meeting<br>28th February 2012 | No interests to declare. | |
| Sixth GDG Meeting<br>3rd April 2012 | No interests to declare. | |
| Seventh GDG Meeting<br>8th May 2012 | Did not attend. | |
| Eighth GDG Meeting<br>19th June 2012 | No interests to declare. | |
| Ninth GDG Meeting<br>24th July 2012 | No interests to declare. | |
| Tenth GDG Meeting<br>4th September 2012 | No interests to declare. | |
| Eleventh GDG Meeting<br>10th October 2012 | No interests to declare. | |
| Twelfth GDG Meeting<br>20th November 2012 | No interests to declare. | |
| Thirteenth GDG Meeting<br>26th March 2013 | No interests to declare. | |

## B.11 Permalloo, Nadia (Co-optee member)

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | No interests to declare. | |
| Second GDG Meeting<br>1st November 2011 | Did not attend. | |
| Third GDG Meeting<br>29th November 2011 | Did not attend. | |
| Fourth GDG Meeting<br>17th January 2012 | Did not attend. | |
| Fifth GDG Meeting<br>28th February 2012 | Did not attend. | |
| Sixth GDG Meeting<br>3rd April 2012 | Did not attend. | |
| Seventh GDG Meeting<br>8th May 2012 | Did not attend. | |
| Eighth GDG Meeting<br>19th June 2012 | Did not attend. | |
| Ninth GDG Meeting<br>24th July 2012 | No interests to declare. | |
| Tenth GDG Meeting<br>4th September 2012 | Did not attend. | |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| Eleventh GDG Meeting<br><br>10th October 2012 | Did not attend. | |
| Twelfth GDG Meeting<br><br>20th November 2012 | Did not attend. | |
| Thirteenth GDG Meeting<br><br>26th March 2013 | Did not attend. | |

## B.12 Thomas, Howard

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br><br>26th September 2011 | Personal pecuniary interest:<br>• Chairman of Imperial College spin-out company. Does not involve any work on hepatitis B.<br>• lecture on Hepatitis C at ID meeting in Berlin 2011, the expenses and honorarium were paid by industrial sponsor | No action taken. |
| Second GDG Meeting<br><br>1st November 2011 | No change in declaration. | No action taken. |
| Third GDG Meeting<br><br>29th November 2011 | No change in declaration. | No action taken. |
| Fourth GDG Meeting<br><br>17th January 2012 | No change in declaration. | No action taken. |
| Fifth GDG Meeting<br><br>28th February | No change in declaration. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 2012 | | |
| Sixth GDG Meeting<br>3rd April 2012 | No change in declaration. | No action taken. |
| Seventh GDG Meeting<br>8th May 2012 | No change in declaration. | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | No change in declaration. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October 2012 | No change in declaration. | No action taken. |
| Twelfth GDG Meeting<br>20th November 2012 | Delivered a workshop on behalf of Wiley Blackwell on how to prepare a paper for Journal Viral Hepatology in Beijing November 2012 and lecture on update of viral hepatitis. | No action taken. |
| Thirteenth GDG Meeting<br>26th March 2013 | No change in declaration. | |

## B.13 Tudor-Williams, Gareth

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br>26th September 2011 | Did not attend. | |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| Second GDG Meeting<br>1st November 2011 | Did not attend. | |
| Third GDG Meeting<br>29th November 2011 | Did not attend. | |
| Fourth GDG Meeting<br>17th January 2012 | Personal non pecuniary interest:<br>• Principle Investigator on a multi-national study (PEARL) sponsored by Roche that is looking at the use of pegylated interferon in children. | No action taken. |
| Fifth GDG Meeting<br>28th February 2012 | No change in declaration. | No action taken. |
| Sixth GDG Meeting<br>3rd April 2012 | No change in declaration. | No action taken. |
| Seventh GDG Meeting<br>8th May 2012 | Non personal pecuniary interest:<br>• Participated in a scientific advisory group for the European Medicines Agency on 3rd May 2012 that discussed tenofovir use in children with HIV infection and HBV infection | |
| Eighth GDG Meeting<br>19th June 2012 | No change in declaration. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | Did not attend. | |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October 2012 | No change in declaration. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| Twelfth GDG Meeting<br><br>20th November 2012 | No change in declaration. | No action taken. |
| Thirteenth GDG Meeting<br><br>26th March 2013 | No change in declaration. | No action taken. |

## B.14 Vilar, Francisco-Javier

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| First GDG meeting<br><br>26th September 2011 | Non personal pecuniary interest:<br>• Gilead have agreed to support an audit in his unit into Hepatitis B, the sponsorship is to support a part-time data collecting clerk.<br>• Principle investigator in a hepatitis C study supported by Roche through an unrestricted grant. | No action taken. |
| Second GDG Meeting<br><br>1st November 2011 | No change in declaration. | No action taken. |
| Third GDG Meeting<br><br>29th November 2011 | Non personal pecuniary interest:<br>Delivering a lecture on 30th November 2011 at the North of England Hepatitis B group. The meeting is supported by Gilead. | No action taken. |
| Fourth GDG Meeting<br><br>17th January 2012 | No change in declaration. | No action taken. |
| Fifth GDG Meeting<br><br>28th February 2012 | No change in declaration. | No action taken. |
| Sixth GDG Meeting | No change in declaration. | No action taken. |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 3rd April 2012 | | |
| Seventh GDG Meeting<br>8th May 2012 | No change in declaration. | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | Personal pecuniary interest:<br>• Contributed to a non-promotional BMS meeting, by giving a talk on clinical cases. Received honorarium.<br>Personal non-pecuniary interest;<br>• Contributing to work on a testing project which is in receipt of Gilead fellowship sponsoring. | No action taken. |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| Eleventh GDG Meeting<br>10th October 2012 | Personal pecuniary interest:<br>• Consultancy for Gilead in hepatitis c treatment delivery for difficult to reach populations (not drug specific). | No action taken. |
| Twelfth GDG Meeting<br>20th November 2012 | Did not attend. | |
| Thirteenth GDG Meeting<br>26th March 2013 | Personal pecuniary interest:<br>• Given 2 HIV lectures for Gilead Spain presenting clinical cases and have been offered doing a 3rd. There was no mention of hepatitis B. | No action taken. |

## B.15 Wise, Sarah

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| | Joined at GDG 6 | |
| Sixth GDG Meeting | No interests to declare. | |

| GDG meeting | Declaration of Interests | Action taken |
|---|---|---|
| 3rd April 2012 | | |
| Seventh GDG Meeting<br>8th May 2012 | Non personal pecuniary interest:<br>• Asked to sit on advisory group for Sanofi-Pasteur MSD on best practice delivery of Hepatitis B vaccine to babies at risk in June 2012 | No action taken. |
| Eighth GDG Meeting<br>19th June 2012 | Did not attend. | |
| Ninth GDG Meeting<br>24th July 2012 | No change in declaration. | No action taken. |
| Tenth GDG Meeting<br>4th September 2012 | No change in declaration. | No action taken. |
| | Resigned from GDG September 2012 | |

# Appendix C: Review Protocols

## C.1 Patient Information

| Review question | What information do patients with CHB and their carers need about the benefits and risks of treatment options? |
|---|---|
| Objectives | To examine the information needs for patients with CHB and their carers about the benefits and risks of treatment options |
| Criteria | **Population:** Children, young people and adults with CHB infection and their carers<br><br>**Factors under investigation:**<br>- Prognosis and risk associated with no treatment<br>- Benefits of treatment (reduced mortality from liver disease/ liver cancer, reduced infectivity within the family)<br>- Side effects of treatments<br>- Risk of transmission during different phases for both untreated and treated people<br><br>**Outcomes**:<br>• Patients' understanding and satisfaction<br>• Quality of life<br><br>**Study design**:<br>Qualitative studies, questionnaire/interview/focus group based studies and surveys |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | - |

## C.2 Settings

| Review question | What is the most appropriate healthcare setting to initiate relevant diagnostic tests (for example liver function tests, HBeAg, quantitative HBsAg, quantitative HBV DNA, anti HCV, anti HDV, anti HIV) in people who are HBsAg positive? |
|---|---|
| Objectives | To determine the most appropriate healthcare setting to initiate relevant diagnostic tests in people who are HBsAg positive. |
| Criteria | **Population:** HBsAg positive children, young people, and adults with chronic hepatitis B virus infection<br>**Study group**: Initiation of diagnostic tests in community/primary setting (GP practice)<br>**Comparison group**: Initiation of diagnostic tests in secondary care (such as hospital)<br>**Outcomes**: any<br>**Study design**: any. |
| Exclusion | Non-UK studies<br>Studies on other types of viral hepatitis (other than hepatitis B) |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | - |

## C.3 Referral thresholds

| Review question | What are the thresholds (e.g. HBV DNA and ALT levels) for referral to specialist services after initial diagnosis and pre-therapeutic tests of CHB? |
|---|---|
| Objectives | To determine thresholds for referral to specialist services after initial diagnosis and pre-therapeutic tests of CHB. |
| Criteria | **Population:** children, young people, and adults with chronic hepatitis B virus infection<br>**Prognostic factors**: thresholds of detectable HBV DNA, thresholds of normal or abnormal ALT levels<br>**Outcomes**: indication for management of CHB (treatment and further investigations)<br>**Study design**: systematic reviews of observational studies, observational studies |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | Subgroup analyses:<br>Children and young people<br>HBeAg positive/negative<br>Pregnant and lactating women |

## C.4 Diagnostics

| Review question | **What is the diagnostic accuracy of non-invasive methods (e.g. transient elastography, serum fibrosis markers, aspartate aminotransferase/ platelet ratio index, magnetic resonance spectroscopy) to assess severity of necro-inflammatory activity and liver fibrosis?** |
|---|---|
| Objectives | To estimate the diagnostic accuracy of non-invasive methods comparing with liver biopsy to assess severity of necro-inflammatory activity and liver fibrosis. |
| Criteria | **Population:** children, young people, and adults with chronic hepatitis B virus infection<br>**Index tests**: serum fibrosis markers (e.g. fibrotest, actitest), transient elastography (e.g. FibroScan), aspartate aminotransferase/ platelet ratio index (APRI), enhanced liver fibrosis (ELF), magnetic resonance spectroscopy<br>**Target condition or reference standard**: liver biopsy (Knodell score, Ishak fibrosis score and METAVIR)<br>**Outcomes**: sensitivity, specificity, area under the curve, positive/negative predictive values, positive/negative diagnostic likelihood ratios, post-test probability (at a set pre-test probability).<br>**Study design**: cross-sectional and retrospective |
| Exclusions | Studies that used scoring systems other than METAVIR, Ishak and Knodell scores for fibrosis staging |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | Analysis by stage of fibrosis |

## C.5 Genotype testing

| Review question | **What is the clinical and cost-effectiveness of genotypic testing in determining whether to offer antiviral treatment in people with CHB?** |
|---|---|
| Objectives | To estimate the clinical and cost-effectiveness of genotypic testing in order to decide whether to offer antiviral treatment. |
| Criteria | Children, young people and adults with chronic hepatitis B virus infection<br>Response to treatment (interferon, lamivudine, adefovir, entecavir, tenofovir), by genotype, measured by:<br>1) Serum HBV DNA reduction (log copies)<br>2) Detectable HBV DNA<br>3) HBeAg loss/ seroconversion<br>4) HBsAg loss/ seroconversion<br>5) ALT normalization<br>6) Incidence of resistance<br>Any composite outcomes of the above mentioned. |
| Search | • Prospective and retrospective cohort studies, including further analyses of RCTs |
| Review strategy | Results will be presented separately for the responses to different antiviral treatments and by HBeAg status (positive and negative). Children will also be presented separately. |

# C.6 Antiviral treatment

## C.6.1 Monotherapies and combinations

| **Review question: In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB?** | |
|---|---|
| Population | Children (2-16years), young people and adults with chronic hepatitis B virus infection |
| Intervention | Pegylated alpha-interferon (will be tested as intervention only for children)<br>Tenofovir<br>Entecavir<br>Adefovir<br>Lamivudine<br>Telbivudine<br>Emtricitabine (in combination with tenofovir) |
| Comparison | Pegylated alpha-interferon<br>Tenofovir<br>Entecavir<br>Adefovir<br>Lamivudine<br>Telbivudine<br>Emtricitabine (in combination with tenofovir)<br>Placebo |
| Outcomes | Post-treatment and follow up:<br>The most important outcomes<br>Log reduction of HBV DNA (indication of drug potency)<br>% with continuing detectable serum hepatitis B virus DNA (potential for add on combination)<br>Incidence of resistance % with ALT normalisation<br>% with HBeAg loss and/or seroconversion<br>% with HBsAg loss and/or seroconversion (long term outcome)<br><br>Quality of life measures () |
| Exclusion | Adult studies comparing any peg-interferon with placebo.<br>Studies comparing the same drug in different doses |
| Search strategy | The databases to be searched are Medline, Embase, The Cochrane Library.<br>All years.<br>Studies will be restricted to English language only |
| The review strategy | Study design:<br>- Systematic reviews of RCTs and/or RCTs (Phase III) only.<br>- Minimum duration of treatment = 1 year<br>- Minimum follow up= any<br>- Minimum total sample size = 50 (main group) |
| Analysis | Subgroups analysis:<br>- HBeAg positive/negative patients<br>-co-infected with hepatitis D and C virus |

| Review question: In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB? | |
|---|---|
| | - Children/adults<br>- By genotype |

## C.6.2 Sequential

| Review question: In people with CHB, what is the clinical and cost-effectiveness of sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB? | |
|---|---|
| Population | Children, young people and adults with chronic hepatitis B virus infection |
| Intervention | Add-on or switching from one drug to another<br>Pegylated alpha-interferon<br>Tenofovir<br>Entecavir<br>Adefovir<br>Lamivudine<br>Telbivudine<br>Emtricitabine (in combination with tenofovir) |
| Comparison | Pegylated alpha-interferon<br>Tenofovir<br>Entecavir<br>Adefovir<br>Lamivudine<br>Telbivudine<br>Emtricitabine (in combination with tenofovir) |
| Outcomes | The most important outcomes<br>Log reduction of HBV DNA (indication of drug potency)<br>% with continuing detectable serum hepatitis B virus DNA (potential for add on combination)<br>Incidence of resistance<br>% with ALT normalisation<br>% with HBeAg loss and/or seroconversion<br>% with HBsAg loss and/or seroconversion (long term outcome)<br>Quality of life measures () |
| Exclusion | -Studies comparing the same drug in different doses |
| Search strategy | The databases to be searched are Medline, Embase, The Cochrane Library.<br>All years.<br>Studies will be restricted to English language only |
| The review strategy | Study design:<br>- Systematic reviews of RCTs, RCTs. |
| Analysis | Subgroups analysis:<br><br>- Children/adults |

### C.6.3 Advanced cirrhosis and liver decompensation

| **Review question: In chronic hepatitis B infected people with cirrhosis, including those with liver decompensation, what is the clinical and cost effectiveness of antiviral treatment to prevent decompensation and/or liver transplantation?** | |
|---|---|
| Population | Adults with chronic hepatitis B virus infection and with compensated/decompensated cirrhosis |
| Intervention | Antiviral treatment (monotherapies or combinations)<br>Pegylated alpha-interferon<br>Tenofovir<br>Adefovir<br>Entecavir<br>Lamivudine<br>Telbivudine<br>Emtricitabine (in combination with tenofovir) |
| Comparison | - Placebo<br>Pegylated alpha-interferon<br>Tenofovir<br>Adefovir<br>Entecavir<br>Lamivudine<br>Telbivudine<br>Emtricitabine (in combination with tenofovir) |
| Outcomes | Log reduction of HBV DNA (indication of drug potency)<br>% with continuing detectable serum hepatitis B virus DNA (potential for add on combination)<br>Incidence of resistance<br>Quality of life measures<br>Incidence of hepatic decompensation and/or liver transplantation<br>Incidence of hepatocellular carcinoma<br>All cause mortality |
| Exclusion | |
| Search strategy | The databases to be searched are Medline, Embase, The Cochrane Library.<br>All years.<br>Studies will be restricted to English language only. |
| The review strategy | Systematic reviews of RCTs<br>Only RCTs |
| Analysis | Subgroup analysis by stage of liver disease:<br>-<br>- compensated vs. decompensated patients |

### C.6.4 Prophylactic treatment

| **Review question** | **In people who are immunocompromised, what is the clinical and cost effectiveness of prophylactic treatment in reducing HBV reactivation and severity of flares?** |
|---|---|
| Objectives | To examine the efficacy of prophylactic treatments in reducing HBV reactivation and severity |

| | |
|---|---|
| | of flares among people who are immunocompromised. |
| Criteria | **Population:** Children, young people and adults with CHB infection who receive immunosuppressive (including all) or cytotoxic chemotherapy.<br><br>**Intervention:** Prophylactic treatment<br>- Lamivudine<br>- Adefovir<br>- Tenofovir<br>- Entecavir<br>- Emtricitabine plus tenofovir<br>- Telbivudine<br><br>**Comparison:**<br>- No treatment or placebo<br>- Lamivudine<br>- Adefovir<br>- Tenofovir<br>- Entecavir<br>-Emtricitabine plus tenofovir<br>-Telbivudine<br>**Outcomes**:<br>Primary outcomes:<br>1. Viral reactivation (HBV DNA)<br>2. Clinical reactivation (ALT)<br>3. Mortality<br>Secondary outcomes:<br>1. Hepatic failure<br>2. Cirrhosis<br>3. Hepatocellular carcinoma<br>4. Resistance<br>**Study design**:<br>Systematic reviews of trials, RCTs/non-randomised trials |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | Subgroup analyses:<br>1. HBsAg positive<br>2. HBsAg negative, anti-HBc positive and anti-HBs negative<br>3. HBsAg negative, anti-HBc positive and anti-HBs positive |

### C.6.5 Pregnancy

| **Protocol** | |
|---|---|
| Population | Pregnant and lactating women with chronic hepatitis B virus infection |
| Intervention | • Tenofovir<br>• Lamivudine<br>• Telbivudine |

| Protocol | |
|---|---|
| | • Emtricitabine plus tenofovir (tenofovir and emtricitabine)<br>• Entecavir<br>• Adefovir |
| Comparison | • No therapy/ control<br>• Tenofovir<br>• Lamivudine<br>• Telbivudine<br>• Emtricitabine plus tenofovir (tenofovir and emtricitabine)<br>• Entecavir<br>• Adefovir |
| Outcomes | Critical outcomes:<br>• newborn (0-9 months) and infant (9-15 first months) HBV DNA positivity<br>• newborn (0-9 months) and infant (9-15 first months) HBeAg seropositivity<br>• newborn (0-9 months) and infant (9-15 first months) HBsAg seropositivity<br>Secondary outcomes:<br>• Maternal HBV DNA reduction<br>• Congenital abnormalities<br>• Adverse events<br>• Incidence of resistance |

## C.7 Monitoring

| **Review question: How frequently should monitoring tests be done to ascertain virological, serological, biochemical response and resolution of fibrosis (HBeAg and antibody, HBsAg and antibody, ALT and transient elastography) and resistance (HBV DNA increase or virological breakthrough) in people with chronic hepatitis B?** | |
|---|---|
| Population | Children, young people and adults with chronic hepatitis B virus infection. |
| Prognostic factors (monitoring tests) | HBV DNA levels<br>HBeAg loss, seroconversion at different points in treatment<br>ALT normalization at different points in treatment<br>HBsAg seroconversion at different points in treatment<br>Incidence of resistance (HBV DNA increase or virological breakthrough) |
| Outcomes | - virological response (undetectable HBV DNA, viral breakthrough)<br>- serological response (HBeAg loss/seroconversion, HBsAg loss/seroconversion)<br>- biochemical response (ALT normalization, ALT flare)<br>- resolution of fibrosis<br>- side effects<br>- resistance<br>We will also consider composite outcomes coming from two or more ofthe above type of responses |
| Exclusion | Literature reviews, commentaries, opinion letter, consensus documents, natural history papers, studies focusing only on drug effectiveness |
| Search strategy | The databases to be searched are Medline, Embase, The Cochrane Library. |

| **Review question: How frequently should monitoring tests be done to ascertain virological, serological, biochemical response and resolution of fibrosis (HBeAg and antibody, HBsAg and antibody, ALT and transient elastography) and resistance (HBV DNA increase or virological breakthrough) in people with chronic hepatitis B?** | |
|---|---|
| | All years.<br>Studies will be restricted to English language only |
| The review strategy | Study design:<br>Systematic reviews of cohort studies<br>Cohorts (both prospective and retrospective)<br>Cross sectional studies |
| Analysis | Stratified analysis by disease state:<br>- HBeAg positive HBV DNA positive, ALT normal<br>-inactive carriers (HBeAg negative, ALT normal)<br>-patients on IFN treatment/ stopping rules<br>- patients on NUC treatment/ stopping rules (patients on different NUCs will be presented separately_<br>-patients off treatment<br>- children with CHB |

## C.8 Surveillance

| **Review question** | **When and how frequently should surveillances testing be offered to detect early hepatocellular carcinoma in people with chronic hepatitis B?** |
|---|---|
| Objectives | To examine the different time intervals of surveillance testing to detect early hepatocellular carcinoma in people with chronic hepatitis B |
| Criteria | **Population:** Children, young people and adults with CHB infection, in particular those with cirrhosis<br><br>**Intervention:**<br><br>Ultrasound and/or serum alpha-fetoprotein assay at:<br>- 12 monthly<br>- 6 monthly<br>- 3 monthly<br><br>**Comparison:**<br><br>- Ultrasound and/or serum alpha-fetoprotein assay at:<br>- 12 monthly<br>- 6 monthly<br>- 3 monthly<br><br>**Outcomes**:<br>• Lesion or hepatocellular carcinoma ≤1, 2 and 3cm in diameter<br>• Survival rate<br>• All-cause mortality<br>• Liver cancer staging<br>• Hepatocellular carcinoma |

| | |
|---|---|
| | • Morbidity (end stage liver failure)<br><br>Exclusion: surveillance vs. no surveillance<br><br>**Study design**:<br>Randomised trials, systematic reviews of observational studies, observational studies |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | Subgroup analyses:<br>4. Cirrhotic status (yes/no)<br>5. Children |

## C.9 In vitro

| **Review question** | **Is the efficacy of tenofovir difference between nucleos(t)ide naïve (wild type) and lamivudine resistance (LAM resistance mutation strains) populations?** |
|---|---|
| Objectives | To examine the efficacy of tenofovir in lamivudine associated resistance strains and wild type. |
| Criteria | **Population:** HBV DNA strains (Hep G2 cells), with (mutant strains) or without (wild type) mutations.<br><br>**Intervention:** Tenofovir<br><br>**Outcomes**:<br>• % of HBV protein production<br>• $EC_{50}$ concentrations<br>• $IC_{50}$ concentrations<br><br>Exclusion: studies that did not compare with wild type.<br><br>**Study design**:<br>Randomised trials, systematic reviews of observational studies, observational studies |
| Search | Medline, Embase, the Cochrane Library<br>All years.<br>Studies will be restricted to English language only. |
| Review strategy | In vivo/ in vitro studies will be included. |

# Appendix D: Literature Search Strategies

## Contents

| | |
|---|---|
| D.1.1 | Systematic reviews (SR) |
| D.1.2 | Randomized controlled trials (RCT) |
| D.1.3 | Observational studies |
| D.1.4 | Economic studies |
| D.1.5 | Quality of life studies |
| **Section D.2** | **Standard population search strategy**<br>This population was used for all search questions unless stated |
| **Section D.3** | **Searches for specific questions with intervention** (and population where different from D.2) |
| D.3.1 | Patient information |
| D.3.2 | Assessment and referral |
| D.3.3 | Assessment of liver disease in secondary specialist care |
| D.3.4 | Genotyping |
| D.3.5 | Antiviral treatment |
| D.3.6 | Monitoring |
| D.3.7 | Surveillance |
| **Section A.4** | **Economic searches** |
| D.4.1 | Economic reviews |
| D.4.2 | Quality of life reviews |

# Introduction

Search strategies used for the **Hepatitis B guideline** were run in accordance with the NICE Guidelines Manual 2009. All searches were run up to 10th October 2012 unless otherwise stated. Any studies added to the databases after this date were not included unless specifically stated in the text.

### Clinical Searches

Searches for **clinical reviews** were run in Medline (OVID), Embase (OVID), and the Cochrane Library (Wiley). Typically, searches were constructed in the following way:

- A PICO format was used for intervention searches. **Population** (P) terms were combined with **Intervention** (I) and sometimes **Comparison** (C) terms (as indicated in the tables under each individual question in Section D.3). An intervention can be a drug, a procedure or a diagnostic test. **Outcomes** (O) are rarely used in search strategies for interventions. Study type filters were added where appropriate (see D.1).

### Economic searches

Searches for **economic reviews** were run in Medline (Ovid), Embase (Ovid), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA were searched via the Cochrane (Wiley) interface. For Medline and Embase an economic filter was added to the standard population (see D.1.4). All other searches were conducted using only population terms.

## D.1.1 Systematic review (SR) search terms

**Medline search terms**

| | |
|---|---|
| 1. | Meta-Analysis/ |

| | |
|---|---|
| 2. | Meta-Analysis as Topic/ |
| 3. | (meta analy* or metanaly* or metaanaly*).ti,ab. |
| 4. | ((systematic* or evidence*) adj2 (review* or overview*)).ti,ab. |
| 5. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 6. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 7. | (search* adj4 literature).ab. |
| 8. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 9. | cochrane.jw. |
| 10. | or/1-9 |

**Embase search terms**

| | |
|---|---|
| 1. | Systematic review/ |
| 2. | Meta-analysis/ |
| 3. | (meta analy* or metanaly* or metaanaly*).ti,ab. |
| 4. | ((systematic or evidence) adj2 (review* or overview*)).ti,ab. |
| 5. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 6. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 7. | (search* adj4 literature).ab. |
| 8. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 9. | ((pool* or combined) adj2 (data or trials or studies or results)).ab. |
| 10. | cochrane.jw. |
| 11. | or/1-10 |

### D.1.2 Randomised controlled studies (RCTs) search terms

**Medline search terms**

| | |
|---|---|
| 1. | Randomized controlled trial.pt. |
| 2. | Controlled clinical trial.pt. |
| 3. | randomi#ed.ab. |
| 4. | placebo.ab. |
| 5. | randomly.ab. |
| 6. | Clinical Trials as topic.sh. |
| 7. | trial*.ti. |
| 8. | or/1-7 |

**Embase search terms**

| | |
|---|---|
| 1. | random*.ti,ab. |
| 2. | factorial*.ti,ab. |
| 3. | (crossover* or cross over*).ti,ab. |
| 4. | ((doubl* or singl*) adj blind*).ti,ab. |
| 5. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 6. | Crossover procedure/ |
| 7. | Single blind procedure/ |
| 8. | Randomized controlled trial/ |

| | |
|---|---|
| 9. | Rouble blind procedure/ |
| 10. | or/1-9 |

### D.1.3 Observational studies search terms

**Medline search terms**

| | |
|---|---|
| 1. | Epidemiologic studies/ |
| 2. | exp Case control studies/ |
| 3. | exp Cohort studies/ |
| 4. | Cross-sectional studies/ |
| 5. | case control.ti,ab. |
| 6. | (cohort adj (study or studies or analys*)).ti,ab. |
| 7. | ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab. |
| 8. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab. |
| 9. | or/1-8 |

**Embase search terms**

| | |
|---|---|
| 1. | Clinical study/ |
| 2. | exp Case control study/ |
| 3. | Family study/ |
| 4. | Longitudinal study/ |
| 5. | Retrospective study/ |
| 6. | Prospective study/ |
| 7. | Cross-sectional study/ |
| 8. | Cohort analysis/ |
| 9. | Follow-up/ |
| 10. | cohort*.ti,ab. |
| 11. | 9 and 10 |
| 12. | case control.ti,ab. |
| 13. | (cohort adj (study or studies or analys*)).ti,ab. |
| 14. | ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab. |
| 15. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab. |
| 16. | or/1-8,11-15 |

### D.1.4 Health economic search terms

**Medline search terms**

| | |
|---|---|
| 1. | exp Economics/ |
| 2. | exp "Costs and cost analysis"/ |
| 3. | (economic* or pharmacoeconomic*).ti,ab. |
| 4. | (cost or costs or costed or costly or costing* or price or prices or pricing).ti. |
| 5. | (expenditure or budget*).ti,ab. |
| 6. | cost-effective*.ti,ab. |
| 7. | (cost adj2 (effective* or reduce* or saving*)).ti,ab. |

| | |
|---|---|
| 8. | (value adj2 money).ti,ab. |
| 9. | Quality-adjusted life years/ |
| 10. | QALY*.ti,ab. |
| 11. | or/1-10 |
| 12. | ((metabolic or energy or oxygen) adj2 (expenditure or cost*)).ti,ab. |
| 13. | 11 not 12 |

**Embase search terms**

| | |
|---|---|
| 1. | exp Economic aspect/ |
| 2. | (economic* or pharmacoeconomic*).ti,ab. |
| 3. | (cost or costs or costed or costly or costing* or price or prices or pricing).ti. |
| 4. | (expenditure or budget*).ti,ab. |
| 5. | (value adj1 money).tw. |
| 6. | cost-effective*.ti,ab. |
| 7. | (cost adj2 (effective* or reduce*or saving*)).ti,ab. |
| 8. | (value adj2 money).ti,ab. |
| 9. | exp Quality Adjusted Life Years/ |
| 10. | QALY*.ti,ab. |
| 11. | or/1-10 |
| 12. | ((metabolic or energy or oxygen) adj2 (expenditure or cost*)).ti,ab. |
| 13. | 11 not 12 |

### D.1.5 Quality of life search terms

**Medline search terms**

| | |
|---|---|
| 1. | Quality-adjusted life years/ |
| 2. | Sickness impact profile/ |
| 3. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 4. | sickness impact profile.ti,ab. |
| 5. | disability adjusted life.ti,ab. |
| 6. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 7. | (euroqol* or eq5d* or eq 5d*).ti,ab. |
| 8. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 9. | (health utility* or utility score* or disutilit*).ti,ab. |
| 10. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 11. | health* year* equivalent*.ti,ab. |
| 12. | (hye or hyes).ti,ab. |
| 13. | rosser.ti,ab. |
| 14. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 15. | (sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab. |
| 16. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 17. | (sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab. |
| 18. | (sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab. |
| 19. | (sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab. |
| 20. | or/1-20 |

**Embase search terms**

| | |
|---|---|
| 1. | Quality adjusted life year/ |
| 2. | "Quality of life index"/ |
| 3. | Short form 12/ or Short form 20/ or Short form 36/ or Short form 8/ |
| 4. | Sickness impact profile/ |
| 5. | (quality adj2 (wellbeing or well being)).ti,ab. |
| 6. | sickness impact profile.ti,ab. |
| 7. | disability adjusted life.ti,ab. |
| 8. | (qal* or qtime* or qwb* or daly*).ti,ab. |
| 9. | (euroqol* or eq5d* or eq 5d*).ti,ab. |
| 10. | (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. |
| 11. | (health utility* or utility score* or disutilit*).ti,ab. |
| 12. | (hui or hui1 or hui2 or hui3).ti,ab. |
| 13. | health* year* equivalent*.ti,ab. |
| 14. | (hye or hyes).ti,ab. |
| 15. | rosser.ti,ab. |
| 16. | (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. |
| 17. | (sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab. |
| 18. | (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. |
| 19. | (sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab. |
| 20. | (sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab. |
| 21. | (sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab. |
| 22. | or/1-21 |

## D.2 Standard population search strategy

**Medline search terms**

| | |
|---|---|
| 1. | exp Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B antibodies/ |
| 4. | exp Hepatitis B antigens/ |
| 5. | exp Hepatitis D/ |
| 6. | Hepatitis delta antigens/ |
| 7. | Hepatitis delta virus/ |
| 8. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 9. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 10. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 11. | or/1-10 |
| 12. | limit 11 to english language |
| 13. | Letter/ |
| 14. | Editorial/ |
| 15. | News/ |
| 16. | exp Historical article/ |
| 17. | Anecdotes as Topic/ |
| 18. | Comment/ |
| 19. | Case report/ |

| | |
|---|---|
| 20. | (letter or comment*).ti. |
| 21. | or/13-20 |
| 22. | 21 not (randomized controlled trial/ or random*.ti,ab.) |
| 23. | animals/ not humans/ |
| 24. | exp Animals, Laboratory/ |
| 25. | exp Animal experimentation/ |
| 26. | exp Models, Animal/ |
| 27. | exp Rodentia/ |
| 28. | (rat or rats or mouse or mice).ti. |
| 29. | or/22-28 |
| 30. | 12 not 29 |

**Embase search terms**

| | |
|---|---|
| 1. | Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B virus X protein/ |
| 4. | exp Hepatitis B antibody/ |
| 5. | exp Hepatitis B antigen/ |
| 6. | Delta agent hepatitis/ |
| 7. | Hepatitis delta virus/ |
| 8. | Hepatitis delta antigen/ |
| 9. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 10. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 11. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 12. | or/1-11 |
| 13. | limit 12 to english language |
| 14. | Letter.pt. or Letter/ |
| 15. | Note.pt. |
| 16. | Editorial.pt. |
| 17. | Case report/ or Case study/ |
| 18. | (letter or comment*).ti. |
| 19. | or/14-18 |
| 20. | 19 not (randomized controlled trial/ or random*.ti,ab.) |
| 21. | Animal/ not Human/ |
| 22. | Nonhuman/ |
| 23. | exp Animal experiment/ |
| 24. | exp Experimental animal/ |
| 25. | Animal model/ |
| 26. | exp Rodent/ |
| 27. | (rat or rats or mouse or mice).ti. |
| 28. | or/20-27 |
| 29. | 13 not 28 |

**Cochrane search terms**

| | |
|---|---|
| #1 | MeSH descriptor Hepatitis B explode all trees |
| #2 | MeSH descriptor Hepatitis B virus, this term only |

| | |
|---|---|
| #3 | MeSH descriptor Hepatitis B Antibodies, this term only |
| #4 | MeSH descriptor Hepatitis B Antigens explode all trees |
| #5 | (hepatitis NEAR/2 (B OR D OR delta)):ti,ab |
| #6 | ("anti HB*" or antiHB* or HBeAg* or "HBe Ag*" or HbsA* or HBcA*):ti,ab |
| #7 | ((HBV or CHB or hep B or hepB or HDV) NOT (heart NEXT block)):ti,ab |
| #8 | MeSH descriptor Hepatitis D explode all trees |
| #9 | MeSH descriptor Hepatitis delta Antigens, this term only |
| #10 | MeSH descriptor Hepatitis Delta Virus, this term only |
| #11 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) |

# D.3 Searches by specific questions

## D.3.1 Patient information

### Q. What are the information needs of patients with CHB and their carers?

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Patient information | None | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | ((client* or patient* or user* or carer* or consumer* or customer* or health) adj5 (information* or educat* or knowledge)).ti,ab,hw. |
| 2. | (information* adj3 (need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab,hw. |
| 3. | ((patient* or user* or carer* or consumer* or customer* or health) adj3 (literature or leaflet* or booklet* or pamphlet* or questionnaire* or survey* or handout* or internet or website* or consult* or interview*)).ti,ab. |
| 4. | Telemedicine/ |
| 5. | Interview/ |
| 6. | Telephone/ |
| 7. | Publications/ |
| 8. | Pamphlets/ |
| 9. | Internet/ |
| 10. | or/1-9 |

**Embase search terms**

| | |
|---|---|
| 1. | ((client* or patient* or user* or carer* or consumer* or customer* or health) adj5 (information* or educat* or knowledge)).ti,ab,hw. |
| 2. | (information* adj3 (need* or requirement* or support* or seek* or access* or disseminat*)).ti,ab,hw. |
| 3. | ((patient* or user* or carer* or consumer* or customer* or health) adj3 (literature or leaflet* or booklet* or pamphlet* or questionnaire* or survey* or handout* or internet or website* or consult* or interview*)).ti,ab. |
| 4. | exp Telehealth/ |
| 5. | exp Interview/ |
| 6. | Telephone/ |
| 7. | Publication/ |
| 8. | Internet/ |

| | |
|---|---|
| 9. | or/1-8 |

**Cochrane search terms**

| | |
|---|---|
| #1. | ((client* or patient* or user* or carer* or consumer* or customer* or health) NEAR/5 (information* or educat* or knowledge)):ti,ab |
| #2. | (information* NEAR/3 (need* or requirement* or support* or seek* or access* or disseminat*)):ti,ab |
| #3. | ((patient* or user* or carer* or consumer* or customer* or health) NEAR/3 (literature or leaflet* or booklet* or pamphlet* or questionnaire* or survey* or handout* or internet or website* or consult* or interview*)):ti,ab |
| #4. | MeSH descriptor Patient Acceptance of Health Care, this term only |
| #5. | MeSH descriptor Patient Education as Topic, this term only |
| #6. | MeSH descriptor Patient Preference, this term only |
| #7. | MeSH descriptor Patient Satisfaction, this term only |
| #8. | MeSH descriptor Consumer Health Information explode all trees |
| #9. | MeSH descriptor Health Knowledge, Attitudes, Practice, this term only |
| #10. | MeSH descriptor Telemedicine, this term only |
| #11. | MeSH descriptor Access to Information, this term only |
| #12. | MeSH descriptor Information Dissemination, this term only |
| #13. | MeSH descriptor Information Seeking Behavior, this term only |
| #14. | MeSH descriptor Pamphlets, this term only |
| #15. | MeSH descriptor Internet, this term only |
| #16. | MeSH descriptor Interviews as Topic explode all trees |
| #17. | MeSH descriptor Telephone, this term only |
| #18. | MeSH descriptor Telemedicine, this term only |
| #19. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) |

## D.3.2 Assessment and referral

### D.3.2.1 Threshold for referral

**Q. What are the thresholds (e.g. HBV DNA and ALT levels) for referral to specialist services after initial diagnosis and pre-therapeutic tests of CHB?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Clinical thresholds for referral | RCTs, SRs and Observational studies [Medline and Embase only] | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Alanine transaminase/ |
| 2. | DNA, viral/ |
| 3. | Biological markers/ |
| 4. | Carrier state/ |
| 5. | Viral load/ |

| | |
|---|---|
| 6. | ((ALT or alanine or DNA or HBsAg) adj4 (level* or baseline* or raise* or increas* or elevat* or normal)).ti,ab. |
| 7. | ((inactive or asymptomatic or healthy) adj3 carrier*).ti,ab. |
| 8. | or/1-7 |
| 9. | Predictive value of tests/ |
| 10. | Disease progression/ |
| 11. | Likelihood function/ |
| 12. | exp "Sensitivity and specificity"/ |
| 13. | prognos*.ti,ab,hw. |
| 14. | (progress* adj3 (disease or predict*)).ti,ab. |
| 15. | (candidate* adj2 (therapy or treatment or antiviral*)).ti,ab. |
| 16. | (cut off or cutoff or threshold* or staging).ti,ab. |
| 17. | (select* adj2 (patient* or treatment or therapy)).ti,ab. |
| 18. | ((indicat* or start* or initiat*) adj3 (treatment or therapy)).ti,ab. |
| 19. | predict*.ti,ab. |
| 20. | natural history.ti,ab. |
| 21. | (sensitivity or specificity).ti,ab. |
| 22. | ((pre test or pretest or post test) adj probability).ti,ab. |
| 23. | (predictive value* or PPV or NPV).ti,ab. |
| 24. | likelihood ratio*.ti,ab. |
| 25. | (ROC curve* or AUC).ti,ab. |
| 26. | ((treatment or management) adj3 (algorithm* or plan* or strateg*)).ti,ab. |
| 27. | or/9-26 |
| 28. | 8 and 27 |

**Embase search terms**

| | |
|---|---|
| 1. | Alanine aminotransferase/ |
| 2. | Virus DNA/ |
| 3. | Biological marker/ |
| 4. | Virus load/ |
| 5. | ((ALT or alanine or DNA or HBsAg) adj4 (level* or baseline* or raise* or increas* or elevat* or normal)).ti,ab. |
| 6. | ((inactive or asymptomatic or healthy) adj3 carrier*).ti,ab. |
| 7. | or/1-6 |
| 8. | Predictive value/ |
| 9. | Disease course/ |
| 10. | "Sensitivity and specificity"/ |
| 11. | prognos*.ti,ab,hw. |
| 12. | (progress* adj3 (disease or predict*)).ti,ab. |
| 13. | (candidate* adj2 (therapy or treatment or antiviral*)).ti,ab. |
| 14. | (cut off or cutoff or threshold* or staging).ti,ab. |
| 15. | (select* adj2 (patient* or treatment or therapy)).ti,ab. |
| 16. | predict*.ti,ab. |
| 17. | natural history.ti,ab. |
| 18. | (sensitivity or specificity).ti,ab. |
| 19. | ((pre test or pretest or post test) adj probability).ti,ab. |

| | |
|---|---|
| 20. | (predictive value* or PPV or NPV).ti,ab. |
| 21. | likelihood ratio*.ti,ab. |
| 22. | (ROC curve* or AUC).ti,ab. |
| 23. | ((treatment or management) adj3 (algorithm* or plan* or strateg*)).ti,ab. |
| 24. | or/8-23 |
| 25. | 7 and 24 |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Alanine Transaminase, this term only |
| #2. | MeSH descriptor DNA, Viral, this term only |
| #3. | MeSH descriptor Biological Markers, this term only |
| #4. | MeSH descriptor Carrier State, this term only |
| #5. | MeSH descriptor Viral Load, this term only |
| #6. | ((ALT or alanine or DNA or HBsAg) NEAR/4 (level* or baseline* or raise* or increas* or elevat* or normal)):ti,ab |
| #7. | ((inactive or asymptomatic or healthy) NEAR/3 carrier*):ti,ab |
| #8. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) |
| #9. | MeSH descriptor Sensitivity and Specificity explode all trees |
| #10. | MeSH descriptor Disease Progression, this term only |
| #11. | MeSH descriptor Likelihood Functions, this term only |
| #12. | MeSH descriptor Prognosis, this term only |
| #13. | (prognos*):ti,ab |
| #14. | (progress* NEAR/3 (disease or predict*)):ti,ab |
| #15. | (candidate* NEAR/2 (therapy or treatment or antiviral*)):ti,ab |
| #16. | ("cut off" or cutoff or threshold* or staging):ti,ab |
| #17. | (select* NEAR/2 (patient* or treatment or therapy)):ti,ab |
| #18. | ((indicat* or start* or initiat*) NEAR/3 (treatment or therapy)):ti,ab |
| #19. | predict*:ti,ab |
| #20. | "natural history":ti,ab |
| #21. | (sensitivity or specificity):ti,ab |
| #22. | (("pre test" or pretest or "post test") NEXT probability):ti,ab |
| #23. | ((predictive NEXT value*) or PPV or NPV):ti,ab |
| #24. | "likelihood ratio":ti,ab |
| #25. | ("ROC curve" or AUC):ti,ab |
| #26. | ((treatment or management) NEAR/3 (algorithm* or plan* or strateg*)):ti,ab |
| #27. | (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) |
| #28. | (#8 AND #27) |

### D.3.2.2 Healthcare setting

**Q. What is the most appropriate healthcare setting to initiate pre-therapeutic tests (HBeAg, quantitative HBsAg, quantitative HBV DNA, anti HCV, anti HDV, anti HIV) in people who are HBsAg positive?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Setting for diagnostic tests | None | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Algorithm/ |
| 2. | Practice guideline/ |
| 3. | Health planning guidelines/ |
| 4. | Patient care planning/ |
| 5. | Patient care management/ |
| 6. | Case management/ |
| 7. | Comprehensive health care/ |
| 8. | Critical pathways/ |
| 9. | (guideline* or guidance or protocol or recommendation* or consensus or algorithm).ti. |
| 10. | or/1-9 |
| 11. | (immuni#ation* or vaccin*).ti. |
| 12. | 10 not 11 |
| 13. | limit 12 to yr="2005 -Current" |
| 14. | "Referral and consultation"/ |
| 15. | Patient selection/ |
| 16. | Physician's practice patterns/ |
| 17. | Clinical competence/ |
| 18. | Health knowledge, attitudes, practice/ |
| 19. | Medical audit/ |
| 20. | Guideline adherence/ |
| 21. | (candidate* adj3 (therapy or treatment)).ti,ab. |
| 22. | (cut off or cutoff or threshold* or test* or assess* or referr*).ti,ab. |
| 23. | (select* adj3 (patient* or treatment or therapy)).ti,ab. |
| 24. | ((indicat* or start* or initiat*) adj3 (treatment or therapy)).ti,ab. |
| 25. | ((treatment or management or care or clinical) adj3 (algorithm* or plan* or strateg* or pathway* or plan* or case)).ti,ab. |
| 26. | (competen* or audit* or knowledge or educat*).ti,ab. |
| 27. | or/14-26 |
| 28. | Primary health care/ |
| 29. | exp General practice/ |
| 30. | (GP* or hepatologist* or gastroenterologist* or gastro enterologist*).ti,ab. |
| 31. | ((primary or general or specialist or family or secondary or tertiary or consultant or hepatology or gastroenterology or gastro enterology) adj5 (care or service* or practice or practitioner* or physician* or doctor* or consultant* or nurse* or treatment or center* or centre* or setting or clinic*)).ti,ab. |
| 32. | or/28-31 |
| 33. | 13 or (27 and 32) |

**Embase search terms**

| | |
|---|---|
| 1. | exp Practice guideline/ |
| 2. | Health care planning/ |
| 3. | Integrated health care system/ |
| 4. | Algorithm/ |
| 5. | (guideline* or guidance or protocol or recommendation* or consensus or algorithm).ti. |
| 6. | or/1-5 |
| 7. | limit 6 to yr="2005 -Current" |

| | |
|---|---|
| 8. | (immuni#ation* or vaccin*).ti. |
| 9. | 7 not 8 |
| 10. | exp Primary health care/ |
| 11. | General practice/ |
| 12. | General practitioner/ |
| 13. | Medical specialist/ |
| 14. | (GP* or hepatologist* or gastroenterologist* or gastro enterologist*).ti,ab. |
| 15. | ((primary or general or specialist or family or secondary or tertiary or consultant or hepatology or gastroenterology or gastro enterology) adj5 (care or service* or practice or practitioner* or physician* or doctor* or consultant* or nurse* or treatment or center* or centre* or setting or clinic*)).ti,ab. |
| 16. | or/10-15 |
| 17. | Patient referral/ |
| 18. | Patient selection/ |
| 19. | Clinical competence/ |
| 20. | Clinical practice/ |
| 21. | Medical audit/ |
| 22. | Professional knowledge/ |
| 23. | (candidate* adj3 (therapy or treatment)).ti,ab. |
| 24. | (cut off or cutoff or threshold* or test* or assess* or referr*).ti,ab. |
| 25. | (select* adj3 (patient* or treatment or therapy)).ti,ab. |
| 26. | ((indicat* or start* or initiat*) adj3 (treatment or therapy)).ti,ab. |
| 27. | ((treatment or management or care or clinical) adj3 (algorithm* or plan* or strateg* or pathway* or plan* or case)).ti,ab. |
| 28. | (competen* or audit* or knowledge or educat*).ti,ab. |
| 29. | or/17-28 |
| 30. | 9 or (16 and 29) |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Referral and Consultation, this term only |
| #2. | MeSH descriptor Algorithms, this term only |
| #3. | MeSH descriptor Patient Care Planning explode all trees |
| #4. | MeSH descriptor Comprehensive Health Care, this term only |
| #5. | MeSH descriptor Patient Selection, this term only |
| #6. | MeSH descriptor Physician's Practice Patterns, this term only |
| #7. | MeSH descriptor Clinical Competence, this term only |
| #8. | MeSH descriptor Health Knowledge, Attitudes, Practice, this term only |
| #9. | MeSH descriptor Medical Audit, this term only |
| #10. | MeSH descriptor Guideline Adherence, this term only |
| #11. | (candidate* near/3 (therapy or treatment)):ti,ab |
| #12. | (cut off or cutoff or threshold* or test* or assess* or referr*):ti,ab |
| #13. | (select* near/3 (patient* or treatment or therapy)):ti,ab |
| #14. | ((indicat* or start* or initiat*) near/3 (treatment or therapy)):ti,ab |
| #15. | ((treatment or management or care or clinical) near/3 (algorithm* or plan* or strateg* or pathway* or plan* or case)):ti,ab |
| #16. | (competen* or audit* or knowledge or educat*):ti,ab |
| #17. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 |

| | |
|---|---|
| | OR #15 OR #16) |
| #18. | MeSH descriptor Primary Health Care, this term only |
| #19. | MeSH descriptor General Practice explode all trees |
| #20. | MeSH descriptor General Practitioners, this term only |
| #21. | (GP* or hepatologist* or gastroenterologist* or "gastro enterologist" or "gastro enterologists"):ti,ab |
| #22. | ((primary or general or specialist or family or secondary or tertiary or consultant or hepatology or gastroenterology or gastro enterology) near/5 (care or service* or practice or practitioner* or physician* or doctor* or consultant* or nurse* or treatment or center* or centre* or setting or clinic*)):ti,ab |
| #23. | (#18 OR #19 OR #20 OR #21 OR #22) |
| #24. | (#17 AND #23) |

### D.3.3 Assessment of liver disease in secondary specialist care

**Q. What is the diagnostic accuracy of non-invasive methods (e.g. transient elastography, serum fibrosis markers, aspartate aminotransferase / platelet ration index, magnetic resonance spectroscopy) to assess severity of necro-inflammatory activity and liver fibrosis?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Comparison | Study filter used | Date parameters |
|---|---|---|---|---|
| Hepatitis B and (cirrhosis or fibrosis)* | Diagnostic accuracy | | RCTs, SRs and Observational studies [Medline and Embase only] | All years - 10/10/2012 |

*Standard population restricted to fibrosis/cirrhosis/necro-inflammation.

**Medline search terms**

| | |
|---|---|
| 1. | exp Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B antibodies/ |
| 4. | exp Hepatitis B antigens/ |
| 5. | exp Hepatitis D/ |
| 6. | Hepatitis delta antigens/ |
| 7. | Hepatitis delta virus/ |
| 8. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 9. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 10. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 11. | or/1-10 |
| 12. | limit 11 to english language |
| 13. | Letter/ |
| 14. | Editorial/ |
| 15. | News/ |
| 16. | exp Historical article/ |
| 17. | Anecdotes as Topic/ |
| 18. | Comment/ |
| 19. | Case report/ |
| 20. | (letter or comment*).ti. |

| | |
|---|---|
| 21. | or/13-20 |
| 22. | 21 not (randomized controlled trial/ or random*.ti,ab.) |
| 23. | Animals/ not Humans/ |
| 24. | exp Animals, Laboratory/ |
| 25. | exp Animal experimentation/ |
| 26. | exp Models, Animal/ |
| 27. | exp Rodentia/ |
| 28. | (rat or rats or mouse or mice).ti. |
| 29. | or/22-28 |
| 30. | 12 not 29 |
| 31. | Liver cirrhosis/ |
| 32. | (cirrh* or fibro* or necro*).ti,ab. |
| 33. | 30 and (31 or 32) |
| 34. | exp "Sensitivity and specificity"/ |
| 35. | (sensitivity or specificity).ti,ab. |
| 36. | ((pre test or pretest or post test) adj probability).ti,ab. |
| 37. | (predictive value* or PPV or NPV).ti,ab. |
| 38. | likelihood ratio*.ti,ab. |
| 39. | Likelihood function/ |
| 40. | (ROC curve* or AUC).ti,ab. |
| 41. | (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. |
| 42. | gold standard.ab. |
| 43. | Disease progression/ |
| 44. | (degree* or stage* or staging or grade* or grading or assess* or score or scoring).ti,ab. |
| 45. | ((clinical or disease) adj3 (progress* or severity)).ti,ab. |
| 46. | or/34-45 |
| 47. | 33 and 46 |

**Embase search terms**

| | |
|---|---|
| 1. | Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B virus X protein/ |
| 4. | exp Hepatitis B antibody/ |
| 5. | exp Hepatitis B antigen/ |
| 6. | Delta agent hepatitis/ |
| 7. | Hepatitis delta virus/ |
| 8. | Hepatitis delta antigen/ |
| 9. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 10. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 11. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 12. | or/1-11 |
| 13. | limit 12 to english language |
| 14. | Letter.pt. or Letter/ |
| 15. | Note.pt. |
| 16. | Editorial.pt. |

| | |
|---|---|
| 17. | Case report/ or Case study/ |
| 18. | (letter or comment*).ti. |
| 19. | or/14-18 |
| 20. | 19 not (randomized controlled trial/ or random*.ti,ab.) |
| 21. | Animal/ not Human/ |
| 22. | Nonhuman/ |
| 23. | exp Animal experiment/ |
| 24. | exp Experimental animal/ |
| 25. | Animal model/ |
| 26. | exp Rodent/ |
| 27. | (rat or rats or mouse or mice).ti. |
| 28. | or/20-27 |
| 29. | 13 not 28 |
| 30. | Liver fibrosis/ |
| 31. | Liver cirrhosis/ |
| 32. | (cirrho* or fibro* or necro*).ti,ab. |
| 33. | Decompensated liver cirrhosis/ |
| 34. | or/30-33 |
| 35. | exp "Sensitivity and specificity"/ |
| 36. | (sensitivity or specificity).ti,ab. |
| 37. | ((pre test or pretest or post test) adj probability).ti,ab. |
| 38. | (predictive value* or PPV or NPV).ti,ab. |
| 39. | likelihood ratio*.ti,ab. |
| 40. | (ROC curve* or AUC).ti,ab. |
| 41. | (diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab. |
| 42. | Diagnostic accuracy/ |
| 43. | Diagnostic test accuracy study/ |
| 44. | gold standard.ab. |
| 45. | Disease course/ |
| 46. | ((clinical or disease) adj3 (progress* or severity)).ti,ab. |
| 47. | (degree* or stage* or staging or grade* or grading or assess* or score* or scoring).ti,ab. |
| 48. | or/35-47 |
| 49. | 29 and 34 and 48 |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Hepatitis B explode all trees |
| #2. | MeSH descriptor Hepatitis B virus, this term only |
| #3. | MeSH descriptor Hepatitis B Antibodies, this term only |
| #4. | MeSH descriptor Hepatitis B Antigens explode all trees |
| #5. | (hepatitis NEAR/2 (B OR D OR delta)):ti,ab |
| #6. | ("anti HB*" or antiHB* or HBeAg* or "HBe Ag*" or HbsA* or HBcA*):ti,ab |
| #7. | ((HBV or CHB or hep B or hepB or HDV) NOT (heart NEXT block)):ti,ab |

| | |
|---|---|
| #8. | MeSH descriptor Hepatitis D explode all trees |
| #9. | MeSH descriptor Hepatitis delta Antigens, this term only |
| #10. | MeSH descriptor Hepatitis Delta Virus, this term only |
| #11. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) |
| #12. | MeSH descriptor Sensitivity and Specificity explode all trees |
| #13. | (sensitivity or specificity):ti,ab |
| #14. | (("pre test" or pretest or "post test") NEXT probability):ti,ab |
| #15. | ("predictive value*" or PPV or NPV):ti,ab |
| #16. | likelihood NEXT ratio*:ti,ab |
| #17. | MeSH descriptor Likelihood Functions, this term only |
| #18. | ("ROC curve*" or AUC):ti,ab |
| #19. | (diagnos* NEAR/2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)):ti,ab |
| #20. | gold NEXT standard:ab |
| #21. | MeSH descriptor Disease Progression, this term only |
| #22. | ((clinical or disease) near/3 (progress* or severity)):ti,ab |
| #23. | (degree* or stage* or staging or grade* or grading or assess* or score* or scoring):ti,ab |
| #24. | (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23) |
| #25. | (#11 AND #24) |
| #26. | MeSH descriptor Liver Cirrhosis, this term only |
| #27. | (cirrho* or fibro* or necro*):ti,ab |
| #28. | (#26 OR #27) |
| #29. | (#25 AND #28) |

### D.3.4 Genotyping

**Q. Does genotype testing enable better decisions on which antiviral treatment to offer and is it cost effective?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention | Comparison | Study filter used | Date parameters |
|---|---|---|---|---|
| Hepatitis B | Antivirals AND Genotype | | RCTs and Observational Studies [Medline and Embase only] | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Antiviral agents/ |
| 2. | (antiviral* or anti viral*).ti,ab. |
| 3. | exp Interferon type I/ |
| 4. | Lamivudine/ |
| 5. | (interferon* or peginterferon*).ti,ab. |
| 6. | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir).ti,ab. |
| 7. | (ETV or TDF or FTC or ADV or 3TC or IFN* or pegIFN*).ti,ab. |
| 8. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 9. | or/1-8 |
| 10. | Genotype/ |

| | |
|---|---|
| 11. | (genotyp* or subgenotyp*).ti,ab. |
| 12. | 9 and (10 or 11) |

**Embase search terms**

| | |
|---|---|
| 1. | Antiviral therapy/ |
| 2. | Antivirus agent/ |
| 3. | (antiviral* or anti viral*).ti,ab. |
| 4. | exp Recombinant interferon/ |
| 5. | Lamivudine/ |
| 6. | Telbivudine/ |
| 7. | Entecavir/ |
| 8. | Emtricitabine/ |
| 9. | tenofovir.hw,ti,ab. |
| 10. | adefovir.hw,ti,ab. |
| 11. | (interferon* or peginterferon*).ti,ab. |
| 12. | (lamivudine or telbivudine or entecavir or emtricitabine).ti,ab. |
| 13. | (ETV or TDF or FTC or ADV or 3TC or IFN* or pegIFN*).ti,ab. |
| 14. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 15. | or/1-14 |
| 16. | Genotype/ |
| 17. | (genotyp* or subgenotyp*).ti,ab. |
| 18. | 15 and (16 or 17) |

**Cochrane search terms**

| | |
|---|---|
| #1 | MeSH descriptor Interferon Type I explode all trees |
| #2 | MeSH descriptor Lamivudine, this term only |
| #3 | (interferon* or peginterferon*):ti,ab |
| #4 | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir):ti,ab |
| #5 | (ETV or TDF or FTC or ADV or 3TC or IFN or pegIFN):ti,ab |
| #6 | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys):ti,ab |
| #7 | MeSH descriptor Antiviral Agents, this term only |
| #8 | (antiviral* or anti viral*):ti,ab |
| #9 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8) |
| #11 | MeSH descriptor Genotype, this term only |
| #12 | (genotyp* or subgenotyp*):ti,ab |
| #13 | (#11 OR #12) |
| #14 | (#9 AND #13) |

## D.3.5 Antivirals

### D.3.5.1 Antiviral treatment choice

Two searches (S1 and S2) covered the following three questions:

**Q1. In people with CHB, what is the clinical and cost effectiveness of pharmacological monotherapies and combinations in achieving remission of the activity of CHB?**

**Q2. In people with CHB, what is the clinical and cost-effectiveness of sequential drug therapy (add-on or switching monotherapies) in achieving remission of the activity of CHB?**

**Q3. In people with CHB and with advanced cirrhosis, including those with liver decompensation, what is the clinical and cost effectiveness of antiviral treatment to prevent recurrent reactivation and liver transplantation?**

### S1: All antivirals with standard population

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Pegylated interferon OR lamivudine OR telbivudine OR entecavir monohydrate OR tenofovir disoproxil OR adefovir dipivoxil OR ribavirin | RCTs and SRs [Medline and Embase only] | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Antiviral agents/ |
| 2. | (antiviral* or anti viral*).ti,ab. |
| 3. | exp Interferon type I/ |
| 4. | Lamivudine/ |
| 5. | Ribavirin/ |
| 6. | (interferon* or peginterferon*).ti,ab. |
| 7. | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir or ribavirin).ti,ab. |
| 8. | (ETV or TDF or FTC or ADV or 3TC or IFN* or pegIFN*).ti,ab. |
| 9. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 10. | or/1-9 |

**Embase search terms**

| | |
|---|---|
| 1. | Antiviral therapy/ |
| 2. | Antivirus agent/ |
| 3. | (antiviral* or anti viral*).ti,ab. |
| 4. | exp Recombinant interferon/ |
| 5. | Lamivudine/ |
| 6. | Telbivudine/ |
| 7. | Entecavir/ |
| 8. | Emtricitabine/ |
| 9. | tenofovir.hw,ti,ab. |
| 10. | adefovir.hw,ti,ab. |
| 11. | ribavirin.hw,ti,ab. |
| 12. | (interferon* or peginterferon*).ti,ab. |
| 13. | (lamivudine or telbivudine or entecavir or emtricitabine).ti,ab. |
| 14. | (ETV or TDF or FTC or ADV or 3TC or IFN* or pegIFN*).ti,ab. |
| 15. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 16. | or/1-15 |

**Cochrane search terms**

| | |
|---|---|
| #1 | MeSH descriptor Antiviral Agents, this term only |
| #2 | (antiviral* or anti viral*):ti,ab |
| #3 | MeSH descriptor Interferon Type I explode all trees |
| #4 | MeSH descriptor Lamivudine, this term only |
| #5 | MeSH descriptor Ribavirin, this term only |
| #6 | (interferon* or peginterferon*):ti,ab |
| #7 | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir or ribavirin):ti,ab |
| #8 | (ETV or TDF or FTC or ADV or 3TC or IFN or pegIFN):ti,ab |
| #9 | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys):ti,ab |
| #10 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) |

### S2: Lamivudine with restricted population

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B and viral resistance* | Lamivudine | Observational [Medline and Embase only] | All years - 10/10/2012 |

*Standard population restricted. Search was not run in Cochrane as only observational studies included.

### Medline search terms

| | |
|---|---|
| 1. | exp Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B antibodies/ |
| 4. | exp Hepatitis B antigens/ |
| 5. | exp Hepatitis D/ |
| 6. | Hepatitis delta antigens/ |
| 7. | Hepatitis delta virus/ |
| 8. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 9. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 10. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 11. | or/1-10 |
| 12. | limit 11 to english language |
| 13. | Letter/ |
| 14. | Editorial/ |
| 15. | News/ |
| 16. | exp Historical article/ |
| 17. | Anecdotes as topic/ |
| 18. | Comment/ |
| 19. | Case report/ |
| 20. | (letter or comment*).ti. |
| 21. | or/13-20 |
| 22. | 21 not (Randomized controlled trial/ or random*.ti,ab.) |
| 23. | Animals/ not Humans/ |
| 24. | exp Animals, Laboratory/ |
| 25. | exp Animal experimentation/ |

| | |
|---|---|
| 26. | exp Models, Animal/ |
| 27. | exp Rodentia/ |
| 28. | (rat or rats or mouse or mice).ti. |
| 29. | or/22-28 |
| 30. | 12 not 29 |
| 31. | exp Drug resistance, Viral/ |
| 32. | Drug resistance/ |
| 33. | resistan*.ti,ab. |
| 34. | or/31-33 |
| 35. | 30 and 34 |
| 36. | (lamivudine or LMV or 3TC or zeffix).ti,ab,hw. |
| 37. | 35 and 36 |
| 38. | Epidemiologic studies/ |
| 39. | exp Case control studies/ |
| 40. | exp Cohort studies/ |
| 41. | Cross-sectional studies/ |
| 42. | case control.ti,ab. |
| 43. | (cohort adj (study or studies or analys*)).ti,ab. |
| 44. | ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab. |
| 45. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab. |
| 46. | or/38-45 |
| 47. | 37 and 46 |

**Embase search terms**

| | |
|---|---|
| 1. | Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B virus X protein/ |
| 4. | exp Hepatitis B antibody/ |
| 5. | exp Hepatitis B antigen/ |
| 6. | Delta agent hepatitis/ |
| 7. | Hepatitis delta virus/ |
| 8. | Hepatitis delta antigen/ |
| 9. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 10. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 11. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 12. | or/1-11 |
| 13. | limit 12 to english language |
| 14. | Letter.pt. or Letter/ |
| 15. | Note.pt. |
| 16. | Editorial.pt. |
| 17. | Case report/ or Case study/ |
| 18. | (letter or comment*).ti. |
| 19. | or/14-18 |
| 20. | 19 not (Randomized controlled trial/ or random*.ti,ab.) |

| | |
|---|---|
| 21. | Animal/ not Human/ |
| 22. | Nonhuman/ |
| 23. | exp Animal experiment/ |
| 24. | exp Experimental animal/ |
| 25. | Animal model/ |
| 26. | exp Rodent/ |
| 27. | (rat or rats or mouse or mice).ti. |
| 28. | or/20-27 |
| 29. | 13 not 28 |
| 30. | Drug resistance/ |
| 31. | Antiviral resistance/ |
| 32. | resistan*.ti,ab. |
| 33. | or/30-32 |
| 34. | 29 and 33 |
| 35. | (lamivudine or 3TC or LMV or zeffix).ti,ab,hw. |
| 36. | 34 and 35 |
| 37. | Clinical study/ |
| 38. | exp Case control study/ |
| 39. | Family study/ |
| 40. | Longitudinal study/ |
| 41. | Retrospective study/ |
| 42. | Prospective study/ |
| 43. | Cross-sectional study/ |
| 44. | Cohort analysis/ |
| 45. | Follow-up/ |
| 46. | cohort*.ti,ab. |
| 47. | 45 and 46 |
| 48. | case control.ti,ab. |
| 49. | (cohort adj (study or studies or analys*)).ti,ab. |
| 50. | ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab. |
| 51. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab. |
| 52. | or/37-44,47-51 |
| 53. | 36 and 52 |

### D.3.5.2 Tenofovir (treatment naïve V lamivudine resistant)

**Q. Is tenofovir's efficacy different when compared in nucleoside naïve and lamivudine resistant HBV DNA strains?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Comparison | Study filter used | Date parameters |
|---|---|---|---|---|
| Hepatitis B* | Tenofovir | Lamivudine and resistance | None | All years - 10/10/2012 |

*Standard population changed so that animal studies were not excluded.

**Medline search terms**

| | |
|---|---|
| 1. | exp Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B antibodies/ |
| 4. | exp Hepatitis B antigens/ |
| 5. | exp Hepatitis D/ |
| 6. | Hepatitis delta antigens/ |
| 7. | Hepatitis delta virus/ |
| 8. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 9. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 10. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 11. | or/1-10 |
| 12. | limit 11 to english language |
| 13. | Letter/ |
| 14. | Editorial/ |
| 15. | News/ |
| 16. | exp Historical article/ |
| 17. | Anecdotes as Topic/ |
| 18. | Comment/ |
| 19. | Case report/ |
| 20. | (letter or comment*).ti. |
| 21. | or/13-20 |
| 22. | 12 not 21 |
| 23. | (tenofovir or TDF or viread).ti,ab. |
| 24. | 22 and 23 |
| 25. | (lamivudine or 3TC or zeffix).ti,ab. |
| 26. | Lamivudine/ |
| 27. | 24 and (25 or 26) |
| 28. | resist*.ti,ab,hw. |
| 29. | 27 and 28 |

**Embase search terms**

| | |
|---|---|
| 1. | Hepatitis B/ |
| 2. | Hepatitis B virus/ |
| 3. | Hepatitis B virus X protein/ |
| 4. | exp Hepatitis B antibody/ |
| 5. | exp Hepatitis B antigen/ |
| 6. | Delta agent hepatitis/ |
| 7. | Hepatitis delta virus/ |
| 8. | Hepatitis delta antigen/ |
| 9. | (hepatitis adj2 (B or D or delta)).ti,ab. |
| 10. | ((HBV or CHB or HDV or hep B or hepB) not heart block).ti,ab. |
| 11. | (anti HB* or antiHB* or HBeAg* or HBe Ag* or HbsA* or HBcA*).ti,ab. |
| 12. | or/1-11 |

| | |
|---|---|
| 13. | limit 12 to english language |
| 14. | Letter.pt. or Letter/ |
| 15. | Note.pt. |
| 16. | Editorial.pt. |
| 17. | Case report/ or Case study/ |
| 18. | (letter or comment*).ti. |
| 19. | or/14-18 |
| 20. | 13 not 19 |
| 21. | Tenofovir/ or Tenofovir disoproxil/ |
| 22. | (tenofovir or TDF of viread).ti,ab. |
| 23. | 20 and (21 or 22) |
| 24. | Lamivudine/ |
| 25. | (lamivudine or 3TC or zeffix).ti,ab. |
| 26. | 23 and (24 or 25) |
| 27. | resist*.ti,ab,hw. |
| 28. | 26 and 27 |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Hepatitis B explode all trees |
| #2. | MeSH descriptor Hepatitis B virus, this term only |
| #3. | MeSH descriptor Hepatitis B Antibodies, this term only |
| #4. | MeSH descriptor Hepatitis B Antigens explode all trees |
| #5. | (hepatitis NEAR/2 (B OR D OR delta)):ti,ab |
| #6. | ("anti HB*" or antiHB* or HBeAg* or "HBe Ag*" or HbsA* or HBcA*):ti,ab |
| #7. | ((HBV or CHB or hep B or hepB or HDV) NOT (heart NEXT block)):ti,ab |
| #8. | MeSH descriptor Hepatitis D explode all trees |
| #9. | MeSH descriptor Hepatitis delta Antigens, this term only |
| #10. | MeSH descriptor Hepatitis Delta Virus, this term only |
| #11. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) |
| #12. | (tenofovir or TDF or viread):ti,ab |
| #13. | (#11 AND #12) |
| #14. | (lamivudine or zeffix or 3TC):ti,ab |
| #15. | (#13 AND #14) |
| #16. | resist*:ti,ab |
| #17. | (#15 AND #16) |

### D.3.5.3 Vertical transmission

**Q. In pregnant/lactating women with chronic hepatitis B what is the clinical and cost-effectiveness of pharmacological or anti-viral therapy in order to reduce risk of vertical transmission from mother to infant?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Antivirals AND pregnancy | None | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | exp Interferon type I/ |
| 2. | Lamivudine/ |
| 3. | (interferon* or peginterferon*).ti,ab. |
| 4. | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir).ti,ab. |
| 5. | (ETV or TDF or FTC or ADV or 3TC or IFN* or pegIFN*).ti,ab. |
| 6. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 7. | or/1-6 |
| 8. | Infectious disease transmission, Vertical/ |
| 9. | Pregnancy complications, Infectious/ |
| 10. | Pregnancy/ |
| 11. | Breast feeding/ |
| 12. | Lactation/ |
| 13. | (pregnan* or trimester* or breastfe* or breast fe* or lactat* or breast milk).ti,ab. |
| 14. | ((in utero or prenatal* or perinatal* or peripartum or intrapartum or antepartum or vertical* or intrafamilial* or familial* or congenital* or intrauterine or intra uterine or matern* or f?etomaternal* or maternof?etal* or neonat* or transplacental* or placenta* or f?etal* or f?etus) adj4 (transmi* or transfer* or infect* or pathogen* or acqui* or prevent* or interrupt* or antiviral* or anti viral*)).ti,ab. |
| 15. | ((matern* or mother*) adj5 (f?eto or f?etal* or f?etus or child* or baby or infant* or newborn* or neonat* or offspring)).ti,ab. |
| 16. | or/8-15 |
| 17. | 7 and 16 |

**Embase search terms**

| | |
|---|---|
| 1. | exp Recombinant interferon/ |
| 2. | Lamivudine/ |
| 3. | Telbivudine/ |
| 4. | Entecavir/ |
| 5. | Emtricitabine/ |
| 6. | tenofovir.hw,ti,ab. |
| 7. | adefovir.hw,ti,ab. |
| 8. | (interferon* or peginterferon*).ti,ab. |
| 9. | (lamivudine or telbivudine or entecavir or emtricitabine).ti,ab. |
| 10. | (ETV or TDF or FTC or ADV or 3TC or IFN* or pegIFN*).ti,ab. |
| 11. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 12. | or/1-11 |
| 13. | Vertical transmission/ |
| 14. | Intrauterine infection/ |
| 15. | Pregnancy/ |
| 16. | Pregnancy complication/ |
| 17. | Breast feeding/ |
| 18. | Lactation/ |
| 19. | (pregnan* or trimester* or breastfe* or breast fe* or lactat* or breast milk).ti,ab. |
| 20. | ((in utero or prenatal* or perinatal* or peripartum or intrapartum or antepartum or vertical* |

| | |
|---|---|
| | or intrafamilial* or familial* or congenital* or intrauterine or intra uterine or matern* or f?etomaternal* or maternof?etal* or neonat* or transplacental* or placenta* or f?etal* or f?etus) adj4 (transmi* or transfer* or infect* or pathogen* or acqui* or prevent* or interrupt* or antiviral* or anti viral*)).ti,ab. |
| 21. | ((matern* or mother*) adj5 (f?eto or f?etal* or f?etus or child* or baby or infant* or newborn* or neonat* or offspring)).ti,ab. |
| 22. | or/13-21 |
| 23. | 12 and 22 |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Interferon Type I explode all trees |
| #2. | MeSH descriptor Lamivudine, this term only |
| #3. | (interferon* or peginterferon*):ti,ab |
| #4. | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir):ti,ab |
| #5. | (ETV or TDF or FTC or ADV or 3TC or IFN or pegIFN):ti,ab |
| #6. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys):ti,ab |
| #7. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6) |
| #8. | MeSH descriptor Infectious Disease Transmission, Vertical, this term only |
| #9. | MeSH descriptor Pregnancy Complications, Infectious, this term only |
| #10. | MeSH descriptor Pregnancy, this term only |
| #11. | MeSH descriptor Breast Feeding, this term only |
| #12. | MeSH descriptor Lactation, this term only |
| #13. | (pregnan* or trimester* or breastfe* or "breast feeding" or lactat* or "breast milk"):ti,ab |
| #14. | ((utero or prenatal* or perinatal* or peripartum or intrapartum or antepartum or vertical* or intrafamilial* or familial* or congenital* or intrauterine or "intra uterine" or matern* or neonat* or transplacental* or placenta* or fetal* or foetal* or foetus or fetus or fetomaternal* or foetomaternal* or maternofetal* or maternofoetal*) NEAR/4 (transmi* or transfer* or infect* or pathogen* or acqui* or prevent* or interrupt* or antiviral* or "anti viral" or "anti virals")):ti,ab |
| #15. | ((matern* or mother*) NEAR/5 (foeto or feto or fetal* or foetal* or foetus or fetus or child* or baby or infant* or newborn* or neonat* or offspring)):ti,ab |
| #16. | (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) |
| #17. | (#7 AND #16) |

### D.3.5.4 Prophylactic treatment

**Q. In people who are immunocompromised, what is the clinical and cost effectiveness of prophylactic treatment in reducing risk of hepatitis B virus reactivation and severity of flares?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Antivirals and (reactivation or immunocompromisation) | RCTs and SRs [Medline and Embase only] | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Antiviral agents/ |
| 2. | (antiviral* or anti viral*).ti,ab. |
| 3. | Lamivudine/ |

| | |
|---|---|
| 4. | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir).ti,ab. |
| 5. | (ETV or TDF or FTC or ADV or 3TC).ti,ab. |
| 6. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 7. | or/1-6 |
| 8. | Virus activation/ |
| 9. | Recurrence/ |
| 10. | Chemoprevention/ |
| 11. | Immunosuppression/ |
| 12. | (reactivat* or re activat* or flare* or recur*).ti,ab. |
| 13. | (prophyl* or preempti* or pre empti*).ti,ab. |
| 14. | chemo*.ti,ab. |
| 15. | (immunocomp* or immuno comp* or immunosup* or immuno sup*).ti,ab. |
| 16. | or/8-15 |
| 17. | 7 and 16 |

**Embase search terms**

| | |
|---|---|
| 1. | Antiviral therapy/ |
| 2. | Antivirus agent/ |
| 3. | (antiviral* or anti viral*).ti,ab. |
| 4. | Lamivudine/ |
| 5. | Telbivudine/ |
| 6. | Entecavir/ |
| 7. | Emtricitabine/ |
| 8. | tenofovir.hw,ti,ab. |
| 9. | adefovir.hw,ti,ab. |
| 10. | (lamivudine or telbivudine or entecavir or emtricitabine).ti,ab. |
| 11. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys).ti,ab. |
| 12. | (ETV or TDF or FTC or ADV or 3TC).ti,ab. |
| 13. | or/1-12 |
| 14. | Virus activation/ |
| 15. | Virus reactivation/ |
| 16. | Chemoprophylaxis/ |
| 17. | Immunosuppressive treatment/ |
| 18. | Prophylaxis/ |
| 19. | Chemotherapy/ |
| 20. | (reactivat* or re activat* or flare* or recur*).ti,ab. |
| 21. | (prophyl* or preempti* or pre empti*).ti,ab. |
| 22. | chemo*.ti,ab. |
| 23. | (immunocomp* or immuno comp* or immunosup* or immuno sup*).ti,ab. |
| 24. | Recurrent disease/ |
| 25. | or/14-24 |
| 26. | 13 and 25 |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Lamivudine, this term only |
| #2. | (lamivudine or telbivudine or entecavir or emtricitabine or tenofovir or adefovir):ti,ab |
| #3. | (ETV or TDF or FTC or ADV or 3TC):ti,ab |
| #4. | (viread or emtricitabine plus tenofovir or hepsera or sebivo or tyzeka or baraclude or zeffix or pegasys):ti,ab |
| #5. | MeSH descriptor Antiviral Agents, this term only |
| #6. | (antiviral* or anti viral*):ti,ab |
| #7. | (#1 OR #2 OR #3 OR #4 OR #5 OR #6) |
| #8. | MeSH descriptor Virus Activation, this term only |
| #9. | MeSH descriptor Recurrence, this term only |
| #10. | MeSH descriptor Chemoprevention, this term only |
| #11. | MeSH descriptor Immunosuppression, this term only |
| #12. | (reactivat* or "re activate" or "re activation" or flare* or recur*):ti,ab |
| #13. | (prophyl* or preempti* or "pre emptive"):ti,ab |
| #14. | (chemo* or immuno*):ti,ab |
| #15. | (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) |
| #16. | (#7 AND #15) |

### D.3.6 Frequency of monitoring

**Q. How frequently should monitoring tests be done to ascertain virological, serological and biochemical response and resolution of fibrosis (HBeAg and antibody, HBsAg and antibody and transient elastography) and resistance (HBV DNA) in people with chronic hepatitis B?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Monitoring frequency | RCTs, SRs and Observational studies [Medline and Embase only] | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Endpoint determination/ |
| 2. | Disease progression/ |
| 3. | Time factors/ |
| 4. | prognos*.ti,ab,hw. |
| 5. | ((interval* or every) adj5 (month* or year* or week*)).ti,ab. |
| 6. | (treatment adj3 (nonresponse* or failure* or response* or duration or outcome*)).ti,ab,hw. |
| 7. | (predict* adj2 value*).ti,ab,hw. |
| 8. | ((review* or recall* or follow up* or regular* or periodic*) adj (interval* or visit* or inspect* or examin* or attend* or test* or measure*)).ti,ab. |
| 9. | ((virologic* or serologic* or clinical or biochemical) adj2 (status or response*)).ti,ab. |
| 10. | (management adj (strateg* or protocol* or plan*)).ti,ab. |
| 11. | (test* or measure* or prevent*).ti. |
| 12. | (endpoint* or clearance or disappearance or seroconversion or breakthrough).ti,ab. |
| 13. | natural histor*.ti,ab. |
| 14. | or/1-13 |
| 15. | monitor*.ab,hw. |
| 16. | 14 and 15 |
| 17. | monitor*.ti. |

| | |
|---|---|
| 18. | (predict* adj2 (treatment* or response* or outcome* or factor*)).ti,ab. |
| 19. | or/16-18 |

**Embase search terms**

| | |
|---|---|
| 1. | Disease course/ |
| 2. | Therapy delay/ |
| 3. | prognos*.ti,ab,hw. |
| 4. | ((interval* or every) adj5 (month* or year* or week*)).ti,ab. |
| 5. | (treatment adj3 (nonresponse* or failure* or response* or duration or outcome* or planning)).ti,ab,hw. |
| 6. | (predict* adj2 value*).ti,ab,hw. |
| 7. | ((review* or recall* or follow up* or regular* or periodic*) adj (interval* or visit* or inspect* or examin* or attend* or test* or measure*)).ti,ab. |
| 8. | ((virologic* or serologic* or clinical or biochemical) adj2 (status or response*)).ti,ab. |
| 9. | (management adj (strateg* or protocol* or plan*)).ti,ab. |
| 10. | (test* or measure* or prevent*).ti. |
| 11. | (endpoint* or clearance or disappearance or seroconversion or breakthrough).ti,ab. |
| 12. | natural histor*.ti,ab. |
| 13. | or/1-12 |
| 14. | monitor*.ab,hw. |
| 15. | 13 and 14 |
| 16. | monitor*.ti. |
| 17. | (predict* adj2 (treatment* or response* or outcome* or factor*)).ti,ab. |
| 18. | 15 or 16 or 17 |

**Cochrane search terms**

| | |
|---|---|
| #1 | MeSH descriptor Endpoint Determination, this term only |
| #2 | MeSH descriptor Time Factors, this term only |
| #3 | MeSH descriptor Disease Progression, this term only |
| #4 | MeSH descriptor Prognosis, this term only |
| #5 | MeSH descriptor Predictive Value of Tests, this term only |
| #6 | MeSH descriptor Treatment Outcome explode tree 1 |
| #7 | prognos*:ti,ab |
| #8 | ((interval* or every) near/5 (month* or year* or week*)):ti,ab |
| #9 | (treatment near/3 (nonresponse* or failure* or response* or duration or outcome*)):ti,ab |
| #10 | (predict* near/2 value*):ti,ab |
| #11 | ((review* or recall* or "follow up" or regular* or periodic*) next (interval* or visit* or inspect* or examin* or attend* or test* or measure*)):ti,ab |
| #12 | ((virologic* or serologic* or clinical or biochemical) near/2 (status or response*)):ti,ab |
| #13 | (management next (strateg* or protocol* or plan*)):ti,ab |
| #14 | (test* or measure* or prevent*):ti |
| #15 | (endpoint* or clearance or disappearance or seroconversion or breakthrough):ti,ab |
| #16 | (natural next histor*):ti,ab |
| #17 | (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) |
| #18 | monitor*:ab |
| #19 | monitoring:kw |

| | |
|---|---|
| #20 | (#18 OR #19) |
| #21 | (#17 AND #20) |
| #22 | monitor*:ti |
| #23 | (predict* near/2 (treatment* or response* or outcome* or factor*)):ti,ab |
| #24 | (#21 OR #22 OR #23) |

### D.3.7 Surveillance for hepatocellular carcinoma

**Q. When and how frequently should surveillance testing be offered to detect early hepatocellular carcinoma in people with chronic hepatitis B?**

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Intervention /Exposure | Study filter used | Date parameters |
|---|---|---|---|
| Hepatitis B | Surveillance and hepatocellular carcinoma | RCTs, SRs and Observational studies [Medline and Embase only] | All years - 10/10/2012 |

**Medline search terms**

| | |
|---|---|
| 1. | Carcinoma, hepatocellular/ |
| 2. | Liver neoplasms/ |
| 3. | (hepatoma* or hepatocarcinoma* or HCC).ti,ab. |
| 4. | ((hepatocellular or liver or hepatic or hepato) adj2 (cancer or carcinoma* or neoplasm*)).ti,ab. |
| 5. | or/1-4 |
| 6. | exp Early diagnosis/ |
| 7. | surveillance.ti,ab,hw. |
| 8. | screen*.ti,ab. |
| 9. | (early and (detect* or diagnos* or stage*)).ti,ab. |
| 10. | or/6-9 |
| 11. | 5 and 10 |

**Embase search terms**

| | |
|---|---|
| 1. | Liver cell carcinoma/ |
| 2. | Liver carcinoma/ |
| 3. | Liver cancer/ |
| 4. | (hepatoma* or hepatocarcinoma* or HCC).ti,ab. |
| 5. | ((hepatocellular or liver or hepatic or hepato) adj2 (cancer or carcinoma* or neoplasm*)).ti,ab. |
| 6. | or/1-5 |
| 7. | Early diagnosis/ |
| 8. | surveillance.ti,ab,hw. |
| 9. | screen*.ti,ab. |
| 10. | (early and (detect* or diagnos* or stage*)).ti,ab. |
| 11. | or/7-10 |
| 12. | 6 and 11 |

**Cochrane search terms**

| | |
|---|---|
| #1. | MeSH descriptor Carcinoma, Hepatocellular, this term only |
| #2. | MeSH descriptor Liver Neoplasms, this term only |
| #3. | (hepatoma* or hepatocarcinoma* or HCC):ti,ab |
| #4. | ((hepatocellular or liver or hepatic or hepato) NEAR/2 (cancer or carcinoma* or |

| | |
|---|---|
| | neoplasm*)):ti,ab |
| #5. | (#1 OR #2 OR #3 OR #4) |
| #6. | MeSH descriptor Early Diagnosis explode all trees |
| #7. | (surveillance or screen*):ti,ab |
| #8. | (early and (detect* or diagnos* or stage*)):ti,ab |
| #9. | (#6 OR #7 OR #8) |
| #10. | (#5 AND #9) |

# D.4 Economic searches

## D.4.1 Economic evaluations

Economic searches were run in Medline and Embase by combining the standard population with the economic filter (D.1.4) and limiting by date range (see table below). Economic searches were executed in the HEED and Cochrane (NHS EED and HTA) databases by simply running a standard population without a date limitation. Search terms for the HEED database are given below.

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Study filter used | Date parameters |
|---|---|---|
| Hepatitis B | Economic [Embase and Medline only] | • 2009 - 10/10/2012 (Medline and Embase)<br>• All years - 10/10/2012 (NHS EED, HTA and HEED) |

**HEED search terms**

| | |
|---|---|
| 1. | AB='hepatitis B' OR 'hep B' OR hepB |
| 2. | TI='hepatitis B' OR 'hep B' OR hepB |
| 3. | CS=1 OR 2 |

## D.4.2 Quality of life studies

Quality of life (QOL) searches were run in Medline and Embase by combining the standard population with the QOL filter (D.1.5) without a date limitation. Search terms for the HEED database are given above.

Search constructed by combining the columns in the following table using the AND Boolean operator

| Population | Study filter used | Date parameters |
|---|---|---|
| Hepatitis B | QOL [Embase and Medline] | All years - 10/10/2012 |