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SPECIAL REPORT

Treatment of chronic hepatitis B virus infection – Dutch national guidelines

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ABSTRACT

The development of this guideline was initiated and coordinated by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen). The aim is the establishment of national standards in the evaluation and antiviral treatment of patients with chronic hepatitis B virus (HBV) infection. This includes recommendations on the initial evaluation of patients, choice and duration of antiviral therapy, follow-up after antiviral therapy and monitoring of patients not currently requiring antiviral therapy.

The initial evaluation of chronic HBV-infected patients should include testing of liver biochemistry, virus serology and abdominal imaging. In patients without cirrhosis, antiviral treatment is recommended for those with a serum HBV DNA of at least 1.0 x 10^5 c/ml (≥2.0 x 10^4 IU/ml) in combination with: a) elevation of serum alanine aminotransferase (ALAT) level above twice the upper limit of normal during at least three months, and/or b) histological evidence of porto-portal septa or interface hepatitis on liver histology. In patients with cirrhosis, antiviral treatment is recommended if serum HBV DNA is 1.0 x 10^4 c/ml (≥2.0 x 10^3 IU/ml) or higher, independent of ALAT levels or histological findings. If the patient has decompensated cirrhosis, antiviral treatment is recommended if serum HBV DNA is 1000 c/ml (≥200 IU/ml) or higher.

Patients who do not have an indication for antiviral treatment should be monitored because there is a risk of (re)activation of disease activity. Monitoring every three to six months is recommended for HBeAg-positive and HBeAg-negative patients with high viraemia (HBV DNA ≥1.0 x 10^5 c/ml or ≥2.0 x 10^4 IU/ml) and normal ALAT levels. For patients with serum HBV DNA below 1.0 x 10^5 c/ml (<2.0 x 10^4 IU/ml) the recommended frequency of monitoring is every three to six months for HBeAg-positive patients and every six to 12 months for HBeAg-negative patients.

Peginterferon (PEG-IFN) therapy should be considered as initial therapy in both HBeAg-positive and HBeAg-negative patients without contraindications for treatment with this drug because of the higher chance of achieving sustained response compared with nucleos(t)ide analogue therapy. In patients starting nucleos(t)ide analogue therapy, the use of lamivudine is not preferred if long-term antiviral treatment is expected due to the high risk of antiviral resistance against this drug. Of the currently licensed nucleos(t)ide analogues, entecavir has the lowest risk of antiviral resistance (compared with lamivudine, adefovir and telbivudine), while suppression of viral replication seems most profound with either entecavir or telbivudine.

The recommended duration of treatment with PEG-IFN is one year for both HBeAg-positive and HBeAg-negative patients. In HBeAg-positive patents, nucleos(t)ide analogue therapy should at least be continued until HBeAg seroconversion and a decline in HBV DNA to below 400 c/ml (80 IU/ml) has been achieved and maintained for six months during therapy. Whether nucleos(t)ide analogue therapy can be safely discontinued in HBeAg-negative patients is unknown; usually prolonged or indefinite antiviral treatment is necessary.

Patients receiving PEG-IFN should be monitored once a month, while three monthly monitoring suffices for those receiving nucleos(t)ide analogues. Genotypic analysis of the HBV polymerase is indicated if an increase in serum HBV DNA of at least 1 $\log_{10}$ c/ml (IU/ml) compared with the nadir value is observed during nucleos(t)ide analogue therapy. Antiviral therapy should be changed as soon as possible in case of confirmed genotypic resistance. Adding a second antiviral agent seems beneficial over switching to another agent.

With the availability of multiple new antiviral drugs for the treatment of chronic hepatitis B, effective treatment is now possible for more patients and for longer periods. However, the complexity of HBV therapy has also increased. Nowadays, virtually all chronic HBV-infected patients can be effectively managed, either by inducing sustained off-treatment response or by maintaining an on-treatment response.

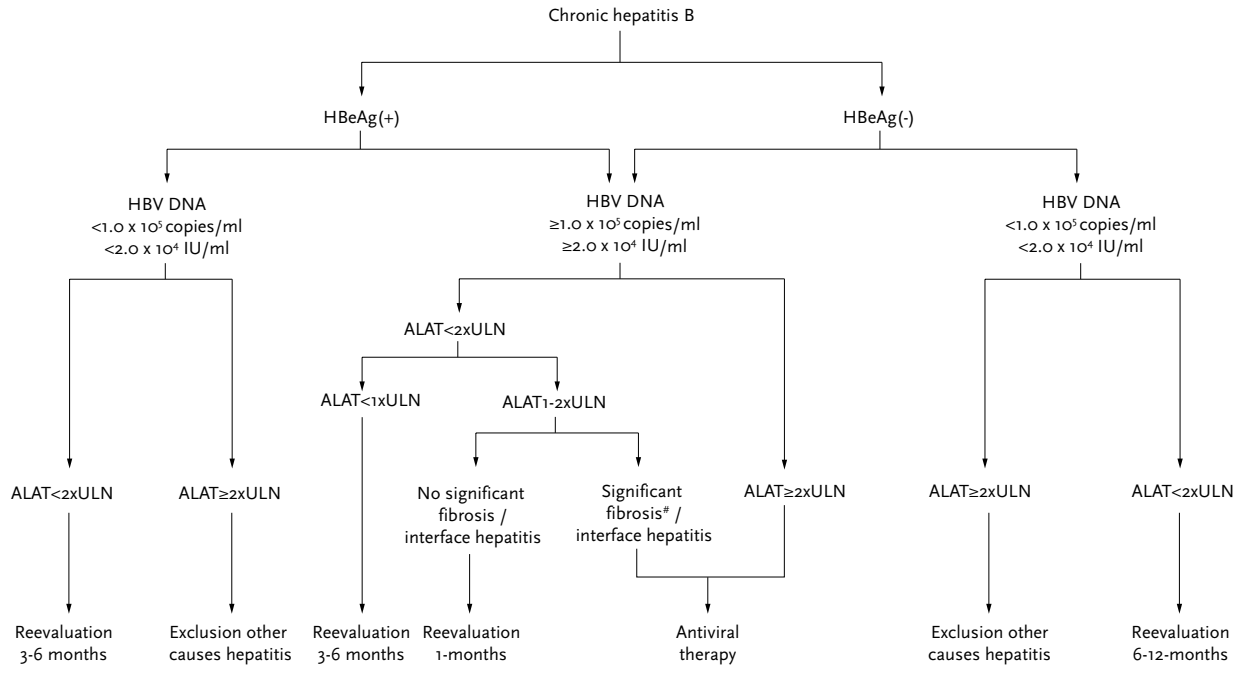
INTRODUCTION

About one-third of the world's population has evidence of HBV infection and chronic hepatitis B affects about 400 million people worldwide.[1,2] More than 500,000 people die yearly of HBV-related liver disease, largely due to complication of cirrhosis or hepatocellular carcinoma.[3] The Netherlands is a low endemic country for HBV infection, the estimated seroprevalence of HBsAg and anti-HBc is about 0.2% and 2.1%, respectively.[4] Risk groups with a higher prevalence of HBV infection include immigrants from areas with intermediate or high prevalence of HBV infection, males who have sex with males and people with multiple sexual contacts. Despite the availability of a safe and effective vaccine for over 20 years now, HBV infection remains an important health problem. Antiviral treatment of chronic hepatitis B has dramatically changed over the last decade; with the availability of multiple new antiviral agents the treatment of chronic HBV infection has become more effective, but more complex as well.

Multiple consensus guidelines for the treatment of chronic hepatitis B have been published in the last few years.[3,5,6] However, there is currently no standard of care for the management and antiviral treatment of chronic HBV-infected patients in the Netherlands. Therefore, a committee was convened by the Netherlands Association of Gastroenterologists and Hepatologists (Nederlandse Vereniging van Maag-Darm-Leverartsen) to formulate consensus-based guidelines for the management and treatment of chronic HBV-infected adults (*figure 1*).

The guideline provides recommendations on the initial evaluation of chronic HBV-infected patients, choice of (initial) antiviral therapy, follow-up during and after antiviral therapy and monitoring of patients currently not requiring antiviral therapy. Management of patients with coinfections of HBV and hepatitis C virus (HCV), hepatitis delta virus (HDV) or human

Figure 1. *Management of chronic hepatitis B virus infected patients*



This flowchart shows the recommendations on the management of chronic HBV-infected patients based on HBeAg status, serum HBV DNA and ALAT levels. # Significant fibrosis: at least porto-portal septa on liver histology. ULN = upper timit of normal.

immunodeficiency virus (HIV) is not discussed in this guideline. The recommendations in this guideline have been defined in accordance with recent international literature, data presented at international symposia and guidelines of the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and the Asian-Pacific Association for the Study of the Liver (APASL).[3,5,6] The level of recommendation was performed according to the Dutch Institute for Healthcare Improvement (CBO) (http://www.cbo.nl/product/ richtlijnen/handleiding_ebro/ article20060207153532) (*tables 1A* and *1B*).

Table 1A. *Quality of studies on which a recommendation is based*

Grade	Definition
A1	Systematic review of at least two independent studies of A2 level
A2	Randomised double-blind controlled study of adequate quality and size
B	Comparative study not fulfilling the characteristics of A2 level studies (including case-control studies and cohort studies)
C	Noncomparative studies
D	Expert opinion

Table 1B. *Quality of evidence on which a recommendation is based*

Grade	Definition
I	Study of level A1 or at least two independent studies of level A2
II	Single level A2 study or at least two independent level B studies
III	Single level B or C study
IV	Expert opinion

NATURAL HISTORY

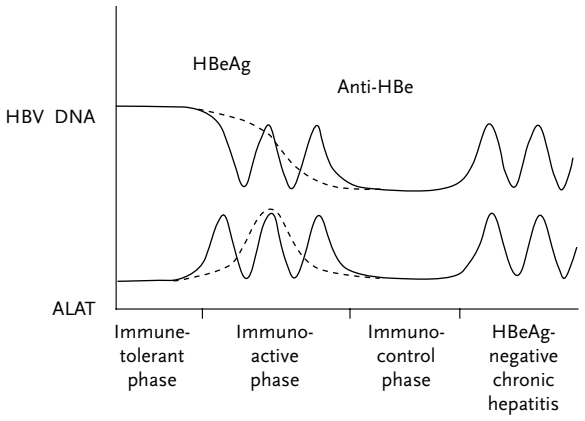
Infection with HBV in adulthood is usually not associated with symptomatic disease and results in chronic infection in less than 5% of cases.[3] However, infection during childhood is associated with a much higher risk of chronicity, up to 90% in case of perinatal transmission.[3] Chronic HBV infection is defined as detectable hepatitis B surface antigen (HBsAg) in serum for at least six months.

Phases of infection

Chronic HBV-infected patients typically present in one of four phases of infection (*figure 2*).[7] In the immunotolerant phase, hepatitis B e antigen (HBeAg) is detectable and serum HBV DNA is high (>1.0 x 10^5 c/ml or >2.0 x 10^4 IU/ml), while serum alanine aminotransferase (ALAT) is normal. Patients infected in early childhood usually remain in this phase of infection for 10 to 30 years.[8] In the immunoactive phase, an active host's immune response against the virus results in a rise in ALAT accompanied by a decline in HBV DNA; loss of HBeAg with seroconversion to anti-HBe can occur. The immune control phase follows HBeAg seroconversion and is characterised by low viraemia (<1.0 x 10^4 c/ml or <2.0 x 10^3 IU/ml) and normalisation of ALAT. Although HBV replication persists, it is profoundly suppressed by an active immune response. In a significant proportion of HBeAg-negative patients, viral replication and hepatic inflammation persist or recur, usually due to the selection of HBV variants with mutation in the HBV genome (precore or core promoter mutants) which hamper the production of HBeAg. These patients develop HBeAg-negative chronic hepatitis. Patients with chronic hepatitis B who acquire infection in adulthood often skip the immunotolerant phase and enter the immuno-active phase shortly after the infection.

Reactivation of HBV infection can occur in case of immunosuppression; it is therefore recommended to determine HBV status in all patients prior to the start of chemotherapy or treatment with selective antibodies.

Figure 2. *Phases of chronic hepatitis B virus infection*



Patients can be categorised based on HBeAg-status, serum HBV DNA and ALAT levels.

Cirrhosis

The annual incidence of cirrhosis in patients with chronic hepatitis B is about 6%, with a five-year cumulative incidence of 20%.[9] The course of the disease strongly varies among individual patients; progression of liver damage particularly occurs in those with persistent hepatic inflammation.[10] Factors associated with an increased risk of developing liver cirrhosis include high serum HBV DNA, coinfection with HCV, HDV or HIV, repeated episodes of acute exacerbation and severe necroinflammation at diagnosis.[3,11,12] The annual risk of hepatic decompensation is about 3% in patients with pre-existent cirrhosis.[3]

Presence of liver cirrhosis is associated with a diminished five-year survival rate of about 84%, for patients with decompensated cirrhosis this is only 14 to 30%.[13-15]

Hepatocellular carcinoma

Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC), the majority of patients with HCC have underlying cirrhosis (80 to 90%).[16] The annual incidence of HCC in European chronic hepatitis B patients is about 2%. In patients from Asia, the risk of developing HCC is higher, with an annual incidence of about 3%.[16] Factors associated with an increased risk of developing HCC in patients with cirrhosis include high age, male sex, persistent hepatic inflammation, HBV DNA >1.0 x 10^4 c/ml (>2.0 x 10^3 IU/ml), HBeAg positivity, coinfection with HCV or HIV, and alcohol abuse.[16-19]

INITIAL EVALUATION

The initial evaluation of patients with chronic HBV infection should include a detailed history, with special emphasis on risk factors for infection with blood-borne viruses and sexual transmitted diseases, alcohol use, and family history of HBV infection and liver cancer. Physical examination should focus on signs of chronic liver disease and cirrhosis (palmar erythema, spider nevi, gynaecomasty, flapping tremor and testicular atrophy), portal hypertension (ascites, splenomegaly and abdominal wall collaterals) and liver failure (jaundice and hepatic encephalopathy).

Laboratory tests should include assessment of liver enzymes (aminotransferases), liver function tests (albumin, bilirubin and prothrombin time), full blood count and kidney function tests. Virus serology should include markers of HBV replication (quantification of HBV DNA, HBeAg and anti-HBe) and in patients at increased risk, also tests for coinfection with HCV, HDV, or HIV. Determination of HBV genotype may be of use in patients starting antiviral therapy, as this may guide the choice of therapy.

Abdominal ultrasound should be performed in all patients, with special emphasis on signs of cirrhosis (irregular liver surface, blunt liver edge and narrowed hepatic veins), portal hypertension (diminished portal flow speed, splenomegaly, venous collaterals and ascites) and focal liver lesions.

Performing a liver biopsy is often indicated, but does not have to be routinely performed in all chronic HBV-infected patients. A liver biopsy should particularly be considered in patients with an indication for antiviral therapy in order to assess baseline necroinflammatory activity and fibrosis stage. If there is any doubt about the need for starting antiviral therapy, liver biopsy is probably of even greater value as it may give additional information on whether antiviral therapy or a conservative approach is justified. For patients in the immune-control phase (inactive HBsAg carrier state) a liver biopsy should be considered if cirrhosis is suspected. Patients in the immune control and HBeAg-negative hepatitis phase are usually older, have been infected with HBV longer and more often develop advanced fibrosis or cirrhosis as compared with patients in other phases of infection.[20] If liver histology shows the presence of cirrhosis it is not recommended to discharge the patient because of the risk of HCC developing in these patients, even in patients with inactive disease. Patients in the immunotolerant phase, on the other hand, rarely have significant fibrosis and progression of disease should only be suspected in case of transition to the immunoactive phase.[21] Performing a liver biopsy can therefore usually be postponed in such cases.

Surveillance for HCC, by abdominal ultrasound every six to 12 months, is recommended for all chronic HBV-infected patients with cirrhosis, in particular in those at increased risk of developing HCC.[6,22] Patients at increased risk of developing HCC include Asian males over 40 years, Asian females over 50 years, patients with a family history of HCC, Africans over 20 years, patients with high HBV DNA levels and those with persistent hepatic inflammation.[23] Also in patients without cirrhosis but with an increased risk of developing HCC, surveillance for HCC should be considered. Surveillance for HCC results in detection of HCC at an earlier stage and thereby improved survival.[24] Routine measurement of α-fetoprotein is in general not useful as this does not improve the efficacy of screening and leads to an increase in false-positive findings.[23] In patients with cirrhosis, upper gastrointestinal endoscopy should be considered to confirm or exclude the presence of oesophageal varices.[25]

Hepatitis A virus (HAV) immunity should be established in all patients with chronic hepatitis B, since the risk of a fulminant course of acute HAV infection is increased compared with healthy controls.[26,27] Despite the fact that the actual risk of fulminant HAV is low, HAV vaccine is recommended for all chronic HBV-infected patients not immune to HAV.

Recommendations	
The initial evaluation of chronic HBV-infected patients should include a detailed history and physical examination. Blood chemistry, full blood count, virus serology, including quantification of serum HBV DNA, and abdominal ultrasound should be performed. Performing a liver biopsy should particularly be considered in case of active hepatitis and if there is any doubt about the need for starting antiviral therapy.	Level 4
Surveillance for hepatocellular carcinoma by abdominal ultrasound every 6 to 12 months is recommended in patients with cirrhosis.	Level 3
Hepatitis A vaccination is recommended in all chronic hepatitis B patients without immunity against the hepatitis A virus because of the increased risk of developing fulminant acute hepatitis A compared with healthy controls.	Level 1

INDICATIONS FOR ANTIVIRAL THERAPY

In a considerable proportion of chronic HBV-infected patients there is no need for antiviral treatment.[28] Whether or not antiviral treatment should be started depends on multiple factors (*table 2*). First, active viral replication should be present, as shown by serum HBV DNA of at least 1.0 x 10^5 c/ml (2.0 x 10^4 IU/ml). In HBeAg-negative patients, the risk of (re)activation of disease activity and progression of disease seems to be already increased in those with serum HBV DNA above 1.0 x 10^4 c/ml (2.0 x 10^3 IU/ml) compared with patients with lower HBV DNA levels.[29] In addition to HBV DNA, the degree of hepatic fibrosis and inflammation plays an important role in assessing the need for antiviral therapy. This is represented by serum ALAT levels and necroinflammatory activity on liver histology. Serum ALAT of at least two times the upper limit of normal (ULN) for a period of three to six months is usually considered an indication for antiviral therapy. In patients with serum HBV DNA above 1.0 x 10^5 c/ml (2.0 x 10^4 IU/ml) and persistent mild hepatic inflammation (ALAT 1 to 2 x ULN), but with significant liver fibrosis (porto-portal septa) or interface hepatitis, antiviral therapy should also be considered. If serum ALAT is elevated but serum HBV DNA is low, other causes of hepatitis should be considered. If no other underlying aetiology can be found and liver biopsy shows hepatitis B virus associated inflammation, antiviral treatment should be considered.

In patients with compensated cirrhosis, antiviral treatment should be considered if HBV DNA is 1.0 x 10^4 c/ml (2.0 x 10^3 IU/ml) or higher. HBV DNA above this level is associated with an increased risk of progression to decompensated cirrhosis or HCC.[17] Patients with decompensated cirrhosis should be offered antiviral therapy if HBV DNA is 1000 c/ml (200 IU/ml) or higher, as suppression of viral replication can significantly improve liver function and survival in these patients.[30,31]

Over 90% of babies born to HBsAg-positive mothers are effectively protected by passive-active immunisation. However, in pregnant patients with very high viraemia (HBV DNA ≥1.0 x 10^9 c/ml or ≥2.0 x 10^8 IU/ml), the risk of vaccination failure in the newborn is about 30%.[32,33] In these women, nucleos(t)ide analogue therapy from week 32 of pregnancy can significantly lower this risk.[33,34] Lamivudine is the antiviral agent of choice because of extensive clinical experience in pregnancy, particularly in HIV infection.[33-35] Switching to another antiviral agent after delivery can be considered if prolongation of antiviral therapy is indicated. In patients becoming pregnant during nucleos(t)ide analogue therapy, the risks of stopping antiviral therapy (in particular acute exacerbation) should be balanced against the risk for the unborn child when continuing the drug. Recommendations on what to do in such cases are not possible as scientific evidence is lacking; consulting a centre with expertise on treatment of chronic HBV infection is recommended.

In HBsAg-positive patients starting chemotherapy or treatment with selective antibodies, prophylactic antiviral treatment with a nucleos(t)ide analogue is recommended until six months after the completion of the immunosuppressive therapy. Prophylactic antiviral therapy has been shown to significantly reduce the risk of reactivation and hepatitis B-related death.[6,36] In patients requiring prophylactic antiviral treatment, who have baseline HBV

Table 2. *Recommendations of management of chronic hepatitis B based on HBeAg status, ALAT and HBV DNA*

Severity of disease	HBeAg status	ALAT	HBV DNA c/ml (IU/ml)	Recommended management
Chronic hepatitis	HBeAg positive	≥2x ULN	≥1.0 x 10^5 (≥2.0 x 10^4)	Antiviral therapy
		<2x ULN	≥1.0 x 10^5 (≥2.0 x 10^4)	3-monthly monitoring, consider liver biopsy in case of persistently elevated ALAT (and antiviral therapy in case of active necroinflammation)
		<2x ULN	<1.0 x 10^5 (<2.0 x 10^4)	3-monthly monitoring
		≥2x ULN	<1.0 x 10^5 (<2.0 x 10^4)	Exclude other cause of hepatitis, consider liver biopsy
	HBeAg negative	≥2x ULN	≥1.0 x 10^5 (≥2.0 x 10^4)	Antiviral therapy
		<2x ULN	≥1.0 x 10^5 (≥2.0 x 10^4)	3-6 monthly monitoring, consider liver biopsy in case of persistently elevated ALAT (and antiviral therapy in case of active necroinflammation)
		<2x ULN	<1.0 x 10^5 (<2.0 x 10^4)	6-12 monthly monitoring
		≥2x ULN	≥1.0 x 10^4 - <1.0 x 10^5 (≥2.0 x 10^3 - <2.0 x 10^4)	Antiviral therapy if no other causes of hepatitis are present
			<1.0 x 10^4 (<2.0 x 10^3)	Exclude other cause of hepatitis, consider liver biopsy
Compensated cirrhosis	-	-	≥1.0 x 10^4 (≥2.0 x 10^3)	Antiviral therapy
Decompensated cirrhosis	-	-	>300 (>60)	Antiviral therapy

ULN = upper limit of normal.

DNA of above 1.0 x 10^4 c/ml (>2.0 x 10^3 IU/ml), the regular endpoints of antiviral therapy should be applied (see also *Choice and duration of antiviral therapy*).[6] Prophylactic antiviral therapy can also be considered in anti-HBc positive patients, since these patients are also at risk for reactivation in case of severe immunosuppression.[36]

Recommendations	
In patients without cirrhosis, antiviral therapy is recommended in those with serum HBV DNA of at least 1.0 x 10^5 c/ml (2.0 x 10^4 IU/ml) in combination with serum ALAT above twice the upper limit of normal for at least 3 months, and/or presence of interface hepatitis or significant fibrosis on liver histology.	Level 1
In patients with cirrhosis, antiviral therapy is recommended if serum HBV DNA is 1.0 x 10^4 c/ml (2.0 x 10^3 IU/ml) or higher, irrespective of serum ALAT or HBeAg status.	Level 2
In patients with decompensated cirrhosis, antiviral therapy should be considered in those with serum HBV DNA of 1000 c/ml (200 IU/ml) or higher, irrespective of serum ALAT or HBeAg status.	Level 3
Antiviral therapy from week 32 of pregnancy until delivery can be considered in pregnant women with serum HBV DNA of 1.0 x 10^9 c/ml (2.0 x 10^8 IU/ml) or higher in order to lower the risk of failure of passive-active immunisation in the newborn.	Level 2

MONITORING OF PATIENTS NOT REQUIRING ANTIVIRAL THERAPY

Patients who do not have an indication for antiviral therapy should be monitored since disease activity may fluctuate over time (*table 2*). Three to six monthly monitoring of serum ALAT is recommended for HBeAg-positive patients with high viraemia (HBV DNA ≥1.0 x 10^5 c/ml or ≥2.0 x 10^4 IU/ml) and normal ALAT, with more frequent monitoring when ALAT becomes elevated. For HBeAg-negative patients with high serum HBV DNA (≥1.0 x 10^5 c/ml or ≥2.0 x 10^4 IU/ml) and normal ALAT, monitoring is also recommended every three to six months. In those with low viraemia, six to 12 monthly monitoring suffices.

Recommendation	
Patients who are currently not candidates for antiviral therapy should be monitored since disease activity may fluctuate over time. For both HBeAg-positive and HBeAg-negative patients with high serum HBV DNA (≥1.0 x 10^5 c/ml or ≥2.0 x 10^4 IU/ml) and normal ALAT, three to six monthly monitoring is recommended. For patients with low serum HBV DNA (<1.0 x 10^5 c/ml or <2.0 x 10^4 IU/ml) the recommended frequency of follow-up is once per three to six months for HBeAg-positive patients and once per six to 12 months for HBeAg-negative patients.	Level 1

GOALS OF ANTIVIRAL THERAPY

The ultimate goal of antiviral therapy for chronic HBV-infected patients is clearance of HBsAg and appearance of anti-HBs. However, since HBsAg seroconversion can only be achieved in a small proportion of patients, other surrogate endpoints of antiviral therapy have been chosen. These endpoints can generally be assessed after one year of treatment and are associated with favourable long-term outcome. The most important endpoints of antiviral therapy include HBeAg seroconversion (loss of HBeAg with appearance of anti-HBe) in previously positive patients, decline in serum HBV DNA below the lower limit of detection of a sensitive polymerase chain reaction (PCR) assay (or comparable test), biochemical response (normalisation of ALAT) and improvement of liver histology (decrease in necroinflammatory activity and no increase in fibrosis). These endpoints indicate the presence of inactive disease in patients with previous active hepatitis. Furthermore, responses can be distinguished in those sustained after discontinuation of therapy versus those that need to be maintained by antiviral therapy. In case of sustained response there is an active immune-response against the virus, as shown by HBeAg or HBsAg seroconversion. In case of treatment-maintained response there is persistent suppression of viral replication by the antiviral drug, but no active immune response. Sustained response is particularly achieved with (peg)interferon therapy, while treatment-maintained response can be achieved with long-term nucleos(t)ide analogue therapy in the majority of patients. Higher rates of sustained HBeAg seroconversion have been achieved with interferon compared with lamivudine.[37] It is not clear whether substantial rates of sustained response can be reached with the new potent nucleos(t)ide analogues after HBeAg seroconversion and subsequent withdrawal of therapy.

ANTIVIRAL DRUGS FOR THE TREATMENT OF CHRONIC HBV INFECTION

Peginterferon

Interferon-alpha (IFN-α) has been used for the treatment of chronic HBV infection since the 1980s. Interferons are natural occurring cytokines with immunomodulatory, antiproliferative and antiviral activity.[38] IFN-α has been a mainstay in the treatment of chronic HBV infection since it was licensed for this indication in the early 1990s, both in HBeAg-positive and HBeAg-negative chronic hepatitis B. In the majority of HBeAg-positive patients IFN-induced HBeAg seroconversion is durable (87%)

and eventually leads to HBsAg loss in about 50% of these responders.[39] The risk of developing cirrhosis and HCC is significantly lower for responders to IFN therapy compared with nonresponders.[39]

The addition of a polyethylene glycol molecule (PEG) to the IFN has resulted in a significant increase in half-life, thereby allowing administration once weekly. In the last few years clinical research has focussed on the use of peginterferon (PEG-IFN) for the treatment of chronic hepatitis B. Two types of peginterferons have been developed (peginterferon-α2a and peginterferon-α2b), of which peginterferon-α2a has been licensed for the treatment of chronic HBV infection in the Netherlands in a weekly dose of 180 µg (subcutaneous) for 48 weeks in both HBeAg-positive and HBeAg-negative patients.

In HBeAg-positive patients, PEG-IFN appears at least as effective as conventional IFN with loss of HBeAg in 35% and seroconversion to anti-HBe in 29 to 32% of patients.[40-43] Addition of lamivudine did not lead to an increase in sustained response rates compared with PEG-IFN monotherapy. PEG-IFN induced HBeAg loss is sustained in 80 to 86% of HBeAg-positive patients.[44,45] HBsAg seroconversion occurs in 3 to 7% of PEG-IFN treated patient within six months after the end of therapy (10 to 20% of those with HBeAg loss).

The likelihood of HBeAg loss after PEG-IFN therapy is associated with the HBV genotype; patients with genotype A or B have a higher chance of achieving HBeAg loss than those with genotype C or D.[42,46] Genotype A infected patients significantly more often show loss of HBeAg and HBsAg than those infected with genotype D.[42,47]

Only one large randomised trial of PEG-IFN therapy has been performed in HBeAg-negative chronic hepatitis B.[48] Combined response of HBV DNA below 2.0 x 10^4 c/ml and normalisation of ALAT occurred in 36% of patients. At 24 weeks post-treatment, serum HBV DNA below 400 c/ml was observed in 19%. As in HBeAg-positive chronic hepatitis B, the addition of lamivudine did not increase response rates in these patients either. HBsAg seroconversion occurred in 4% of PEG-IFN treated HBeAg-negative patients (over 10% of those with combined response).[48]

Major disadvantages of PEG-IFN therapy are the subcutaneous administration and frequent side effects (*table 3*). Particularly flu-like symptoms, cytopenia and psychiatric adverse events are frequently observed,[49] but rarely require discontinuation of therapy.[49,50]

PEG-IFN is contraindicated in patients with advanced cirrhosis (albumin <35 g/l, bilirubin >34 µmol/l or prolongation of prothrombin time by more than 4 seconds) because of the increased risk of decompensation in case of acute exacerbation.[51,52] Other important contraindications of treatment with PEG-IFN are severe psychiatric comorbidity (depression and suicidal ideation), severe cardiac disease and autoimmune hepatitis (or other autoimmune disorders). A major advantage of PEG-IFN therapy is the high rate of sustained response (over 80% in HBeAg-positive patients and about 40% of HBeAg-negative patients who initially responded to the treatment).[44,45,53]

Table 3. *Undesirable effects during treatment with peginterferon alpha*[49,100-102]

Frequency	Undesirable effects
>30% (very frequent)	Flu-like symptoms Headache Fatigue Pyrexia Chills Myalgia Thrombocytopenia Induction of autoantibodies
1-30% (frequent)	Anorexia Erythema at injection site Insomnia Alopecia Lack of motivation Lack of concentration Irritability, agitation Emotional instability Depression Diarrhoea Autoimmune disease (thyreoiditis, Sjögren's disease) Neutropenia Change of taste
<1% (rare)	Polyneuropathy Paranoia of suicidal ideation Diabetes mellitus Retinopathy Optic neuritis Hearing loss Seizures Loss of libido Cardiotoxicity

Nucleos(t)ide analogues

In the last decade there has been a major advance in the treatment of chronic hepatitis B with nucleos(t)ide analogues. These antiviral agents inhibit the viral polymerase and thereby viral replication. Advantages of nucleos(t)ide analogues are the oral administration, rapid decline in HBV DNA and minimal side effects. A major disadvantage is that the majority of patients need prolonged or even indefinite therapy, as sustainability of response after discontinuation of therapy is limited. Furthermore, the risk of antiviral resistance increases with the duration of antiviral therapy. Antiviral resistance is caused by the selective selection of naturally occurring mutations in the HBV polymerase. Rapid and profound viral suppression reduces the risk of antiviral resistance.[54]

Lamivudine

Lamivudine was the first nucleoside analogue licensed for the treatment of chronic HBV infection in 1999. Lamivudine should be given in a dosage of 100 mg daily and has excellent safety and tolerability. In HBeAg-positive

patients, treatment with lamivudine for one year results in HBeAg seroconversion plus serum HBV DNA below 1.0 x 10^5 c/ml (2.0 x 10^4 IU/ml) in 16 to 22% of patients.[55-60] The rate of HBeAg seroconversion increases with increasing duration of therapy to 29, 40 and 47% after two, three and four years of therapy, respectively.[57,58,61] Decline in HBV DNA below 7.0 x 10^5 c/ml (1.4 x 10^5 IU/ml) was observed in 65% of patients.[62]

In HBeAg-negative patients, serum HBV DNA below 400 c/ml (<80 IU/ml) was observed in 68 to 73% of patients after one year of lamivudine. Of these patients 68 to 96% also had a biochemical response.[48,63,64] In HBeAg-negative patients the rate of virological response declined with increasing duration of therapy, largely due to the increasing risk of antiviral resistance. Response rates at year two, three and four were 67, 60 and 39%, respectively.[63,65,66] Treatment with lamivudine has been shown to result in a decrease of disease progression and development of HCC in patients with advanced fibrosis or cirrhosis compared with untreated controls.[67]

The major disadvantage of lamivudine is the high incidence of antiviral resistance. The majority of patients with viral breakthrough have mutations in the tyrosine-methionine-aspartate-aspartate motif (YMDD) of the HBV polymerase.[66] The most frequently observed mutation is a substitution of methionine for valine or isoleucine at position 204 of the HBV polymerase.[68] Lamivudine resistance occurred in 24% of patients after one year, which increased to 71% after five years.[69] The selection of resistance mutations is often followed by an increase in ALAT.[66] Another disadvantage of lamivudine is the high risk of relapse after discontinuation of therapy; half of patients with lamivudine-induced HBeAg seroconversion had a relapse at two to three years after therapy.[37,70]

Adefovir

Adefovir is a nucleotide analogue with activity against wild-type and lamivudine-resistant HBV. Adefovir was licensed for the treatment of chronic hepatitis B in the Netherlands in 2003 in a daily dosage of 10 mg. Higher dosages may be more effective, but are associated with nephrotoxicity.[71]

In HBeAg-positive patients, a one-year course of adefovir resulted in HBeAg seroconversion in 12%, serum HBV DNA below 1.0 x 10^3 c/ml (200 IU/ml) in 21% and normalisation of ALAT in 48% of patients.[71] The rate of HBeAg seroconversion increased with increasing duration of therapy to 29% after two years and 43% after three years of treatment. The proportion of patients with HBV DNA below 1.0 x 10^3 c/ml (200 IU/ml) increased to 45 and 56% after two and three years, respectively.[72]

Serum HBV DNA below 1.0 x 10^3 c/ml (200 IU/ml) and normalisation of ALAT were observed in 51 and 72% of HBeAg-negative patients after one year of adefovir.[73] After five years of therapy, the proportion of patients with HBV DNA below 1.0 x 10^3 c/ml (200 IU/ml) increased to 67% and to 69% for ALAT normalisation.[74,75] Histological response was observed in 75 to 80% of adefovir-treated patients at year five.[74] However, more recent studies suggested lower response rates during adefovir therapy, with serum HBV DNA above 1.0 x 10^4 c/ml (2.0 x 10^3 IU/ml) in 50% of patients after six months of therapy.[76]

HBeAg loss occurred in 20% of lamivudine-resistant patients treated with adefovir.[77] The proportion of lamivudine-resistant patients with HBV DNA below 400 c/ml (80 IU/ml) was 19% after one year of adefovir therapy.[77]

Antiviral resistance to adefovir occurs less frequently and later during the course of therapy compared with lamivudine. The most important mutations in the HBV polymerase associated with adefovir resistance include a substitution of asparagine for threonine at position 236 and a substitution of alanine for valine or threonine at position 181.[75,78] The reported incidence of adefovir resistance is 0% at year one, 22% at year two and 28% at year five of antiviral therapy.[74,76] In lamivudine-resistant patients treated with adefovir monotherapy the rate of antiviral resistance was 6 to 18% after one year and 21 to 38% after two years.[77,79,80]

Entecavir

Entecavir is a guanine analogue, which was licensed for the treatment of chronic hepatitis B in the Netherlands in 2006. In nucleoside-naive patients, entecavir is given in a daily dosage of 0.5 mg. A daily dose of 1 mg should be used in patients with pre-existent lamivudine resistance. Three large randomised trials have compared entecavir with lamivudine for the treatment chronic hepatitis B.[62,81,82] Decline in HBV DNA was significantly greater with entecavir than lamivudine in both HBeAg-positive and HBeAg-negative patients.[62,81]

HBeAg seroconversion occurred in 21% of entecavir-treated HBeAg-positive patients after one year, while serum HBV DNA below 300 c/ml (60 IU/ml) or below 7.0 x 10^5 c/ml (1.4 x 10^5 IU/ml) was observed in 67 and 91% of patients.[62] The cumulative proportion of patients with undetectable HBV DNA (300 c/ml (60 IU/ml) increased to 82% after three years of therapy.[83] After one year of entecavir treatment, serum ALAT normalised in 68% of patients, which increased to 90% of patients after three years.[83] The proportion of patients with HBeAg loss also increased, to 39% after three years of therapy.[83]

In HBeAg-negative patients, treatment with entecavir resulted in normalisation of ALAT and HBV DNA below 300 c/ml (200 IU/ml) in 78 and 89, and 90 and 94% of patients after one and two years of therapy, respectively.[81,84] Histological response was observed in 70% of entecavir-treated patients after one year.[81]

Response to entecavir was lower in lamivudine-resistant patients, with undetectable HBV DNA in 19% and ALAT normalisation in 61% of patients after 48 weeks of entecavir therapy.[82] HBeAg loss was observed in 8% of these patients.[82]

The rate of entecavir resistance was extremely low in nucleoside-naive patients with antiviral resistance observed in less than 1% of patients after four years of entecavir therapy.[85-87] However, in lamivudine-resistant patients the risk of antiviral resistance is much higher with entecavir resistance in 12, 20, 25 and 40% after one to four years of therapy, respectively.[86-88] These findings implicate cross-resistance of lamivudine and entecavir; entecavir resistance requires pre-existent lamivudine resistance mutations.

Telbivudine

Telbivudine is a nucleoside analogue belonging to the same group of antiviral agents as lamivudine. Telbivudine is administrated orally in a daily dosage of 600 mg. Telbivudine has been licensed for the treatment of chronic hepatitis B in the Netherlands since 2007. In both HBeAg-positive and HBeAg-negative patients, telbivudine resulted in more profound viral suppression than lamivudine.[89]

After one year of treatment with telbivudine HBeAg seroconversion occurred in 22% of HBeAg-positive patients, increasing to 29% after two years of therapy.[89,90] The proportion of patients with serum HBV DNA below 300 c/ml (60 IU/ml) was 60% after one year and 54% after two years of telbivudine therapy. Eighty percent of patients who stopped telbivudine treatment after achieving HBeAg seroconversion had sustained response after a mean period of 35 weeks post-treatment, which was comparable with lamivudine therapy.[91]

Treatment with telbivudine resulted in HBV DNA below 300 c/ml (60 IU/ml) in 88% of HBeAg-negative patients after one year and 79% after two years. Combined response of HBV DNA below 1.0 x 10^5 c/ml (<2.0 x 10^4 IU/ml) and normalisation of ALAT was observed in 75 and 74% of patients after one and two years of therapy, respectively.

Since telbivudine and lamivudine belong to the same group of nucleoside analogues, there is cross-resistance between the two drugs. A substitution of methionine for isoleucine at position 204 is associated with telbivudine resistance. Telbivudine resistance was observed in 2 to 3% of patients after one year and in 7 to 17% after two years of telbivudine therapy.[89,90] The risk of antiviral resistance was strongly associated with viral load at week 24 of treatment. The two-year rate of telbivudine resistance was 4% in HBeAg-positive patients and 2% in HBeAg-negative patients if serum HBV DNA was below 300 c/ml (60 IU/ml) after 24 weeks of therapy. At week 24, HBV DNA below this level was observed in 45 and 80% of HBeAg-positive and HBeAg-negative patients, respectively.[89]

CHOICE AND DURATION OF (INITIAL) THERAPY

When deciding on the antiviral drug to be given, several factors have to be taken into account (*table 4*). The major advantage of PEG-IFN is the higher chance of achieving sustained response compared with nucleos(t)ide analogues with a finite duration of therapy. Disadvantages are the subcutaneous administration and the frequent occurrence of side effects. The major advantages of nucleos(t)ide analogues are the favourable tolerability and the oral administration. Disadvantages are the long duration of therapy and the subsequent risk of antiviral resistance. The costs of a one-year course of nucleos(t)ide analogue therapy are lower than of PEG-IFN, but will easily be higher when long-term therapy is needed.

Table 4. *Choice of initial therapy based on patient characteristics*

Patient characteristics	Peginterferon	Nucleos(t)ide analogue
HBeAg status	HBeAg positive	HBeAg negative
HBV genotype	A or B	C or D
HBV DNA	≤1.0 x 10^9 c/ml (2.0 x 10^8 IU/ml)	>1.0 x 10^9 c/ml (2.0 x 10^8 IU/ml)
ALAT	>2-10 ULN	1-2 or >10 ULN
Severity of liver disease	Compensated	Compensated or decompensated

ULN = upper limit of normal. The above-mentioned characteristics may be of help in choosing an antiviral agent, but do not provide strict recommendations.

PEG-IFN should always be considered as first-line therapy in eligible patients because of the higher chance of achieving sustained off-treatment response compared with nucleos(t)ide analogues (*table 5*), particularly in HBeAg-positive patients. Sustained transition to the immune-control phase (inactive HBsAg carrier state) can be achieved in 30 to 35% of HBeAg-positive patients and 25% of HBeAg-negative patients treated with PEG-IFN, implicating that treatment-induced response is sustained in about 85 and 40% of HBeAg-positive and HBeAg-negative patients, respectively.[45,53] Relapse occurs in at least 40 and 90% of HBeAg-positive and HBeAg-negative patients after discontinuation of nucleos(t)ide analogue therapy, respectively.[64,73,75,92] The latter applies especially to the older nucleos(t)ide analogues. There are insufficient data available for the newer, more potent, nucleos(t)ide analogues.

Patients with a high chance of response to PEG-IFN therapy are those with genotype A or B, with serum HBV DNA below 1.0 x 10^9 c/ml (2.0 x 10^8 IU/ml) and serum ALAT above twice the upper limit of normal.[42,93,94] The licensed duration of peginterferon therapy is one year for both HBeAg-positive and HBeAg-negative chronic hepatitis B. However, the optimal

Table 5. *Response after one year of antiviral therapy and antiviral resistance after 1 to 5 years of therapy*

	HBeAg positive		HBeAg negative						
	HBeAg seroconversion		Undetectable HBV DNA		Antiviral resistance				
Antiviral therapy	**End of therapy**	**Post-treatment**	**End of therapy**	**Post-treatment**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Alpha-interferon	35%[38,103-107]	30%[39,41,103-108]	60%[109-115]	35%[109-112,115]	-	-	-	-	-
Peginterferon	40%[40-43]	35%[40-44]	63%[48]	19%[48]	-	-	-	-	-
Lamivudine	19%[55,56,58-60]	12%[44,70,92]	65%[48, 63, 65]	10%[48, 64]	24%[116]	42%[116]	53%[116]	70%[116]	74%[117]
Adefovir	12%[71]	NA	51%[73]	NA	0%[74]	3%[74]	11%[74]	18%[74]	28%[74]
Adefovir in lamivudine resistance	20%[77]	NA	19%[#77]	NA	6-18%[77,79,80]	21-38%[77,79,80]	NA	NA	NA
Entecavir	21%[62]	NA	90%[81]	NA	0.1%[85]	0.3%[85]	0.4%[87]	0.8%[86]	NA
Entecavir in lamivudine resistance	8%[82]	NA	26%[#118]	NA	12%[85]	20%[85]	25%[87]	40%[86]	NA
Telbivudine	22%[89]	NA	88%[89]	NA	2-3%[89]	7-17%[90]	NA	NA	NA

[#]HBV DNA <400 c/ml in a mixed group of HBeAg-positive and HBeAg-negative patients. NA = not available.

duration of PEG-IFN therapy has not been established. In HBeAg-positive patients, response rates after 24 to 32 weeks of treatment seem comparable with those observed after one year, but head-to-head comparison is not available.[40-43] Since early prediction of response to PEG-IFN is not possible in chronic HBV-infected patients, the recommended the duration of therapy is one year for all patients.

Nucleos(t)ide analogue therapy should be considered in patients not responding to or not eligible for PEG-IFN therapy. This includes patients with autoimmune disease, pre-existent psychiatric disorders or advanced cirrhosis (signs of diminished liver function or portal hypertension). When choosing a nucleos(t)ide analogue, potency and risk of resistance play an important role (*table* 5). Because of the high risk of antiviral resistance, lamivudine should no longer be considered to be the initial therapy in patients who require long-term therapy. However, because of extensive clinical experience, lamivudine can be given to pregnant patients with very high viraemia during the last trimester of pregnancy.[33]

Of the currently available nucleos(t)ide analogues, entecavir has the most favourable resistance profile (in comparison with lamivudine, adefovir and telbivudine) (*table* 5),[87] while entecavir and telbivudine seem most potent.[62,89,95] However, little is known about the long-term safety of entecavir and telbivudine. In patients with lamivudine resistance, treatment with entecavir is not recommended because of the high risk of antiviral resistance. Adefovir add-on therapy is recommended for these patients. The role of telbivudine in the treatment is not yet established. The role of *de-novo* combination therapy of nucleos(t)ide analogues is also unclear. A combination of antiviral drugs could potentially prevent the selection of resistance mutations, but supporting scientific evidence is not available.

In HBeAg-positive patients, nucleos(t)ide analogue therapy should be continued at least until HBeAg seroconversion and HBV DNA below 400 c/ml (80 IU/ml) have been achieved and maintained for six months. It is unclear when nucleos(t)ide analogue therapy can be safely discontinued in HBeAg-negative patients, this may be possible in case of HBsAg seroconversion and HBV DNA below 400 c/ml (80 IU/ml). Nucleos(t)ide analogue therapy therefore needs to be continued for long periods in virtually all HBeAg-negative patients.

Recommendations	
PEG-IFN should be considered the first-line therapy in patients without contraindications because of the higher chance of achieving sustained response compared with nucleos(t)ide analogues.	Level 1
Nucleos(t)ide analogue therapy should be considered in patients not eligible for, not tolerating or not responding to PEG-IFN therapy.	Level 1
Lamivudine is not recommended in patients in whom long-term nucleos(t)ide analogue is expected because of the high risk of antiviral resistance.	Level 1
Of the currently available nucleos(t)ide analogues, entecavir has the lowest risk of antiviral resistance (compared with lamivudine, adefovir and telbivudine). Entecavir and telbivudine seem to provide the most potent viral suppression.	Level 2
The recommended duration of PEG-IFN therapy is one year for both HBeAg-positive and HBeAg-negative patients.	Level 3
In HBeAg-positive patents, nucleos(t)ide analogue therapy should at least be continued until HBeAg seroconversion and a decline in HBV DNA below 400 c/ml (80 IU/ml) have been achieved and maintained for six months during therapy.	Level 2
In HBeAg-negative patients, it is unknown whether nucleos(t)ide analogues can be safely discontinued. Long-term or indefinite antiviral treatment is usually necessary.	Level 2

MONITORING OF ANTIVIRAL THERAPY

PEG-IFN treated patients should be monitored monthly; an additional visit at week two can be considered. Frequently occurring side effects such as depression, irritability, neutropenia and thrombocytopenia require monthly monitoring and blood count. If necessary, PEG-IFN dosage should be reduced or treatment temporarily discontinued. PEG-IFN dosage should be reduced if the neutrophil count is below 0.75 x 10^9/l or the platelet count below 50 x 10^9/l. The dose can reduced by 25% of the original dose until the respective cell fractions have normalised. Temporary discontinuation of PEG-IFN therapy is indicated if the neutrophil count is below 0.50 x 10^9/l or the platelet count below 25 x 10^9/l. Severe side effects such as depression or severe flu-like may also require dose reduction or even (temporary) discontinuation of therapy.

Recommendations on laboratory testing during PEG-IFN and nucleos(t)ide analogue therapy are shown in *table 6*. The recommended frequency of HBV DNA quantification during antiviral therapy is every three to six months, dependent on the risk of antiviral resistance. Testing of serum ALAT is recommended every three months. Prior to the start of nucleos(t)ide analogue therapy a quantitative HBV DNA test and HBV serology should be performed in order to evaluate response to therapy. The recommended frequency of monitoring during nucleos(t)ide analogue therapy is every three months, particularly for the early detection of antiviral resistance. Monitoring of serum creatinine is indicated every three months and nucleos(t)ide analogue dosage or frequency of administration should be reduced in case of severely decreased creatinine clearance (<50 ml/min) (*table 7*). Although nucleos(t)ide analogue therapy generally has an excellent safety and tolerability profile, severe side effects such as lactic acidosis have been described.[96]

Recommendation	
The recommended frequency of monitoring is monthly during PEG-IFN therapy and every three months during nucleos(t)ide analogue therapy.	Level 2

Antiviral resistance

Primary nonresponse is defined as a less than 2 $\log_{10}$ c/ml (or IU/ml) decline in HBV DNA after 24 weeks of nucleos(t)ide analogue therapy.[6] Potential causes of primary nonresponse include antiviral resistance, but also noncompliance, decreased absorption or rapid breakdown.[97] The risk of antiviral resistance is minimal if serum HBV DNA is 400 c/ml or lower after 24 weeks of therapy. Addition of adefovir or

Table 6. *Recommendations on minimal laboratory testing during antiviral therapy*

	Start of therapy	PEG-IFN 4-weekly*	PEG-IFN 3-monthly	Nucleos(t)ide analogues 3-monthly
Aminotransferases (ASAT, ALAT)	X	X		X
Lever function (bilirubin, albumin, prothrombin time)	X		X	X
Kidney function (creatinine)§	X		X	X
Blood count (platelets, neutrophil count)	X	X		
Endocrinology (TSH)	X#		X	
Virus serology (HBsAg,¥ anti-HBs,¥ HBeAg, anti-HBe)	X		X	X
Quantitative HBV DNA	X		X£	X£

***Also after 2 weeks of therapy; §assessment of 24-hour creatinine clearance is recommended in patients with elevated creatinine; #only for PEG-IFN treated patients; ¥HBsAg and anti-HBs only after HBeAg seroconversion or repeatedly undetectable HBV DNA (HBV DNA <400 c/ml or <80 IU/ml); £quantitative HBV DNA every 3-6 months.**

Table 7. *Adjustment of nucleos(t)ide analogue dosing in accordance with creatinine clearance*

Creatinine clearance	Lamivudine	Adefovir	Entecavir in naive patients	Entecavir in lamivudine resistance	Telbivudine
<5 ml/min/haemodialysis/ CAPD	10 mg/day (starting dose 35 mg)	10 mg/7 days¥·	0.05 mg/day	0.1 mg/day	600 mg/4 days‡
5-9 ml/min/haemodialysis/ CAPD	15 mg/day (starting dose 35 mg)	10 mg/7 days¥	0.05 mg/day	0.1 mg/day	600 mg/4 days‡
10-14 ml/min	15 mg/day (starting dose 35 mg)	10 mg/3 days	0.15 mg/day	0.3 mg/day	600 mg/3 days
15-19 ml/min	25 mg/day (starting dose 100 mg)	10 mg/3 days	0.15 mg/day	0.3 mg/day	600 mg/3 days
20-29 ml/min	25 mg/day (starting dose 100 mg)	10 mg/2 days	0.15 mg/day	0.3 mg/day	600 mg/3 days
30-49 ml/min	50 mg/day (starting dose 100 mg)	10 mg/2 days	0.25 mg/day	0.5 mg/day	600 mg/2 days
≥50 ml/min	100 mg/day	10 mg/day	0.5 mg/day	1 mg/day	600 mg/day

CAPD = continuous ambulant peritoneal dialysis. ¥No recommendations can be made for adefovir-treated patients with creatinine clearance <10 ml/min; ‡telbivudine should be administered after haemodialysis. Source: Farmacotherapeutisch Kompas (http://www.fk.cvz.nl/).

switching to entecavir is recommended in telbivudine-treated patients with serum HBV DNA above 400 c/ml (80 IU/ml) after 24 weeks of therapy. This should also be considered in patients treated with lamivudine. Antiviral resistance is rare in adefovir-treated patients during the first year of antiviral treatment. However, addition of telbivudine or switching to entecavir should be considered in patients with serum HBV DNA above 1000 c/ml (200 IU/ml) after 12 months of therapy because of the increasing risk of antiviral resistance in these patients.

Antiviral resistance should be suspected if serum HBV DNA increases during nucleos(t)ide analogue therapy. If virological breakthrough, defined as a 1 $\log_{10}$ c/ml (or IU/ml) increase in HBV DNA, is observed in compliant patients, genotypic analysis of the HBV polymerase is indicated.[97] A rise in HBV DNA is the first sign of antiviral resistance and is often followed by a rise in ALAT without intervention.[97]

In case of antiviral resistance it is recommended to change antiviral therapy as soon as possible since response to the second drug is better when started at the time of virological breakthrough than at the time of biochemical breakthrough.[98] Adding a second drug seems favourable over switching to another drug, since this significantly reduces the risk of antiviral resistance to the second drug.[99] However, adding a second nucleos(t)ide analogue does not lead to more profound viral suppression compared with monotherapy of the new drug.[99] Adding adefovir is preferred over switching to entecavir in lamivudine-resistant patients because of the lower risk of antiviral resistance. If entecavir is started, lamivudine should be discontinued. In adefovir-resistant patients, treatment with entecavir is preferred.[6] *Table 8* shows the recommendations for the management of antiviral resistance. In case of resistance to other antiviral agents or multiple drugs, consulting a centre with expertise on this topic is recommended.

Table 8. *Treatment options for patients with antiviral resistance*

Type of antiviral resistance	Treatment options‡
Lamivudine resistance	Adefovir add-on (Switch to entecavir)
Adefovir resistance	Entecavir add-on (Telbivudine add-on) (Lamivudine add-on) (Switch to entecavir)
Entecavir resistance	Adefovir add-on
Telbivudine resistance	Adefovir add-on (Switch to entecavir)

‡**Controlled studies are often not available. Treatment options between brackets are not preferred.**

Recommendations	
In telbivudine-treated patients, changing antiviral therapy is recommended if serum HBV DNA is higher than 400 c/ml (80 IU/ml) after 24 weeks of therapy because of the risk of antiviral resistance.	Level 2
In adefovir-treated patients, changing antiviral therapy is recommended if serum HBV DNA is higher than 1000 c/ml (200 IU/ml) after 12 months of therapy because of the risk of antiviral resistance.	Level 4
Confirmation of the HBV DNA measurement and genotypic analysis of the HBV polymerase is indicated in compliant patients with virological breakthrough, as defined by a more than 1 $\log_{10}$ c/ml (or IU/ml) increase in serum HBV DNA, as this often is associated with antiviral resistance.	Level 1
Antiviral treatment should be changed as soon as possible in case of antiviral resistance.	Level 2
Adding a second nucleos(t)ide analogue is preferable over switching to another drug because of the lower risk of antiviral resistance to the second drug.	Level 3
In lamivudine-resistant patients, addition of adefovir is preferred over switching to entecavir because of the high risk of entecavir resistance in these patients.	Level 2

FOLLOW-UP AFTER ANTIVIRAL THERAPY

Liver biochemistry, quantification of HBV DNA and HBV serology should be repeated three to six months post-treatment in PEG-IFN treated patients to assess the presence of sustained response. This is also recommended for responders to nucleos(t)ide analogue treatment who stopped antiviral therapy, although more frequent monitoring after discontinuation can be considered because of the higher risk of relapse compared with PEG-IFN.[37]

In HBeAg-negative patients with serum HBV DNA below 1.0 x 10^5 c/ml (2.0 x 10^4 IU/ml) and normal ALAT, yearly monitoring of ALAT for three years suffices. These patients could also be monitored by their general practitioner. The Dutch Society of General Practitioners (NHG) also recommends this frequency of follow-up in their guideline 'Viral hepatitis and other liver diseases'. If a rise in serum ALAT is observed, the patient should be referred to the treating specialist. In patients with HBsAg seroconversion (loss of HBsAg and anti-HBs >10 IU/l), monitoring of disease activity and prophylactic treatment should only be considered in case of severe immunosuppression, e.g. chemotherapy or treatment with selective antibodies.

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Guidelines Committee for the Netherlands Association of Gastroenterologists and Hepatologists: H.L.A. Janssen, chairman; E.H.C.J. Buster, H.C. Gelderblom, secretaries; C.M. Bakker, J.T. Brouwer, K.J. van Erpecum, R.J. de Knegt, H.W. Reesink, S.W. Schalm, H.L. Zaaijer, members.

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