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

NICE guideline

Draft for consultation, January 2013

If you wish to comment on this version of the guideline, please be aware that all the supporting information and evidence is contained in the full version.

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Introduction

Chronic hepatitis B describes a spectrum of disease usually characterised by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or serum for longer than six months. In some people, chronic hepatitis B is inactive and does not present significant health problems, but others may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The progression of liver disease is associated with hepatitis B virus (HBV) DNA levels in the blood. Without antiviral treatment, the 5-year cumulative incidence of cirrhosis ranges from 8 to 20%. People with cirrhosis face a significant risk of decompensated liver disease if they remain untreated. Five-year survival rates among people with untreated decompensated cirrhosis can be as low as 15%.

The goal of treatment for chronic hepatitis B is to prevent cirrhosis, HCC and liver failure. In clinical practice surrogate markers are used to monitor progression of disease and treatment response, and include normalisation of serum alanine aminotransferase (ALT) levels, decrease in inflammation scores with no worsening or improvement in fibrosis on liver biopsies, suppression of serum HBV DNA to undetectable levels, loss of HBeAg and seroconversion to HBe antibody (anti-HBe), and loss of HBsAg and seroconversion to HBs antibody (anti-HBs).

Antiviral therapy suppresses HBV replication and decreases hepatic inflammation and fibrosis, thereby reducing the likelihood of serious clinical disease. Treatment has evolved since the introduction of interferon alpha, peginterferon alpha and now several nucleoside and nucleotide analogues are approved for use in adults with chronic hepatitis B. With multiple treatment options that are efficacious and safe, the key questions are which patients need immediate treatment and what sequence and combination of drug regimens should be used, and which patients can be monitored and treatment delayed.

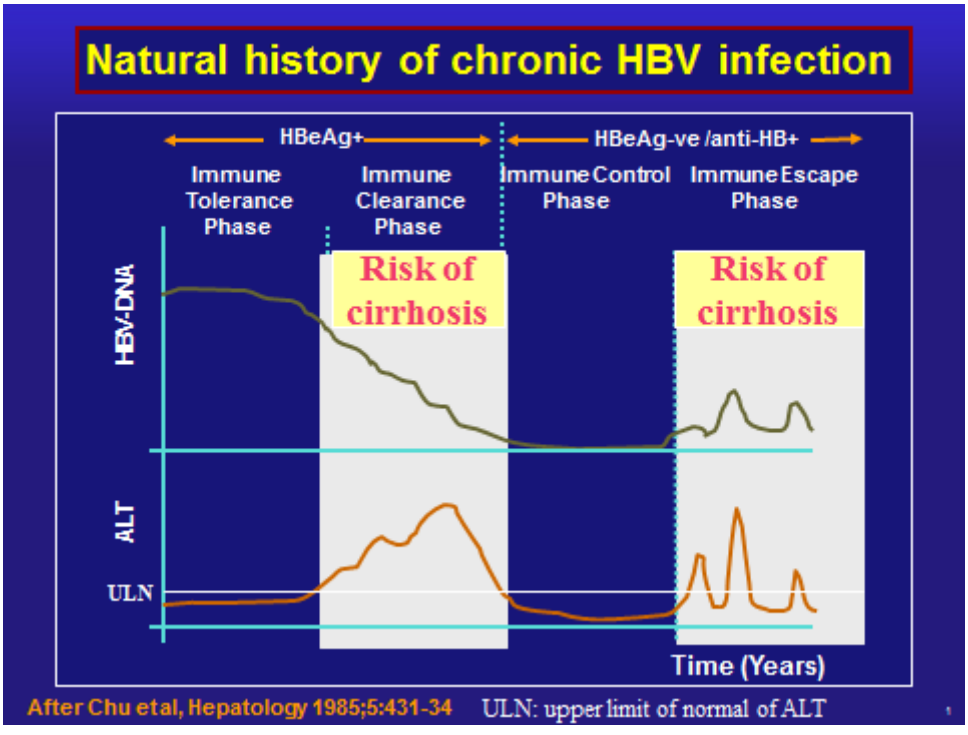
In this guideline we consider the following:

- where children, young people and adults with chronic hepatitis B should be assessed
- criteria for offering antiviral treatment
- the efficacy, safety and cost effectiveness of currently available treatments
- selection of first-line therapy
- management of treatment failure or drug resistance
- whether there is a role for combination therapy
- when it is possible to stop treatment
- monitoring for treatment response, severity of fibrosis and development of HCC.

The spontaneous mutation rate of HBV DNA is high. Exposure of HBV to nucleoside or nucleotide analogues selects for mutations in the polymerase gene that confer resistance or decreased susceptibility to the drugs. The relative risk of drug resistance must be taken into account when considering treatment with nucleoside or nucleotide analogues, including the level of cross resistance between different agents.

Figure 1 depicts the natural history of chronic HBV infection.

Figure 1. Natural history of chronic HBV infection



Substantial progress has been made in the treatment of chronic hepatitis B in the past decade but when treatment should be started in people without cirrhosis remains a topic of debate. Although currently available treatment is effective in suppressing HBV replication, it fails to eradicate the virus necessitating long treatment duration and perhaps lifelong treatment.

In this guideline we also consider:

- assessment of liver disease, including the use of non-invasive tests and genotype testing
- management of pregnant and breastfeeding women and prevention of vertical transmission
- management issues in children and young people
- prophylactic treatment during immunosuppressive therapy
- information needs of people with chronic hepatitis B and their carers.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

Patient-centred care

This guideline offers best practice advice on the care of children, young people and adults with chronic hepatitis B.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If the patient is under 16, healthcare professionals should follow the guidelines in the Department of Health's Seeking consent: working with children. Families and carers should also be given the information and support they need to help the child or young person in making decisions about their treatment.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with chronic hepatitis B. Diagnosis and management should be reviewed throughout the transition process, and

there should be clarity about who is the lead clinician to ensure continuity of care.

Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values

and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Terms used in this guidance

Chronic hepatitis B

Chronic hepatitis B is defined as persistence of hepatitis B surface antigen (HBsAg) for 6 months or more after acute infection with hepatitis B virus (HBV).

HBV DNA

HBV DNA level, or 'viral load', is an indicator of viral replication. Higher HBV DNA levels are usually associated with an increased risk of liver disease and HCC. HBV DNA level typically falls in response to effective antiviral treatment.

Hepatitis B surface antigen (HBsAg)

Hepatitis B surface antigen is a viral protein detectable in the blood in acute and chronic hepatitis B infection.

HBsAg seroconversion

The development of antibodies against HBsAg is known as HBsAg seroconversion. It signifies clearance of HBsAg and resolution of the chronic infection.

Hepatitis B e antigen (HBeAg)

Hepatitis B e antigen (HBeAg) is an indicator of viral replication, although some variant forms of the virus do not express HBeAg (see 'HBeAg-negative chronic hepatitis B' below). Active infection can be described as HBeAg-positive or HBeAg-negative according to whether HBeAg is secreted.

HBeAg-negative chronic hepatitis B

HBeAg-negative hepatitis B is a form of the virus that does not cause infected cells to secrete HBeAg. People can be infected with the HBeAg-negative form of the virus from the beginning, or the viral mutation can emerge later in the course of infection in people initially infected with the HBeAg-positive form of the virus.

HBeAg seroconversion

HBeAg seroconversion occurs when people infected with the HBeAg-positive form of the virus develop antibodies against the ‘e’ antigen. The seroconverted disease state is referred to as the ‘inactive HBV carrier state’ because people continue to express hepatitis B surface antigen (HBsAg). Once seroconversion has taken place, most people remain in the inactive HBV carrier state. However, increasing HBV DNA and recurrent hepatitis after seroconversion indicate the emergence of the HBeAg-negative strain of the virus.

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Assessment and referral

- Arrange the following tests for adults who are hepatitis B surface antigen (HBsAg) positive:
  - hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
  - HBV DNA level
  - lgM antibody to hepatitis B core antigen (anti-HBc lgM)
  - hepatitis C virus antibody (anti-HCV)
  - hepatitis delta virus antibody (anti-HDV)
  - HIV antibody (anti-HIV)
  - additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
  - surveillance for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing. **[1.2.1]**
- Include the results of the initial tests with the referral (see recommendation 1.2.1). **[1.2.3]**

Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

- Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease. **[1.5.15]**
- Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion after first-line treatment with peginterferon alfa-2a. **[1.5.17]**
- Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated. **[1.5.18]**

Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

- Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease. **[1.5.22]**
- Offer tenofovir disoproxil or entecavir as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a. **[1.5.24]**

Women who are pregnant or breastfeeding

- Offer tenofovir disoproxil to women with HBV DNA >10^7 $\log_{10}$ IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[1]. **[1.5.36]**

Prophylactic treatment during immunosuppressive therapy

- In people who are HBsAg positive and have HBV DNA >2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[2].
  - Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable. **[1.5.46]**
- In people who are HBsAg positive and have HBV DNA <2000 IU/ml, offer prophylaxis:
  - consider entecavir or tenofovir disoproxil[3] if immunosuppressive therapy is expected to last longer than 6 months

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[1] At the time of consultation (January 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[2] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[3] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained

- consider lamivudine[4] if immunosuppressive therapy is expected to last less than 6 months
  - ◊ monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months
- start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy. **[1.5.47]**

and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[4] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

1 Recommendations

The following guidance is based on the best available evidence. The full guideline [hyperlink to be added for final publication] gives details of the methods and the evidence used to develop the guidance.

1.1 Patient information

1.1.1 Provide information on the following topics to people with chronic hepatitis B or to family members or carers (if appropriate) before starting antiviral treatment:

- the natural history of chronic hepatitis B, including stages of disease and long-term prognosis
- routes of hepatitis B virus (HBV) transmission
- the benefits of antiviral treatment, including reduced risk of serious liver disease and death and reduced risk of transmission of HBV to others
- treatment options, including peginterferon alfa-2a and nucleoside or nucleotide analogues
- short- and long-term treatment goals
- causes of treatment failure, including non-adherence to prescribed medicines, and options for re-treatment
- risks of treatment, including adverse effects and drug resistance.

1.1.2 Provide information on self-injection techniques to people beginning peginterferon alfa-2a or to family members or carers.

1.1.3 NICE has produced public health guidance on ways to promote and offer testing to people at increased risk of infection with hepatitis B. This clinical guideline should be used in conjunction with the public health guideline (NICE public health guideline 43; Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection).

1.1.4 NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).

1.2 Assessment and referral in primary care

Adults who are HBsAg positive

1.2.1 Arrange the following tests for adults who are hepatitis B surface antigen (HBsAg) positive:

- hepatitis B e antigen (HBeAg)/antibody (anti-HBe) status
- HBV DNA level
- IgM antibody to hepatitis B core antigen (anti-HBc lgM)
- hepatitis C virus antibody (anti-HCV)
- hepatitis delta virus antibody (anti-HDV)
- HIV antibody (anti-HIV)
- additional laboratory tests including alanine aminotransferase (ALT) or aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- surveillance for hepatocellular carcinoma (HCC), including hepatic ultrasound and alpha-fetoprotein testing.

1.2.2 Refer all adults who are HBsAg positive to a hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

1.2.3 Include the results of the initial tests with the referral (see recommendation 1.2.1).

Pregnant women who test HBsAg positive at antenatal screening

1.2.4 Refer pregnant women who are HBsAg positive to a hepatologist, or to a gastroenterologist or infectious disease specialist with an interest in hepatology, for assessment within 6 weeks of receiving

the screening test result and to allow treatment in the third trimester (see recommendation 1.5.36).

Adults with decompensated liver disease

1.2.5 Refer adults who develop decompensated liver disease immediately to a hepatologist or to a gastroenterologist with an interest in hepatology.

Children and young people who are HBsAg positive

1.2.6 Arrange the following tests for children and young people who are HBsAg positive:

- HBeAg/anti-HBe status
- HBV DNA level
- anti-HBc lgM
- anti-HCV
- anti-HDV
- anti-HIV
- additional laboratory tests, including ALT or AST, GGT, serum albumin, total bilirubin, total globulins, full blood count and prothrombin time
- surveillance for HCC, including hepatic ultrasound and alpha-fetoprotein testing.

1.2.7 Refer all children and young people who are HBsAg positive to a paediatric hepatologist or to a gastroenterologist or infectious disease specialist with an interest in hepatology.

1.2.8 Include the results of the initial tests with the referral (see recommendation 1.2.6).

1.3 Assessment of liver disease in secondary specialist care

Adults with chronic hepatitis B

Please refer to recommendations 1.5.2 to 1.5.6 for detailed guidance on offering antiviral treatment.

1.3.1 Ensure all healthcare professionals who refer adults for non-invasive tests for liver disease are trained to interpret the results and aware of co-factors that influence liver elasticity (for example, fatty liver caused by obesity or alcohol misuse).

1.3.2 Discuss the accuracy, limitations and risks of the different tests for liver disease with the patient.

1.3.3 Offer transient elastography as the initial test for liver disease in adults newly referred for assessment.

1.3.4 Offer antiviral treatment without a liver biopsy to adults with a transient elastography score ≥11 kPa[5], in line with recommendation 1.5.5.

1.3.5 Consider liver biopsy to confirm the level of fibrosis in adults with a transient elastography score between 6 to 10 kPa[6]. Offer antiviral treatment in line with recommendations 1.5.2 to 1.5.6.

1.3.6 Offer liver biopsy to adults with a transient elastography score <6 if they are younger than 30 years and have HBV DNA >2000 IU/ml and abnormal ALT (≥30 IU/ml for males and ≥19 IU/ml for females) on 2 consecutive tests conducted 3 months apart[7]. Offer antiviral treatment in line with recommendations 1.5.2 to 1.5.6.

1.3.7 Do not offer liver biopsy to adults with a transient elastography score <6 kPa who have normal ALT (<30 IU/ml in males and <19 IU/ml in females) and HBV DNA <2000 IU/ml as they are unlikely to

[5] Adults with a transient elastography score ≥11 kPa are very likely to have cirrhosis and confirmation by liver biopsy is not needed.
[6] The degree of fibrosis cannot be accurately predicted in adults with a transient elastography score between 6 to 10 kPa. Some people may choose to have a liver biopsy in these circumstances to confirm the extent of liver disease.
[7] Adults with a transient elastography score <6 kPa are unlikely to have significant fibrosis.

have advanced liver disease or need antiviral treatment (see recommendations 1.5.2 to 1.5.6)[8].

1.3.8 Offer an annual reassessment of liver disease using transient elastography to adults who are not taking antiviral treatment.

Children and young people with chronic hepatitis B

1.3.9 Discuss the accuracy, limitations and risks of liver biopsy in determining the need for antiviral treatment with the child or young person and with parents or carers (if appropriate).

1.3.10 Offer liver biopsy to assess liver disease and the need for antiviral treatment to children and young people with HBV DNA >2000 IU/ml and abnormal ALT (≥30 IU/ml for males and ≥19 IU/ml for females) on 2 consecutive tests conducted 3 months apart. Offer biopsy under a general anaesthetic to children who are too young to tolerate the procedure under a local anaesthetic.

1.4 Genotype testing

1.4.1 Do not offer genotype testing to determine initial treatment in people with chronic hepatitis B.

1.5 Antiviral treatment

Adults with chronic hepatitis B

Recommendations 1.5.7 to 1.5.11 are reproduced from existing NICE technology appraisals on options for the treatment of chronic hepatitis B, and 1.5.12 to 1.5.14 update guidance in NICE technology appraisal 96[9]. The GDG has reviewed the evidence and has made recommendations on treatment

[8] Adults with a transient elastography score <6 kPa are unlikely to have significant fibrosis.

[9] Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96), Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153), Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154) and Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).

sequences and combination drug regimens (see recommendations 1.5.15 to 1.5.27).

Recommendations 1.5.7 to 1.5.40 do not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

1.5.1 Discuss treatment options, adverse effects and long-term prognosis with the patient before starting treatment.

1.5.2 Offer antiviral treatment to adults aged 30 years and older who have HBV DNA >2000 IU/ml and abnormal ALT (≥30 in males and ≥19 in females) on 2 consecutive tests conducted 3 months apart.

1.5.3 Offer antiviral treatment to adults younger than 30 years who have HBV DNA >2000 IU/ml and abnormal ALT (≥30 in males and ≥19 in females) on 2 consecutive tests conducted 3 months apart if there is evidence of necroinflammation or fibrosis on liver biopsy or a transient elastography score >6 kPa.

1.5.4 Offer antiviral treatment to adults who have HBV DNA >20,000 IU/ml and abnormal ALT (≥30 in males and ≥19 in females) on 2 consecutive tests conducted 3 months apart regardless of age or the extent of liver disease.

1.5.5 Offer antiviral treatment to adults with cirrhosis regardless of HBeAg status, HBV DNA and ALT levels.

1.5.6 Consider antiviral treatment in adults with HBV DNA >2000 IU/ml and evidence of necroinflammation or fibrosis on liver biopsy.

1.5.7 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]

1.5.8 Entecavir, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Entecavir for the treatment of chronic hepatitis B (NICE technology appraisal guidance 153).]

1.5.9 Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated. [This recommendation is from Tenofovir disoproxil fumarate for the treatment of hepatitis B (NICE technology appraisal guidance 173).]

1.5.10 Telbivudine is not recommended for the treatment of chronic hepatitis B. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

1.5.11 People currently receiving telbivudine should have the option to continue therapy until they and their clinicians consider it appropriate to stop. [This recommendation is from Telbivudine for the treatment of chronic hepatitis B (NICE technology appraisal guidance 154).]

1.5.12 Adefovir dipivoxil is not recommended for the treatment of chronic hepatitis B.

1.5.13 Offer tenofovir disoproxil or entecavir to people currently receiving adefovir dipivoxil, depending on previous antiviral exposure:

- offer tenofovir disoproxil to people with a history of lamivudine resistance.

1.5.14 Antiviral treatment should be initiated only by an appropriately qualified healthcare professional with expertise in the management

of viral hepatitis. Continuation of therapy under shared-care arrangements with a GP is appropriate.

Treatment sequence in adults with HBeAg-positive chronic hepatitis B and compensated liver disease

1.5.15 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease.

1.5.16 Stop peginterferon alfa-2a 12 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and offer second-line treatment in line with recommendations 1.5.17 and 1.5.18.

1.5.17 Offer tenofovir disoproxil as second-line treatment to people who do not undergo HBeAg seroconversion after first-line treatment with peginterferon alfa-2a.

1.5.18 Offer entecavir as an alternative second-line treatment to people who cannot tolerate tenofovir disoproxil or if it is contraindicated.

1.5.19 In people taking tenofovir disoproxil who have detectable HBV DNA at 48 weeks of treatment and no history of lamivudine resistance, consider adding lamivudine to tenofovir disoproxil.

- In people with a history of lamivudine resistance, consider adding entecavir to tenofovir disoproxil.

1.5.20 Consider stopping nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people without cirrhosis.

1.5.21 Do not stop nucleoside or nucleotide analogue treatment 12 months after HBeAg seroconversion in people with cirrhosis.

Treatment sequence in adults with HBeAg-negative chronic hepatitis B and compensated liver disease

1.5.22 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease.

1.5.23 Stop peginterferon alfa-2a 12 weeks after starting treatment if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and offer second-line treatment in line with recommendation 1.5.24.

1.5.24 Offer tenofovir disoproxil or entecavir as second-line treatment to people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a.

1.5.25 Consider switching from tenofovir disoproxil to entecavir, or from entecavir to tenofovir disoproxil, as third-line treatment in people who have detectable HBV DNA at 48 weeks of treatment.

1.5.26 Consider stopping nucleoside or nucleotide analogue treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in people without cirrhosis.

1.5.27 Do not stop nucleoside or nucleotide analogue treatment after achieving undetectable HBV DNA and HBsAg seroconversion in patients with cirrhosis.

Children and young people with chronic hepatitis B and compensated liver disease

1.5.28 Discuss treatment options, adverse effects and long-term prognosis with the child or young person and with parents or carers before starting treatment (if appropriate).

1.5.29 Offer antiviral treatment if there is evidence of significant fibrosis (METAVIR stage ≥F2 or Ishak stage ≥3) or abnormal ALT (≥30 IU/ml for males and ≥19 IU/ml for females) on 2 consecutive tests conducted 3 months apart.

1.5.30 Consider a 48-week course of peginterferon alfa-2a as first-line treatment in children and young people with chronic hepatitis B and compensated liver disease[10].

1.5.31 Consider a nucleoside or nucleotide analogue as second-line treatment in children and young people with detectable HBV DNA after first-line treatment with peginterferon alfa-2a[11].

Adults with decompensated liver disease

1.5.32 Manage decompensated liver disease in adults in conjunction with a liver transplant centre.

1.5.33 Do not offer peginterferon alfa-2a to people with chronic hepatitis B and decompensated liver disease.

1.5.34 Offer tenofovir disoproxil as first-line treatment in people with decompensated liver disease.

- Reduce the dose of tenofovir disoproxil in people with renal impairment, in line with guidance in the British National Formulary.
- Offer entecavir to people at high risk of renal or bone toxicity associated with tenofovir disoproxil.

Women who are pregnant or breastfeeding

1.5.35 Discuss with pregnant women the benefits and risks of antiviral treatment for them and their baby.

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[10] At the time of consultation (January 2013), peginterferon alfa-2a did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[11] At the time of consultation (January 2013), peginterferon alfa-2a, entecavir and tenofovir disoproxil did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

1.5.36 Offer tenofovir disoproxil to women with HBV DNA >10^7 $\log_{10}$ IU/ml in the third trimester to reduce the risk of transmission of HBV to the baby[12].

1.5.37 Monitor quantitative HBV DNA 2 months after starting tenofovir disoproxil and ALT monthly after the birth to detect postnatal HBV flares in the woman.

1.5.38 Stop tenofovir disoproxil 4 to 12 weeks after the birth unless the mother meets criteria for long-term treatment (see recommendations 1.5.2 to 1.5.6).

1.5.39 Offer active and passive hepatitis B immunisation in infants and follow up in line with the guidance below:

- Hepatitis B antenatal screening and newborn immunisation programme: best practice guidance
- Immunisation against infectious disease (the Green book)
- Hepatitis B and C: ways to promote and offer testing. NICE public health guidance 43 (2012)
- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009).

1.5.40 Advise women that there is no risk of transmitting HBV to their babies through breastfeeding if guidance on hepatitis B immunisation has been followed, and that they may continue antiviral treatment while they are breastfeeding.

Adults who are co-infected with hepatitis C

1.5.41 Offer peginterferon alfa and ribavirin in adults co-infected with chronic hepatitis B and C.

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[12] At the time of consultation (January 2013), tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Adults who are co-infected with hepatitis D

1.5.42 Offer a 48-week course of peginterferon alfa-2a in people co-infected with chronic hepatitis B and hepatitis delta infection who have evidence of significant fibrosis (METAVIR stage ≥F2 or Ishak stage ≥3).

1.5.43 Consider stopping treatment if HDV RNA is detectable after 6 months to 1 year of treatment. Otherwise, continue treatment and re-evaluate treatment response annually.

1.5.44 Stop treatment after HBsAg seroconversion.

Prophylactic treatment during immunosuppressive therapy

1.5.45 Perform the following tests in people who are anti-HBc positive, and therefore at high risk of hepatitis B reactivation, before starting immunosuppressive therapy for autoimmune or atopic diseases, chemotherapy, bone marrow or solid organ transplantation:

- HBsAg
- antibody to hepatitis B surface antigen (anti-HBs)
- plasma or serum HBV DNA level
- ALT.

1.5.46 In people who are HBsAg positive and have HBV DNA >2000 IU/ml, offer prophylaxis with entecavir or tenofovir disoproxil[13].

- Start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable.

[13] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

1.5.47 In people who are HBsAg positive and have HBV DNA <2000 IU/ml, offer prophylaxis:

- consider entecavir or tenofovir disoproxil[14] if immunosuppressive therapy is expected to last longer than 6 months
- consider lamivudine[15] if immunosuppressive therapy is expected to last less than 6 months
  - monitor HBV DNA monthly in people treated with lamivudine and change to tenofovir disoproxil if HBV DNA remains detectable after 3 months
- start prophylaxis before beginning immunosuppressive therapy and continue for a minimum of 6 months after stopping immunosuppressive therapy.

1.5.48 For people who are HBsAg negative and anti-HBc positive:

- monitor HBV DNA level monthly in people who have HBV DNA <2000 IU/ml
- offer prophylaxis with lamivudine to people with HBV DNA >2000 IU/ml if immunosuppressive therapy is expected to last less than 6 months or with entecavir or tenofovir disoproxil if it is expected to last longer than 6 months[16].

1.6 Monitoring

[14] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[15] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

[16] At the time of consultation (January 2013), entecavir, lamivudine and tenofovir disoproxil did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Monitoring in people who do not meet criteria for antiviral treatment

Adults with HBeAg-positive disease in the immune-tolerant phase

1.6.1 Monitor ALT levels every 24 weeks in adults with HBeAg-positive disease who are in the immune-tolerant phase (defined by active viral replication and normal ALT levels [<30 IU/ml in males and <19 IU/ml in females]).

1.6.2 Monitor ALT every 12 weeks on at least 3 consecutive occasions if there is an increase in ALT levels.

Adults with inactive chronic hepatitis B (immune-control phase)

1.6.3 Monitor ALT and HBV DNA levels every 48 weeks in adults with inactive chronic hepatitis B infection (defined as e antigen [HBeAg] negative on 2 consecutive tests with normal ALT [<30 IU/ml in males and <19 IU/ml in females] and HBV DNA <2000 IU/ml).

Children and young people

1.6.4 Monitor ALT levels every 12 weeks in children and young people with HBeAg-positive disease who have normal ALT levels (<30 IU/ml for males and <19 IU/ml for females) and no evidence of significant fibrosis (METAVIR stage <F2 or Ishak stage <3).

1.6.5 Review annually children and young people with HBeAg-negative disease who have normal ALT (<30 IU/ml for males and <19 IU/ml for females), no evidence of significant fibrosis (METAVIR stage <F2 or Ishak stage <3) and HBV DNA <2000 IU/ml.

1.6.6 Review every 24 weeks children and young people with HBeAg-negative disease who have abnormal ALT (≥30 IU/ml for males and ≥19 IU/ml for females) and HBV DNA >2000 IU/ml.

Children, young people and adults with HBeAg or HBsAg seroconversion after antiviral treatment

1.6.7 In people with HBeAg seroconversion after antiviral treatment, monitor HBeAg, anti-HBe, HBV DNA level and liver function at 4,

12 and 24 weeks after HBeAg seroconversion and then every 6 months.

1.6.8 Monitor HBsAg and anti-HBs annually in people with HBsAg seroconversion after antiviral treatment and discharge people who are anti-HBs positive on 2 consecutive tests.

Monitoring in people taking antiviral treatment

Children, young people and adults taking peginterferon alfa-2a

1.6.9 Review injection technique and adverse effects weekly during the first month of treatment in people taking peginterferon alfa-2a[17].

1.6.10 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels) and thyroid function before starting peginterferon alfa-2a and 2, 4, 12, 24, 36 and 48 weeks after starting treatment to detect adverse effects[17].

1.6.11 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting peginterferon alfa-2a and 12, 24 and 48 weeks after starting treatment to determine treatment response[17].

Children, young people and adults with compensated liver disease taking entecavir or lamivudine

1.6.12 Monitor full blood count, liver function (including bilirubin, albumin and ALT) and renal function (including urea and electrolyte levels) in people with compensated liver disease before starting entecavir or lamivudine, 4 and 12 weeks after starting treatment and then every 6 months to detect adverse effects[17].

[17] At the time of consultation (January 2013), peginterferon alfa-2a, entecavir and tenofovir disoproxil did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

1.6.13 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting entecavir or lamivudine, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[17].

1.6.14 Monitor HBV DNA levels every 12 weeks in people with HBeAg-negative disease who have been taking lamivudine for 5 years or longer[17].

Children, young people and adults with compensated liver disease taking tenofovir disoproxil

1.6.15 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), and phosphate levels in people with compensated liver disease before starting tenofovir disoproxil, 4 and 12 weeks after starting treatment and then every 6 months to detect adverse effects[17].

1.6.16 Monitor HBV DNA and quantitative HBsAg levels and HBeAg status before starting tenofovir disoproxil, 12, 24 and 48 weeks after starting treatment and then every 6 months to determine treatment response and medicines adherence[17].

Children, young people and adults with decompensated liver disease who are taking entecavir or lamivudine

1.6.17 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio), blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting entecavir or lamivudine and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in ‘Children, young people and adults with compensated liver disease taking entecavir or lamivudine’[17].

Children, young people and adults with decompensated liver disease who are taking tenofovir disoproxil

1.6.18 Monitor full blood count, liver function (including bilirubin, albumin and ALT), renal function (including urea and electrolyte levels and urine protein/creatinine ratio) and phosphate, blood clotting, HBV DNA level and HBeAg status in people with decompensated liver disease before starting tenofovir disoproxil and weekly after starting treatment to assess treatment response and adverse effects. When the person is no longer decompensated, follow the recommendations in 'Children, young people and adults with compensated liver disease taking tenofovir disoproxil'[17].

1.7 Surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B

1.7.1 Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage ≥F2 or Ishak stage ≥3) or cirrhosis.

1.7.2 In people without significant fibrosis or cirrhosis (METAVIR stage <F2 or Ishak stage <3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA ≥ 20,000 IU/ml.

1.7.3 Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage <F2 or Ishak stage <3) who have HBV DNA <20,000 IU/ml and are younger than 40 years.

2 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

2.1 Stopping antiviral treatment in HBeAg-negative disease

Further research should be undertaken to evaluate the clinical and cost effectiveness of HBsAg quantitative assays in determining treatment duration in HBeAg-negative disease.

Why this is important

In HBeAg-positive disease, HBeAg seroconversion is a predictor of durable response to antiviral treatment and can be used as a milestone after which treatment can be stopped. At present, similar parameters have not been defined in HBeAg-negative disease. Quantitative HBsAg may have a role in determining treatment duration in this setting. Establishing threshold levels for HBsAg titre associated with durable off-treatment control in HBeAg-negative disease would transform current treatment strategies. People on long-term nucleoside or nucleotide analogues could safely stop treatment once they achieved a threshold level of HBsAg. Further research is needed to define these levels of HBsAg and to determine when treatment in HBeAg-negative disease can be safely stopped.

2.2 ALT values for children and young people

Further research should be undertaken to examine whether the upper limit of normal ALT values for adults (<30 IU/ml for males and <19 IU/ml for females) are appropriate for use in children and young people with chronic hepatitis B when making decisions on when to initiate treatment.

Why this is important

Recent studies have highlighted the imprecision of using biochemical activity as a measure of immune activity in children and young people with chronic hepatitis B. Researchers have found T-cell exhaustion and even HBV-specific immune responses in children and young people considered to have immune-tolerant disease. These findings need to be validated in larger studies to see if upper limit of normal ALT values derived from adults accurately reflect disease activity in children and young people. Further research is needed to investigate whether there is a genuine state of immune tolerance in children

and young people reflected in lower levels of biochemical activity and a lower upper limit of normal ALT value.

2.3 Long-term safety of tenofovir disoproxil in chronic hepatitis B

Further research should be undertaken to determine the long-term safety of tenofovir disoproxil, including the risk of clinically significant hypophosphataemia and related bone toxicity, in people with chronic hepatitis B. The cost effectiveness of routine monitoring for phosphate loss and bone disease in people with chronic hepatitis B who are receiving tenofovir disoproxil treatment needs further evaluation.

Why this is important

Tenofovir disoproxil is recommended as an option for treatment of people with chronic hepatitis B, and is typically prescribed for long-term use. Kidney dysfunction has been reported in people treated with tenofovir disoproxil, including rare cases of proximal renal tubular dysfunction that appear related to long-term exposure but are not well understood. Adverse renal effects such as hypophosphataemia may have an impact on bone architecture which could result in clinical problems such as fragility fractures. Monitoring for phosphate loss and bone disease could have a role in preventing clinically significant bone problems in people with chronic hepatitis B receiving long-term tenofovir disoproxil. However, the cost effectiveness and clinical utility of routine monitoring needs to be established before recommendations can be made about its use.

2.4 Prophylactic treatment in people receiving immunosuppressive therapy

Further research should be undertaken to determine whether long-term use of mild immunosuppressive agents for autoimmune and allergic problems presents a risk for reactivation of HBV infection in people with previous or current chronic hepatitis B, including occult HBV infection. The cost effectiveness of routine tests for HBV in this population, including HBV DNA

for occult HBV infection, and the need for prophylactic treatment with nucleoside or nucleotide analogues needs further evaluation.

Why this is important

Reactivation of HBV may occur spontaneously or arise during immunosuppression. Solid organ transplantation, chemotherapy and immunosuppressive drugs used to treat autoimmune diseases are key causes of HBV reactivation. Antiviral agents can be used as prophylaxis to prevent reactivation of HBV infection in people receiving immunosuppressive therapy but the optimal treatment and duration of therapy are unknown. Decision-making and cost-effectiveness studies are needed to determine optimal screening strategies to identify people at risk of HBV reactivation. People with occult HBV (including people coming from high endemicity regions) might carry a low, but not negligible, risk of viral reactivation. Prospective studies are needed to assess the risk of HBV reactivation in people receiving mild immunosuppressants or biological treatment for autoimmune diseases, to identify risk factors that predict HBV reactivation in this population, and evaluate treatment or pre-emptive strategies using existing nucleoside and nucleotide analogues.

3 Other information

3.1 Scope and how this guideline was developed

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover.

How this guideline was developed

NICE commissioned the National Clinical Guideline Centre to develop this guideline. The Centre established a Guideline Development Group (see section 4), which reviewed the evidence and developed the recommendations.

The methods and processes for developing NICE clinical guidelines are described in The guidelines manual.

3.2 Related NICE guidance

Details are correct at the time of consultation on the guideline (January 2013). Further information is available on the NICE website.

Published

General

- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Medicines adherence. NICE clinical guidance 76 (2011).

Condition-specific

- Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. NICE public health guidance 43 (2012).
- Increasing the uptake of HIV testing among men who have sex with men. NICE public health guidance 34 (2011).
- Increasing the uptake of HIV testing among black Africans in England. NICE public health guidance 33 (2011).
- Alcohol-use disorders. NICE clinical guideline 115 (2011).
- Reducing differences in the uptake of immunisations. NICE public health guidance 21 (2009).
- Tenofovir disoproxil fumarate for the treatment of hepatitis B. NICE technology appraisal guidance 173 (2009).

- Antenatal care. NICE clinical guideline 62 (2008).
- Entecavir for the treatment of chronic hepatitis B. NICE technology appraisal guidance 153 (2008).
- Telbivudine for the treatment of chronic hepatitis B. NICE technology appraisal guidance 154 (2008).
- Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B.NICE technology appraisal guidance 96 (2006).
- Obesity. NICE clinical guideline 43 (2006).

Under development

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

- Hepatitis C. NICE clinical guideline. Publication date to be confirmed.

4 The Guideline Development Group, National Collaborating Centre and NICE project team

4.1 Guideline Development Group

Aftab Ala
Consultant Gastroenterologist and Hepatologist, Frimley Park Hospital NHS Foundation Trust, Surrey

Elizabeth Boxall
Consultant clinical scientist

Steven Bradley (September 2011 – January 2012)
Patient and carer member

Ashley Brown (co-optee)
Consultant Hepatologist, Imperial College, London

Joyeta Das (co-optee)
Lead Pharmacist, Hepatology, Imperial College Healthcare NHS Trust, London

Geoffrey Dusheiko
Professor of Medicine, UCL Division of Liver and Digestive Health and Royal Free Hospital, University College London Medical School

Patrick Kennedy
Consultant Hepatologist and Senior Lecturer, Barts and the London NHS Trust

Emily Lam
Patient and carer member

Alan Mitchell
Clinical Director, Renfrewshire Community Health Partnership and East Renfrewshire Community Health and Care Partnership

Angela Narbey
Nurse consultant, liver disease, Queen Elizabeth Hospital, Woolwich

Nadia Permaloo (co-optee)
Regional antenatal screening coordinator, London – hosted by Inner North West London NHS for the National Screening Committee

Howard Thomas (Chair)
Emeritus Professor, Department of Hepatology and Gastroenterology Division of Medicine, Imperial College, London

Gareth Tudor-Williams
Reader in Paediatric Infectious Diseases, Imperial College, London

Javier Vilar
Consultant in Infectious Diseases, North Manchester General Hospital, Pennine Acute Hospitals

Sarah Wise (April – September 2012)
Patient and carer member

4.2 National Clinical Guideline Centre

Sarah Bermingham
Health Economist

Grant Hill-Cawthorne
Clinical Advisor

Ralph Hughes
Health Economist

Amy Kelsey
Project Manager

Rosa Lau
Research Fellow

Gill Ritchie

Guideline Lead

Grammati Sarri
Senior Research Fellow

Laura Sawyer
Senior Health Economist

Maggie Wesby
Clinical Effectiveness Lead

Richard Whittome
Information Scientist

4.3 NICE project team

Elaine Clydesdale
Guideline Coordinator

Sarah Dunsdon
Guideline Commissioning Manager

Nicole Elliott
Associate Director

James Hall
Editor

Prashanth Kandaswamy
Health Economist

Anna Poppa
Editor

Nichole Taske
Technical Lead