The 2012 revised Dutch national guidelines for the treatment of chronic hepatitis B virus infection


1Department of Gastroenterology and Hepatology, Albert Schweitzer Hospital, Dordrecht, the Netherlands; 2Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands; 3Department of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands; 4Department of Gastroenterology and Hepatology, Atrium MC, Heerlen, the Netherlands; 5Department of Gastroenterology and Hepatology, Academic Medical Center Amsterdam, Amsterdam, the Netherlands; 6Department of Gastroenterology and Hepatology, Reinier de Graaf Gasthuis, Delft, the Netherlands; 7Department of Gastroenterology and Hepatology, University Medical Center St. Radboud, Nijmegen, the Netherlands; 8Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, the Netherlands; 9Department of Gastroenterology and Hepatology, University Medical Center Leiden, Leiden, the Netherlands; 10Department of Internal Medicine, Medisch Spectrum Twente, Enschede, the Netherlands; 11Department of Gastroenterology and Hepatology, University Medical Center Maastricht, Maastricht, the Netherlands; 12Department of Gastroenterology and Hepatology, VU Medical Center, Amsterdam, the Netherlands; 13Department of Gastroenterology and Hepatology, Haaglanden Medical Center, The Hague, the Netherlands; 14Department of Gastroenterology and Hepatology, Alkmaar Medical Center, Alkmaar, the Netherlands; 15Department of Gastroenterology and Hepatology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands; 16Department of Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem the Netherlands; *corresponding author: e-mail: h.janssen@erasmusmc.nl

In 2008, the Netherlands Association of Gastroenterologists and Hepatologists (Nederlands Vereniging van Maag-Darm-Leverartsen) published the Dutch national guidelines for the treatment of chronic hepatitis B virus infection. New insights into the treatment of chronic hepatitis B with relevance for clinical practice have been adopted in these concise, revised guidelines. The most important changes include the choice of initial antiviral therapy, licensing of tenofovir for the treatment of chronic hepatitis B and the management of antiviral resistance.

**Key Words**
Hepatitis B virus, guidelines, antiviral therapy, pregnancy

**Abstract**
In 2008, the Netherlands Association of Gastroenterologists and Hepatologists (Nederlands Vereniging van Maag-Darm-Leverartsen) published the Dutch national guidelines for the treatment of chronic hepatitis B virus infection. New insights into the treatment of chronic hepatitis B with relevance for clinical practice have been adopted in these concise, revised guidelines. The most important changes include the choice of initial antiviral therapy, licensing of tenofovir for the treatment of chronic hepatitis B and the management of antiviral resistance.

**Choice of Antiviral Therapy**
In May 2010, the European Medicines Agency (EMA) changed the licence of lamivudine; lamivudine is no longer recommended as first-line therapy for the treatment of chronic hepatitis B if other (newer) antiviral agents are available and reimbursed. Since treatment with adefovir and telbivudine also results in a higher risk of antiviral resistance compared with entecavir and tenofovir,1,4 these drugs are no longer recommended as first-line therapy. Pegylated interferon (PEG-IFN), entecavir and tenofovir are now the preferred first-line drugs for the treatment of chronic hepatitis B.

Recommendation
PEG-IFN, entecavir and tenofovir should be considered as first-line therapy for chronic hepatitis B. Lamivudine, adefovir and telbivudine are no longer drugs of choice because of the higher risk of antiviral resistance compared with entecavir and tenofovir.
TENOFOVIR FOR THE TREATMENT OF CHRONIC HEPATITIS B

Shortly after the publication of the 2008 guidelines, tenofovir was licensed for the treatment of chronic hepatitis B virus infection. The drug has been used for the treatment of HIV since 2002. As in HIV, tenofovir is administered as tenofovir disoproxil fumarate in a dosage of 245 mg once daily.

The efficacy of tenofovir was evaluated in two randomised controlled trials in which patients received either tenofovir or adefovir. These trials showed that in both HBeAg-positive and HBeAg-negative patients tenofovir was superior to adefovir; viral suppression was more profound, alanine aminotransferase (ALAT) normalisation rates were higher and HBsAg loss occurred more often in tenofovir-treated patients. In HBeAg-positive patients, one year of tenofovir therapy resulted in HBeAg seroconversion in 21% of patients and serum HBV DNA below 80 IU/ml (400 copies/ml) in 76% of patients. After three years of continuous tenofovir therapy, the proportion of patients with undetectable HBV DNA and negative HBeAg increased to 95% and 34%, respectively. ALAT normalisation was observed in 68% of patients after one year and increased to 74% after three years of therapy.

The proportion of patients with clearance of HBsAg also increased with increasing duration of therapy to 8% and 10% after three and four years of tenofovir therapy, respectively. In HBeAg-negative patients, HBV DNA levels below 80 IU/ml (400 copies/ml) were observed in 93% of patients after one year, with normalisation of ALAT in 76% of patients. After three years, these rates were 99% and 81%.

In patients with insufficient decline of HBV DNA during treatment with lamivudine or adefovir (HBV DNA >2 x 10⁷ IU/ml [>1.0 x 10⁸ copies/ml]) after at least six months of therapy, treatment with tenofovir resulted in serum HBV DNA below 80 IU/ml (400 copies/ml) in 79% of patients after a mean treatment duration of two years. Presence of lamivudine-resistant strains did not influence response to tenofovir. However, presence of mutations associated with adefovir resistance resulted in serum HBV DNA below 80 IU/ml (400 copies/ml) in about 50% of patients without evidence of mutations associated with tenofovir resistance.

No mutations associated with tenofovir resistance have been identified so far.

TENOFOVIR AND RENAL INSUFFICIENCY

The interval of tenofovir administration should be increased in patients with renal insufficiency (creatinine clearance <50 ml/min). For patients with a creatinine clearance of 30-49 ml/min the recommended dosage interval is 48 hours. For patients with a creatinine clearance ≤30 ml/min the European Medicines Agency (EMA) recommends to use another antiviral agent when possible. If there is no possibility for treatment with another antiviral agent with expected comparable efficacy, the recommended dosage interval for tenofovir is every 72 to 96 hours in case of a creatinine clearance of 10-29 ml/min. In haemodialysis patients, tenofovir should be administered once weekly after dialysis.

Renal toxicity has been observed in patients receiving tenofovir. Progressive renal proximal tubular dysfunction with loss of phosphate, proteinuria, loss of amino acids and glucosuria has been described. Mild to moderate proximal tubular dysfunction was found in 22-53% of HIV-infected patients treated with tenofovir. The Fanconi syndrome is caused by this proximal tubular dysfunction and can result in a diminished glomerular filtration rate. In severe cases the associated loss of phosphate can result in osteomalacia. Increase in serum creatinine levels and hypophosphataemia generally occurs late in the course of the renal disease. More sensitive markers for the early detection of tubular dysfunction are normoglycaemic glucosuria, hyperalbuminuria, hyper β₂-microglobulinuria and the renal tubular reabsorption of phosphate (TmP-GFR).

Tenofovir-associated proximal tubular dysfunction has not (yet) been well studied in HBV-infected patients. If tenofovir therapy is considered in a patient with renal insufficiency, the following aspects should be carefully weighted: the indication for antiviral therapy, the potential benefits and adverse events of tenofovir therapy, as well as alternative treatment options.

NEW INSIGHTS FOR ENTECAVIR AND PEGINTERFERON (PEG-IFN)

For entecavir and PEG-IFN the results of new studies with a longer duration of follow-up have become available. After five years of continuous treatment with entecavir serum HBV DNA was below 60 IU/ml (300 copies/ml) in 94% of patients. Antiviral resistance was found in 1.2% of these patients. After a mean period of three years, 81% patients with an initial response to PEG-IFN (HBeAg negative at six-months post-treatment) were still HBeAg negative and 30% of these patients had cleared serum HBsAg (with an overall HBsAg clearance rate of 11%). Shortening of the treatment duration of peginterferon from 12 months to six resulted in lower response rates, as did lowering the weekly dosage to 90 μg (compared with the standard 180 μg).

Recent studies have provided data which can be helpful in estimating the chance of response prior to starting PEG-IFN therapy and for the early prediction of...
non-response during therapy. A model for the prediction of response to PEG-IFN therapy has been developed for HBeAg-positive patients (see also www.liver-gi.nl/peg-ifn). The best candidates for PEG-IFN are those with HBV genotype A and high ALAT (≥2 times the upper limit of normal) or HBV DNA <2.0 x 10^6 IU/ml (<1.0 x 10^6 copies/ml). The same applies for HBV genotype B or C infected patients with both high ALAT levels and HBV DNA <2.0 x 10^5 IU/ml (<1.0 x 10^5 copies/ml). Quantitative measurement of serum HBsAg is useful for the early prediction of non-response to PEG-IFN. There was virtually no chance of response in HBeAg-negative patients who had no decline of serum HBsAg and a less than 2log₁₀ decline in HBV DNA after 12 weeks of PEG-IFN therapy. Discontinuation of therapy should therefore be considered in these patients. Serum HBsAg levels after 12 weeks of peginterferon therapy also seem to be associated with a chance of response in HBeAg-positive patients. However, no firm recommendations can be provided for HBeAg-positive patients at this moment.

FOLLOW-UP OF ANTIVIRAL THERAPY

Treatment with nucleos(t)ide analogues is generally well tolerated. Severe adverse events have been described in a small proportion of patients. As mentioned above, cases of Fanconi syndrome, renal insufficiency and osteomalacia have been observed in patients treated with adefovir and tenofovir. It is therefore recommended to monitor serum creatinine and phosphate levels every three months in tenofovir-treated patients (also see above). Lactate acidosis was previously described in HIV-infected patients treated with nucleos(t)ide analogues and has also been observed in HBV-infected patients with decompensated cirrhosis during entecavir therapy. It is therefore recommended to monitor lactate levels in patients with (decompensated) cirrhosis who are treated with nucleos(t)ide analogues. The revised recommendations for monitoring antiviral therapy are shown in table 1.

Because of the very low risk of antiviral resistance in patients treated with entecavir or tenofovir, HBV DNA does not need to be measured every three months after the first year of therapy. Measurement of HBV DNA every 6–12 months seems sufficient in these patients. With increasing duration of therapy, increasing rates of undetectable HBV DNA have been observed in tenofovir and entecavir treated patients (without pre-existing lamivudine resistance). Currently available data suggest that there is no increased risk of antiviral resistance in patients who show a slow but gradual decline in HBV DNA during treatment with these antiviral agents. Therefore, there is no need for more frequent measurement of HBV DNA or a change in antiviral therapy.

Antiviral therapy can possibly be discontinued in patients who have confirmed HBeAg seroconversion during treatment with nucleos(t)ide analogues (at least a six-month interval between two tests). However, a recent study showed that about half of patients had reversion to detectable HBeAg after stopping nucleos(t)ide analogue therapy. It may therefore be better to only stop nucleos(t)ide analogue therapy in case of HBsAg loss.

### Recommendation

| Level 4 | It is recommended to perform quantitative measurement of HBV DNA every three months during the first year of therapy. Measurement every six to 12 months suffices thereafter. |
| Level 2 | There is no need to change to antiviral therapy in patients with persistently detectable, but declining HBV DNA levels during treatment with entecavir or tenofovir. For entecavir-treated patients this does not apply to those with previous lamivudine therapy. |

### Table 1. Recommendations on minimal laboratory testing during antiviral therapy with peginterferon (PEG-IFN) or nucleos(t)ide analogues (entecavir or tenofovir)

<table>
<thead>
<tr>
<th>Start of therapy</th>
<th>PEG-IFN</th>
<th>Nucleos(t)ide analogues year 1</th>
<th>Nucleos(t)ide analogues after year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminotransferases (ASAT, ALAT)</td>
<td>Once 4-weekly</td>
<td>3-monthly</td>
<td>6-12 monthly</td>
</tr>
<tr>
<td>Liver function (bilirubin, albumin, prothrombin time)</td>
<td>Once 3-monthly</td>
<td>3-monthly</td>
<td>6-12 monthly</td>
</tr>
<tr>
<td>Kidney function (creatinine, phosphate)</td>
<td>Once 3-monthly</td>
<td>3-monthly</td>
<td>3-monthly</td>
</tr>
<tr>
<td>Lactate</td>
<td>Once 4-weekly</td>
<td>3-monthly</td>
<td>3-monthly</td>
</tr>
<tr>
<td>Blood count (platelets, neutrophil count)</td>
<td>Once 3-monthly</td>
<td>3-monthly</td>
<td>3-monthly</td>
</tr>
<tr>
<td>Endocrinology (TSH)</td>
<td>Once 3-monthly</td>
<td>3-6 monthly</td>
<td>6-12 monthly</td>
</tr>
<tr>
<td>Virus serology (HBsAg, anti-HBs, HBeAg, anti-HBe, HBV genotype is recommended if PEG-IFN therapy is considered)</td>
<td>Once 3-6 monthly</td>
<td>3-6 monthly</td>
<td>6-12 monthly</td>
</tr>
<tr>
<td>Quantitative HBV DNA</td>
<td>Once 3-6 monthly</td>
<td>3-6 monthly</td>
<td>6-12 monthly</td>
</tr>
</tbody>
</table>

1 Also after 2 weeks of therapy; 2 assessment of 24-hour creatinine clearance is recommended in patients with elevated creatinine; 3 only for tenofovir; 4 only for patients with cirrhosis; 5 HBsAg and anti-HBs only after HBeAg seroconversion or repeatedly undetectable HBV DNA (HBV DNA <300 IU/ml [<400 copies/ml]).
**ANTIVIRAL RESISTANCE**

The recommendations on antiviral resistance have also been revised. Lamivudine, adefovir and telbivudine may be unsafe in patients with severe fibrosis or cirrhosis (Metavir 3-4 or comparable in other fibrosis scoring systems) due to the high risk of antiviral resistance. These patients are at risk of developing decompensated liver disease in case of viral breakthrough with subsequent hepatitis flares. Antiviral resistance can even occur after several years of profound viral suppression. Therefore, changing antiviral therapy to entecavir or tenofovir is recommended in these patients, even if there are no signs of antiviral resistance. In all other lamivudine, adefovir and telbivudine treated patients switching to entecavir or tenofovir can be considered.

Treatment recommendations for patients with documented antiviral resistance are shown in table 2. It has been shown that adding adefovir to lamivudine was superior to switching to adefovir in patients with lamivudine resistance.18 However, there is no evidence that add-on therapy with entecavir or tenofovir is more effective in case of lamivudine or adefovir resistance.21,22 Adding entecavir or tenofovir to ongoing treatment with another antiviral agent is therefore not recommended. Since there are no known mutations in the HBV polymerase that result in tenofovir resistance, genotypical analysis is currently not recommended for tenofovir-treated patients.

**Recommendation**

| Level 4 | Changing antiviral therapy to entecavir or tenofovir is recommended in lamivudine, adefovir and telbivudine treated patients with severe fibrosis or cirrhosis, even if there are no signs of antiviral resistance. Changing antiviral therapy can be considered in all other patients receiving lamivudine, adefovir and telbivudine. |

**PREGNANCY AND HEPATITIS B**

Several factors have to be considered in women with chronic hepatitis B virus infection who are trying to conceive. These include the potential adverse events and benefits of postponing antiviral therapy, continuing antiviral therapy during pregnancy and delaying pregnancy until after the completion of antiviral therapy (with PEG-IFN).

Tenofovir has pregnancy classification B and there is already some experience with tenofovir during pregnancy in HIV-infected women. Treatment with tenofovir can therefore be considered in the third trimester of pregnancy (from week 32) in patients with HBV DNA >2.0 x 10^8 IU/ml (>1.0 x 10^9 copies/ml). In such patients, additional treatment with lamivudine, which has pregnancy classification C, results in a significantly lower chance of HBV infection in the newborn baby compared with stand-alone passive-active immunisation.25-26 Continuation of tenofovir or lamivudine after delivery is recommended if there is also an indication for antiviral therapy for the mother (based on viral load, hepatitis and/or liver fibrosis). Antiviral therapy can be stopped three months after delivery in all other patients. Monitoring of transaminase levels is recommended because an increase in hepatitis activity can occur. ALAT elevations were observed in more than half of pregnant women who discontinued lamivudine after delivery. This seemed to occur particularly in those with elevated ALAT at the start of lamivudine therapy.27 Because of the lower risk of antiviral resistance, tenofovir is preferred over lamivudine if a prolonged course of antiviral treatment is expected. In women who become pregnant during antiviral therapy, the risk of increased hepatic inflammation after stopping antiviral therapy should be balanced against the risk of teratogenicity. Congenital abnormalities were found in 2.6% of about 9000 registered pregnancies during treatment with lamivudine. For tenofovir this rate was 2.2% in nearly 1400 pregnancies.19 These rates are comparable with those observed in a matched control group. No recommendations can be made about breast feeding during treatment with lamivudine and tenofovir since data are lacking. It is known that both drugs are excreted in breast milk.

At this moment no firm recommendations can be made about in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) for HBV carriers; data are mostly limited to in vitro findings.15 Appropriate semen storage is no longer an issue nowadays and is crucial for male HBV carriers. Based on the available data, IVF seems safe in both male and female HBV carriers. ICSI seems safe for male HBV carriers when standard semen washing procedures are applied. Integration of HBV DNA in the genome of the embryo might occur in female HBV carriers. However, HBV DNA was not detected after accidental exposure of embryos to HBV.16

---

**Table 2. Recommended antiviral drugs in case of antiviral resistance**

<table>
<thead>
<tr>
<th>Type of antiviral resistance</th>
<th>Recommended treatment option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine resistance</td>
<td>Switch to tenofovir</td>
</tr>
<tr>
<td>Adefovir resistance</td>
<td>Switch to entecavir</td>
</tr>
<tr>
<td>Entecavir resistance</td>
<td>Switch to tenofovir</td>
</tr>
<tr>
<td>Telbivudine resistance</td>
<td>Switch to entecavir</td>
</tr>
</tbody>
</table>

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


12. Liaw YF, Xie Q, Han KB, et al. Shorter duration and lower dose of peginterferon alfa-2a therapy results in inferior HBeAg seroconversion rates compared with the duration and dose of 48 weeks and 180 μg NEPTUNE study. Hepatology. 2010;52:439A-430A.


15. Rijckborst V, Hansen BE, Ferenci P, et al. Early on-treatment HBsAg and HBV DNA levels identify HBeAg-negative patients not responding to 48 or 96 week of peginterferon alfa-2a therapy. Hepatology. 2010;52:552A-553A.


