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REVIEW ARTICLE: CHRONIC HEPATITIS B - ANTIVIRAL OR IMMUNOMODULATORY THERAPY?

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**REVIEW ARTICLE: CHRONIC HEPATITIS B - ANTIVIRAL OR
IMMUNOMODULATORY THERAPY?**

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3 **REVIEW ARTICLE: CHRONIC HEPATITIS B - ANTIVIRAL OR**
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5 **IMMUNOMODULATORY THERAPY?**
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10 Vincent Rijckborst¹, Milan J. Sonneveld¹, Harry L.A. Janssen¹
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14 ¹Department of Gastroenterology and Hepatology, Erasmus MC University Medical
15
16 Center, Rotterdam, The Netherlands.
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40 **Contact information**

41
42 Prof. H.L.A. Janssen, MD PhD

43
44 Department of Gastroenterology and Hepatology

45
46 Erasmus MC, University Medical Center Rotterdam

47
48 's Gravendijkwal 230, room Ha 204

49
50 3015 CE Rotterdam, The Netherlands

51
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53 Tel: +31 (0) 10 703 5942

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55 Fax: +31 (0) 10 436 5916

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57 E-mail: h.janssen@erasmusmc.nl
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SUMMARY

Background: First-line treatment options for chronic hepatitis B (CHB) consist of nucleos(t)ide analogues (NA) with a high barrier to resistance (entecavir and tenofovir) or the immunomodulatory agent peginterferon (PEG-IFN). The optimal choice for individual patients remains controversial.

Aim: To review treatment options for CHB, with a focus on deciding between prolonged NA therapy or a finite course of PEG-IFN.

Methods: A comprehensive literature search was undertaken.

Results: Long-lasting, treatment-maintained suppression of hepatitis B virus (HBV) DNA without resistance is achievable in most patients by entecavir or tenofovir. A sustained off-treatment response is however unlikely and long-term therapy must be anticipated. PEG-IFN offers a higher rate of sustained response in a subgroup of patients, but is frequently complicated by side-effects. Pretreatment predictors of response, including HBV genotype, alanine aminotransferase and HBV DNA levels, aid in selecting patients for PEG-IFN therapy. Furthermore, on-treatment markers such as quantitative hepatitis B surface antigen may be applied to identify nonresponders early during the PEG-IFN treatment course, thereby preventing unnecessary treatment.

Conclusions: Both NA and PEG-IFN can be prescribed as first-line treatment options for CHB. However, PEG-IFN should only be considered for patients with a high chance of response based on pretreatment and on-treatment factors.

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INTRODUCTION

Chronic hepatitis B (CHB) remains a major cause of liver disease worldwide. Although the global prevalence has fallen since the introduction of effective vaccination programmes, there are still more than 350 million people who are chronically infected with the hepatitis B virus (HBV).¹ Progression of HBV-related liver disease to cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC) is estimated to result in 0.5-1.2 million annual deaths.¹

The immunomodulatory agent interferon (IFN)-alpha has been a mainstay in the treatment of CHB since it was licensed for this indication in the early 1990s. In the last decade great strides have been made in the treatment of CHB with the introduction of nucleos(t)ide analogues (NA) and pegylated forms of IFN (PEG-IFN). The increasing number of treatment options has added to the complexity of antiviral therapy for CHB, leading to the development of multiple international practice guidelines in recent years.²⁻⁴ All of these guidelines support both NA and PEG-IFN as first-line treatment options, but the optimal choice for individual patients remains controversial. This review will focus on deciding between NA and PEG-IFN therapy.

MANAGEMENT OF CHRONIC HEPATITIS B

Phases of infection

Patients with CHB may present in any one of four, not necessarily sequential, phases of infection.⁵ During the immunotolerant phase, which is common among perinatally infected patients, the hepatitis B e antigen (HBeAg) is detectable and the serum HBV DNA level is high (>100,000 copies/mL or >20,000 IU/mL), while the serum alanine aminotransferase (ALT) concentration is within the normal range and liver histology

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3 shows minimal inflammation. In the immunoactive phase, the host immune response
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5 results in a decline in HBV DNA level, elevated ALT level and hepatic inflammation on
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7 liver biopsy. During this phase HBeAg loss and seroconversion to anti-HBe can occur.
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9 HBeAg seroconversion is often followed by the inactive carrier state characterized by a
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11 low serum HBV DNA level (<10,000 copies/mL or <2,000 IU/mL) and normalization of
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13 ALT. However, in a significant proportion of HBeAg-negative patients viral replication
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15 recurs or persists at higher levels, resulting in HBeAg-negative CHB. This phase of the
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17 infection develops through presence of viral strains harbouring mutations in the precore
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19 or basal core promoter region that reduce or abolish the expression of HBeAg.⁶
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25 **Patients eligible for antiviral treatment**

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27 There continues to be a debate as to when antiviral treatment should be initiated in
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29 patients with precirrhotic HBV-related liver disease.⁷ The guidelines of the American
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31 Association for the Study of Liver Diseases (AASLD) and those of the Asian-Pacific
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33 Association for the Study of the Liver (APASL) advocate treatment for patients who
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35 remain HBeAg positive with serum HBV DNA levels >20,000 IU/mL in combination with
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37 persistently elevated ALT levels (>2 times the upper limit of normal (ULN) over a 3-6
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39 month period).^{3, 4} According to the AASLD guidelines, the same HBV DNA and ALT
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41 criteria apply to HBeAg-negative patients, but it is emphasized that treatment should also
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43 be considered for these patients if the HBV DNA concentration is >2,000 IU/mL
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45 combined with a liver biopsy showing moderate to severe necroinflammation and/or
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47 fibrosis.⁴ The APASL guidelines recommend to consider antiviral treatment for HBeAg-
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49 negative patients with an HBV DNA level >2,000 IU/mL and ALT levels persistently >2 x
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51 ULN.³ According to the 2009 HBV guidelines of the European Association for the Study
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53 of the Liver (EASL) antiviral therapy should be considered, irrespective of HBeAg status,
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3 if HBV DNA levels are >2,000 IU/mL, ALT levels are >1 x ULN and if a liver biopsy
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5 shows moderate to severe necroinflammation and/or fibrosis.²
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8 9 10 **Treatment goals**

11 Since complete eradication of HBV is rarely achieved due to persistence of covalently
12 closed circular DNA (cccDNA) in host hepatocytes,⁸ the main goal of antiviral treatment
13 is to prevent progression to cirrhosis, hepatic decompensation and HCC.⁹ Since these
14 events develop only after decades of infection, clinical studies have focussed on various
15 short-term, surrogate outcomes to assess treatment efficacy.^{4, 9} The most widely used
16 surrogate markers include suppression of HBV DNA levels and HBeAg loss with or
17 without appearance of anti-HBe in HBeAg-positive patients (virologic response),
18 normalization of serum ALT (biochemical response) and improvement of liver histology
19 (histological response).⁴
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22 Parameters used to assess treatment response differ between NA and PEG-IFN therapy
23 because of their different modes of action. NA suppress viral replication by competitively
24 inhibiting viral polymerase activity, while PEG-IFN has both immunomodulatory and
25 weak antiviral properties.^{10, 11} During NA therapy, maintained suppression of HBV DNA is
26 the main goal given the risk of developing antiviral resistance associated with detectable
27 HBV DNA levels.¹² The main goal of PEG-IFN therapy is to achieve immunological
28 control over HBV resulting in a sustained response after a finite treatment course.
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31 In HBeAg-positive patients treated with PEG-IFN, HBeAg seroconversion is frequently
32 used as a primary endpoint since it is associated with increased survival and a reduced
33 risk of developing HCC.¹³⁻¹⁵ In contrast, suppression of serum HBV DNA below the
34 detection limit of a sensitive polymerase chain reaction (PCR) assay is often applied for
35 NA therapy in HBeAg-positive CHB. In HBeAg-negative patients, suppression of HBV
36 DNA levels in combination with normalization of ALT is considered the most important
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3 treatment goal. Whilst HBV DNA undetectability is pursued during NA treatment, an HBV
4 DNA level <2,000 IU/mL (~10,000 copies/mL) is often used to define a sustained off-
5 treatment response to PEG-IFN therapy.² Large population-based studies have shown
6 that an HBV DNA concentration below this threshold is associated with a low risk of
7 cirrhosis and HCC.^{13, 16, 17} Hepatitis B surface antigen (HBsAg) seroclearance is the
8 ultimate surrogate endpoint as it is associated with improved outcomes, provided that it
9 occurs at a younger age and precedes the development of cirrhosis.¹⁸
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20 **Approved therapies**

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22 Current treatment options can be summarized into NA therapy (lamivudine (LAM),
23 adefovir (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir (TDF)) and IFN-based
24 therapy (conventional IFN and PEG-IFN), which have all been investigated in
25 randomized clinical trials. Virologic and biochemical response rates for HBeAg-positive
26 and HBeAg-negative CHB at 1 year of therapy are summarized in table 1. These trials
27 used different virologic assays and were not head-to-head comparisons for all the
28 agents. Efficacy results of up to 5 years of continuous treatment are available for several
29 NA. Furthermore, long-term off-treatment follow-up results for PEG-IFN have been
30 reported.
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44 **ANTIVIRAL AGENTS**

45 **Low barrier to resistance**

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48 **Lamivudine** LAM was the first NA approved for the treatment of CHB in the late 1990s.
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3 suppressed to undetectable levels (<300 copies/mL) in 36% of patients at 1 year of
4 therapy.¹⁹ Extended therapy resulted in increasing cumulative rates of HBeAg
5 seroconversion, reaching 47% at 4 years²⁰⁻²². In HBeAg-negative CHB, HBV DNA
6 undetectability (<300 copies/mL) was achieved in as much as 72% of patients after 1
7 year of LAM therapy.²³ However, virologic response rates (HBV DNA <1000 copies/mL)
8 progressively decreased during longer-term continuous LAM therapy to 34% at 4
9 years.²⁴

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Amelioration of necroinflammatory and fibrosis scores on liver biopsy was observed in
patients with LAM induced viral suppression,²⁵ and the risk of hepatic decompensation
and HCC in patients with advanced liver disease (bridging fibrosis or cirrhosis) was
reduced.²⁶ However, LAM is not considered a first-line agent for CHB anymore because
of its low barrier to resistance resulting in a high rate of drug-resistant mutations in the
tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase. LAM
resistance occurred in up to 70% of patients after 5 years of therapy (figure 1).² The
development of antiviral resistance is usually followed by a rise in HBV DNA and
reactivation of disease.^{12, 25, 27}

Intermediate barrier to resistance

Adefovir ADV was the second agent licensed for the treatment of CHB. Treatment with
ADV 10 mg daily for 1 year resulted in HBeAg seroconversion in 12% of HBeAg-positive
patients and 21% achieved HBV DNA negativity by PCR (<400 copies/mL).²⁸ At 5 years
on ADV therapy, HBeAg seroconversion was observed in 48% of patients and 39% had
an HBV DNA level <1000 copies/mL.²⁹ After 1 year of ADV therapy in HBeAg-negative
CHB, 51% of patients became negative for HBV DNA (<400 copies/mL).³⁰ The
percentage of patients receiving prolonged ADV therapy who had HBV DNA <1000

copies/mL increased to 67% at 5 years and improvement of histological findings was observed in >70% of patients.^{31, 32}

The rate of selection for ADV resistant HBV is lower compared with LAM: ADV resistant mutations were not present after 1 year. However, following 5 years of ADV therapy resistant mutations were detected in up to 29% of patients, which, in addition to the low antiviral potency of ADV, precludes its use as a first-line agent (figure 1).²

Telbivudine LdT demonstrated significantly greater antiviral efficacy compared with LAM for the treatment of both HBeAg-positive and HBeAg-negative CHB.³³ In HBeAg-positive patients, HBeAg seroconversion was observed in 23% and 30% of patients after 1 and 2 years of LdT therapy, respectively.^{33, 34} HBV DNA suppression (<300 copies/mL) was observed in 56% of patients at year 2.³³ In HBeAg-negative patients, HBV DNA became undetectable in 88% of patients after 1 year of LdT.³³ The corresponding rate at 2 years decreased to 82%.³⁴

Despite the high potency of LdT, virologic response rates deteriorate over time due to the emergence of LdT resistance. LdT resistance mutations are cross-resistant with LAM and were found in up to 22% of patients after 2 years of therapy (figure 1).^{2, 12} The role of LdT is therefore limited in the treatment of patients with CHB.

High barrier to resistance

Entecavir ETV showed greater antiviral potency than LAM in the treatment of patients with CHB. In HBeAg-positive patients, HBV DNA was suppressed to below the limit of detection (300 copies/mL) in 67% of patients and HBeAg seroconversion occurred in 21% of patients after 1 year.¹⁹ Cumulative rates of HBV DNA undetectability increased to 80% and 94% at 2 and 5 years of ETV therapy, respectively.^{35, 36} In patients with HBeAg-negative CHB, HBV DNA was undetectable in 90% of patients after 1 year of therapy.²³ The efficacy of ETV in NA naïve patients was recently confirmed in two large

investigator-initiated studies. A European cohort study showed that a virologic response (HBV DNA <400 copies/mL or 80 IU/mL) was achieved in 79% of patients even through a short-term follow-up.³⁷ Preliminary results of an Italian study demonstrated that ETV therapy resulted in undetectable levels of HBV DNA in 91% and 97% of HBeAg-negative patients at 1 and 2 years, respectively.³⁸

Very low rates of ETV resistance have been reported in NA-naïve patients,² but resistance developed in up to 53% of LAM-experienced patients after 5 years of treatment (figure 1). Only one additional mutation in the HBV polymerase is required to develop resistance in the presence of LAM-resistant mutations.^{12, 39}

Tenofovir TDF is the most recently approved NA for the treatment of CHB after demonstrating superior antiviral efficacy compared with ADV for both HBeAg-positive and HBeAg-negative disease.⁴⁰ In the treatment of HBeAg-positive CHB, HBeAg seroconversion and HBV DNA undetectability (<400 copies/mL) were observed in 21% and 76% of patients at 1 year of therapy, respectively.⁴⁰ At 3 years of therapy, the rate of HBeAg seroconversion increased to 26% and 78% of patients had undetectable HBV DNA.⁴¹ In HBeAg-negative patients, HBV DNA undetectability was achieved in 93% of patients after 1 year of TDF therapy,⁴⁰ and 88% after 3 years (intention-to-treat analysis).⁴² **However, when considering all patients on-treatment at year 3, 99% of patients had undetectable HBV DNA.** Recently, a large investigator-initiated study showed that 79% of patients who failed previous NA treatment had HBV DNA levels <400 copies/mL after a median follow-up of almost 2 years. However, the presence of ADV, but not LAM, resistance impaired TDF efficacy.⁴³

Furthermore, it was recently shown that TDF resistance is absent after 3 years of continuous therapy (figure 1), although solid conclusions based on these data are hampered by the study protocol that allowed viremic patients to add emtricitabine at week 72.^{41, 42}

IMMUNOMODULATORY AGENTS

IFN has been used for the treatment of CHB for almost three decades. Modification of IFN through the attachment of a polyethyleneglycol (PEG) molecule improved pharmacokinetic and pharmacodynamic properties. PEG-IFN is administered once-weekly by subcutaneous injection, which results in a relatively continuous drug exposure during the dosing interval. Two types of PEG-IFN have been developed: PEG-IFN alfa-2a and PEG-IFN alfa-2b.⁴⁴ PEG-IFN alfa-2a proved to be at least as effective as conventional IFN in HBeAg-positive patients, with a comparable tolerability profile.⁴⁵

Peginterferon

The efficacy of PEG-IFN alfa-2a and PEG-IFN alfa-2b for HBeAg-positive CHB has been evaluated in 2 pivotal trials.^{46, 47} PEG-IFN alfa-2a monotherapy during 1 year resulted in HBeAg seroconversion in 27% of patients, whereas this was 22% in patients treated with PEG-IFN alfa-2b. Six months after treatment discontinuation, HBeAg seroconversion rates were 32% and 29%, respectively. **Sustained off-treatment viral suppression (serum HBV DNA <400 copies/mL) was achieved in 7-14% of patients.** In both studies, PEG-IFN monotherapy was compared with PEG-IFN and LAM combination therapy. Although combination therapy was associated with more potent viral suppression during the treatment phase, sustained off-treatment response rates were comparable with monotherapy.^{46, 47} At 6 months after discontinuation of PEG-IFN therapy, HBsAg seroconversion occurred in 3-5% of HBeAg-positive patients.

Long-term follow-up (mean duration 3 years) results of 172 HBeAg-positive patients treated with PEG-IFN alfa-2b ± LAM showed that among initial responders (defined as HBeAg negativity 26 weeks after treatment) HBeAg clearance was sustained in 81% of

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3 cases and the rate of HBsAg loss increased to 30%. Overall, HBsAg loss was achieved
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5 in 11% of patients at the last visit.⁴⁸
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8 In HBeAg-negative patients, PEG-IFN alfa-2a monotherapy for 1 year resulted in a
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10 sustained off-treatment response (HBV DNA <20,000 copies/mL and normal ALT at 6
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12 months after treatment) in 36% of patients.⁴⁹ Serum HBV DNA was <400 copies/mL in
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14 19% of patients and 4% had lost HBsAg at 6 months after treatment. In parallel with
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16 HBeAg-positive disease, addition of LAM to PEG-IFN was beneficial in terms of on-
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18 treatment viral suppression, but did not result in higher sustained off-treatment response
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20 rates.⁴⁹ While PEG-IFN may be given for less than 1 year for HBeAg-positive CHB
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22 without reducing its efficacy,⁴⁵ extending therapy beyond 1 year may result in lower
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24 relapse rates after treatment discontinuation in HBeAg-negative disease. A recent study
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26 showed that a sustained off-treatment response to PEG-IFN alfa-2a, defined as HBV
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28 DNA ≤ 2000 IU/mL at 1 year after treatment discontinuation, was achieved in 31% of
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30 genotype D infected HBeAg-negative patients treated for 2 years compared with 10% of
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32 those treated for 1 year ($p=0.01$).⁵⁰
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36 Results of long-term follow-up studies have shown that the off-treatment sustainability of
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38 response to IFN-based therapy is lower in patients with HBeAg-negative compared with
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40 HBeAg-positive CHB. A virologic response, defined as HBV DNA <10,000 copies/mL at
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42 6 months after PEG-IFN alfa-2a treatment, was durable in 43% of patients with an initial
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44 response after 3 years of follow-up. The rate of HBsAg loss increased to 9%.⁵¹
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48 SAFETY

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53 Assessment of safety of both NA and PEG-IFN therapy should consider their mode of
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55 action and typical duration of use. NA generally have favorable side-effect profiles.
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57 However, all NA theoretically pose a risk for most inhibit not only viral, but also human
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3 DNA polymerases.⁵² In addition, some agents inhibit human mitochondrial DNA
4 polymerases which may result in a clinical syndrome including lactic acidosis,
5 neuropathy and myopathy.⁵² Fortunately, most NA used for CHB have shown little
6 adverse events during the first years of therapy. Adverse events did not occur more
7 frequently during LAM treatment compared with placebo,⁵³ and the side-effect profile of
8 ETV was indistinguishable from that of LAM.¹⁹ In contrast, ADV is known to be
9 nephrotoxic in up to one third of patients.⁵⁴ Renal toxicity has also been described in
10 HIV-infected patients treated with TDF, necessitating creatinine monitoring especially
11 during prolonged treatment.⁵² Nevertheless, TDF was well-tolerated and safe during the
12 first year of therapy in patients with CHB.⁴⁰

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25 One year of PEG-IFN therapy is associated with considerable side-effects. The most
26 frequently reported are flu-like syndrome, headache, myalgia, fatigue and local reactions
27 at the site of injection.^{46, 47, 49} These symptoms typically present early during therapy,
28 while neuropsychiatric side-effects such as depression and agitation tend to present in
29 the later stages.⁵⁵ Other clinically relevant side effects, including anorexia, thyroid
30 dysfunction and hepatitis flares, occur less frequently. Decompensated cirrhosis is an
31 absolute contraindication, but PEG-IFN is generally well-tolerated and effective in
32 patients with early cirrhosis.⁵⁶ PEG-IFN has myelosuppressive effects, but neutropenia
33 and thrombocytopenia rarely result in clinically significant infections and bleedings.⁵⁵ Of
34 particular note is the recently described neuropathy syndrome described in patients
35 treated with a combination of PEG-IFN and LdT, which precludes clinical use of this
36 combination regimen.⁵⁷ In general, NA show favorable side-effect profiles in comparison
37 to PEG-IFN, but long-term safety data for the new agents are lacking.

55 TREATMENT STRATEGIES

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When to use peginterferon therapy?

Both treatment modalities have substantial advantages and limitations (table 2).⁵⁸ PEG-IFN therapy should always be considered for HBeAg-positive CHB, because a sustained off-treatment response is achieved in approximately one third of patients.⁴⁶⁻⁴⁸ Furthermore, HBsAg loss, which approximates clinical cure, is more likely to be achieved during PEG-IFN therapy compared with NA.^{48, 51} However, the clinical use of PEG-IFN is compromised by its side-effects and costs.⁵⁵ Selection of patients with the highest probability of achieving a response is therefore essential. This is even more critical in HBeAg-negative disease, where a sustained off-treatment response is achieved in not more than 20% of patients.⁵¹

Patients should ideally be selected for PEG-IFN therapy based on their individual probability of response. Pros and cons of PEG-IFN can then be weighed on an individual basis. In case of a low baseline probability of response to PEG-IFN, it should be advised to initiate NA therapy. In addition, NA are the treatment regimen of choice for several patient groups, such as patients presenting with hepatic decompensation, those receiving chemotherapy, immunocompromised patients, and pregnant women with a very high level of viral replication (HBV DNA >10⁹ copies/mL).⁵⁹

Baseline prediction of response to peginterferon in HBeAg-positive patients In recent years, many reports demonstrated the importance of HBV genotypes for IFN-based therapy.^{60, 61} HBV has been classified into 8 genotypes (A-H) defined by divergence of more than 8% in the entire genome.⁶² The main HBV genotypes (A-D) have a distinct distribution throughout the world, with a predominance of A and D in Europe and North America and B and C in Asia, and appear to have a strong effect on the outcome of HBV infection.⁶³⁻⁶⁵ The association between HBV genotypes and responsiveness to IFN was confirmed in our study that pooled the data from the 2 large trials investigating the efficacy of PEG-IFN in HBeAg-positive CHB (N=721).⁶⁶ Baseline

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3 factors associated with an increased likelihood of a sustained off-treatment response
4 (HBeAg loss and HBV DNA <2,000 IU/mL 6 months after treatment) included genotype
5 A, older age, female sex, higher serum ALT levels and lower serum HBV DNA levels
6 (table 3). A multivariable prediction model was constructed which allowed for individual
7 prediction of a sustained off-treatment response to PEG-IFN based on the
8 aforementioned baseline data.⁶⁶ The so-called *PEG-IFN treatment index* can be found at
9 <http://www.liver-gi.nl/peg-ifn>, and can guide the clinician when considering patients for
10 PEG-IFN therapy. General recommendations on whether to consider PEG-IFN therapy
11 for patients with HBeAg-positive CHB, based on a predicted probability of response
12 >30%, are shown in table 4.⁶⁶

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Nonetheless, considerable uncertainty remains on the individual level and additional
predictors of response may augment the baseline prediction model. In parallel with HBV
DNA, quantitative assays for HBeAg and HBsAg have become available.⁶⁷ Fried et al.
reported that patients with lower baseline HBeAg levels have a higher probability of
sustained off-treatment HBeAg seroconversion.⁶⁸ HBsAg, another HBV marker, is
secreted from the hepatocyte during viral replication as part of the HBV nucleocapsid, or
as part of noninfectious viral particles.⁶⁷ Serum HBsAg levels correlate with the amount
of intrahepatic cccDNA, at least in HBeAg-positive patients.⁶⁹⁻⁷² **However, baseline
serum HBsAg levels were not associated with a sustained off-treatment response in the
2 large PEG-IFN studies for HBeAg-positive CHB.**^{73, 74}

Baseline prediction of response to peginterferon in HBeAg-negative patients

Currently, data on baseline predictors of response to PEG-IFN in HBeAg-negative CHB
are limited (table 3). A post-hoc analysis of HBeAg-negative patients participating in the
registration trial of PEG-IFN alfa-2a found that younger age, female gender, higher
baseline ALT and lower baseline HBV DNA levels were associated with a higher
probability of achieving a sustained off-treatment response (HBV DNA levels <20,000

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3 copies/mL combined with normal ALT at 6 months after treatment).⁷⁵ Unfortunately, the
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5 authors did not provide tools for easy clinical application of their findings and calculation
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7 of the probability of response for individual patients is therefore cumbersome. Moreover,
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9 several studies showed that serum HBsAg levels were comparable between responders
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11 and non-responders to PEG-IFN therapy.⁷⁶⁻⁷⁸
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14 15 16 **Which nucleos(t)ide analogue to use?**

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18 ETV and TDF are potent NA with a high barrier to resistance and are therefore
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20 recommended as first-line treatment options by the practice guidelines of EASL and
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22 AASLD.^{2, 4} In support of these recommendations, a recent study demonstrated that ETV
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24 and TDF are the most effective treatment options for CHB during the first year of
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26 treatment.⁷⁹ Furthermore, it was estimated that long-term liver-related mortality may be
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28 reduced by 80% if all patients with high HBV DNA and ALT levels are treated with NA
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30 with a high barrier to resistance, compared with only 47% if NA with a low barrier to
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32 resistance would be used.⁸⁰ Nevertheless, both AASLD and EASL guidelines do not take
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34 into consideration the cost-effectiveness ratio of these agents. A recent study from Spain
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36 suggested that TDF has a superior cost-effectiveness profile compared with other NA
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38 including ETV, although the cost-effectiveness ratio would be similar in countries with
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40 similar costs for both agents.⁸¹ For less potent antiviral agents, the so-called road map
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42 model may be applied to adapt therapy in patients at high risk for the development of
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44 resistance after a set duration of treatment (detectable HBV DNA at 24 weeks for NA
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46 with a low barrier to resistance).^{3, 82} Nevertheless, even patients with undetectable HBV
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48 DNA at 24 weeks of treatment with NA with a low barrier to resistance may develop
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50 resistance,⁸³ which is a major drawback for using this approach.
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58 **Treatment adaptation**

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3 ***Nucleos(t)ide analogues*** Previous studies have shown that the development of antiviral
4 resistance is mainly related to the level of ongoing viral replication.^{83, 84} Since long-term
5 oral therapy appears to be necessary in a majority of patients treated with NA, treatment
6 adaptation at an early stage in case of suboptimal suppression of HBV DNA levels is
7 required to prevent antiviral resistance, in particular when NA with a low barrier to
8 resistance are used.⁸⁵ In case treatment adaptation is required, a treatment strategy
9 associated with minimal risk of the development of multidrug resistant HBV by taking into
10 account cross-resistance profiles should be adopted.¹² Nevertheless, it is currently
11 unknown whether the road map concept also applies to NA with a high barrier to
12 resistance as evidence for the advantages of adapting treatment in patients with
13 detectable serum HBV DNA levels during therapy with ETV or TDF is lacking.⁸⁶

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27 According to current guidelines for the treatment of CHB, finite treatment with NA may be
28 a reasonable option in HBeAg-positive patients.²⁻⁴ Treatment may be stopped after the
29 achievement of HBeAg seroconversion combined with undetectable HBV DNA and an
30 additional 6–12 months of consolidation therapy.²⁻⁴ However, studies on the durability of
31 HBeAg seroconversion during NA therapy have reported conflicting results.^{87, 88} A recent
32 study conducted in our center showed that no more than 31% of patients achieved a
33 durable remission (HBeAg negativity and HBV DNA <10,000 copies/mL) after HBeAg
34 seroconversion.⁸⁹ Furthermore, among patients who discontinued NA therapy after
35 HBeAg seroconversion and at least 6 months of consolidation therapy, only 22% of
36 patients had a sustained response.⁸⁹ Therefore, ongoing NA therapy, irrespective of the
37 achievement of HBeAg seroconversion, appears to be necessary. NA therapy should
38 thus at least be continued until the occurrence of HBsAg loss, both in HBeAg-positive
39 and HBeAg-negative disease, although HBsAg loss is rarely observed during NA
40 therapy.
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3 **Peginterferon** Even in the face of careful selection of patients for PEG-IFN, a
4 considerable number of patients fail to achieve a response. On-treatment predictors of
5 response to PEG-IFN may guide clinicians in their decision of whether to continue PEG-
6 IFN or switch to NA therapy in specific patients.
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10 In HBeAg-positive disease, the usefulness of HBV DNA levels in prediction of response
11 during the first months of PEG-IFN therapy is limited. Different patterns of decline were
12 observed during PEG-IFN alfa-2b therapy and even patients with a late or post-treatment
13 decline of HBV DNA had a considerable chance of achieving a response.⁹⁰ High HBeAg
14 levels after 24 weeks of PEG-IFN alfa-2a therapy had a somewhat greater negative
15 predictive value upon HBeAg seroconversion in comparison with HBV DNA (96% versus
16 86%).⁶⁸ Recent studies have explored the role of on-treatment HBsAg levels for
17 prediction of response to PEG-IFN in HBeAg-positive CHB. A preliminary report showed
18 that PEG-IFN alfa-2a treated patients with HBsAg levels <1500 IU/mL at week 12 had
19 51% chance of sustained off-treatment HBeAg seroconversion compared with only 16%
20 of those with HBsAg levels >20,000 IU/mL.⁷³ Unfortunately, a considerable proportion of
21 responders would be lost if one would discontinue therapy in patients with HBsAg levels
22 >20,000 IU/mL. We recently reported that HBeAg-positive patients treated with PEG-IFN
23 alfa-2b who experienced no HBsAg decline from baseline at week 12 of the treatment
24 course had only 3% chance (negative predictive value (NPV) 97%) of a sustained off-
25 treatment response (HBeAg loss and HBV DNA <10,000 copies/mL at 26 weeks after
26 treatment) and no chance of HBsAg loss (figure 2A).⁷⁴ These patients should therefore
27 be advised to discontinue PEG-IFN therapy.
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30 In parallel with HBeAg-positive disease, prediction of response to PEG-IFN using HBV
31 DNA levels is difficult in HBeAg-negative patients.⁹¹ Recent studies have focussed on
32 the predictive value of on-treatment HBsAg levels, the only viral marker that remains
33 detectable in HBeAg-negative patients with suppressed HBV DNA levels. Low HBsAg
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3 levels at the end of 1 year of PEG-IFN treatment were associated with the highest
4 probability of achieving a sustained off-treatment response, suggesting that HBsAg
5 decline during therapy may allow discrimination between responders and non-
6 responders.⁷⁷ Indeed, high predictive values for on-treatment HBsAg declines at weeks
7 12 and 24 on sustained off-treatment response (HBV DNA <70 copies/mL at 24 weeks
8 after treatment) were reported in a cohort of 48 patients treated with PEG-IFN alfa-2a for
9 1 year: only 10% of patients who did not achieve a 0.5 log decline in serum HBsAg from
10 baseline to week 12 of therapy achieved a response (NPV 90%).⁷⁸ We recently showed
11 that on-treatment decline of HBsAg at week 12 alone was of limited value in prediction of
12 sustained off-treatment response (HBV DNA <10,000 copies/mL and normal ALT 24
13 weeks after treatment).⁷⁶ Nevertheless, it was possible to establish a stopping rule by
14 combining early on-treatment declines of HBsAg and HBV DNA (figure 2B). None of the
15 patients (20% of the study population) without HBsAg decline combined with <2 log HBV
16 DNA decline achieved a sustained off-treatment response (NPV 100%).⁷⁶ The majority of
17 patients in our study were Caucasians infected with genotypes D and A, so these
18 findings need to be confirmed in patients with genotypes B and C.

COMBINATION THERAPY

Currently available agents for CHB are licensed for use as monotherapies and also
guidelines recommend to start with monotherapy.^{2, 4} Combination therapy could however
offer advantages in the treatment of CHB, including a combination of immunomodulatory
and antiviral effects, synergistic antiviral effects and a higher barrier towards resistance.
Furthermore, combination therapy has improved treatment outcomes in many other
chronic infections.⁹² Combining PEG-IFN with NA is the most appealing approach, but
the addition of LAM, ADV and ribavirin to PEG-IFN therapy did not result in higher

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3 sustained response rates.^{46, 47, 49, 93, 94} New trials on a combination of PEG-IFN with ETV
4 or TDF are therefore needed. In addition, studies exploring different ways of combining
5 PEG-IFN with NA are indicated since most studies started and ended combination
6 therapy at the same time. Pilot studies have suggested that lowering HBV DNA by NA
7 before PEG-IFN therapy may improve outcomes, but contradictory results have been
8 reported.^{95, 96}

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Studies on the efficacy of de novo combination therapy with NA are scarce and only
combinations of NA which are no longer considered as first-line treatment were
investigated.⁹⁷⁻⁹⁹ Although it was shown that combination therapy can delay the
development of resistance,⁹⁷ there are no data to support de novo combination therapy
with NA that have a high barrier to resistance in NA-naïve patients. Moreover, a recent
study in patients with incomplete viral suppression during therapy with ADV showed that
TDF monotherapy and the combination of TDF and emtricitabine, which is structurally
similar to LAM, had similar efficacy.¹⁰⁰

Overall, there is insufficient evidence to recommend de novo combination therapy in
CHB as first-line therapy. Nevertheless, current guidelines recommend that a
combination of NA may be considered in patients at high risk of complications in the
event of virologic breakthrough such as those with advanced liver disease.^{2, 4}

CONCLUSIONS

The treatment of CHB has greatly improved over the past decade with the introduction of
potent NA with a high barrier to resistance and PEG-IFN. The advantages and limitations
of both treatment options should be considered when a patient has an indication to
initiate antiviral therapy. NA can be prescribed to all adult CHB patients in whom
treatment is indicated and offer easy daily oral dosing, are well tolerated and NA with a
high barrier to resistance can maintain suppression of viral replication for prolonged

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3 periods of time. However, an off-treatment sustained response is unlikely in a majority of
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5 patients. A sustained off-treatment response is more likely to be achieved in a subgroup
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7 of patients with a finite course of PEG-IFN therapy, but treatment is frequently
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9 complicated by the occurrence of side-effects.
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11 Both NA and PEG-IFN can be given as first-line treatment option for CHB. However,
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13 PEG-IFN should only be considered for patients with a high chance of response.
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16 Predictors of response at baseline, such as HBV genotype, ALT and HBV DNA levels,
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18 aid in selecting patients for PEG-IFN therapy, especially in HBeAg-positive disease.
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20 Furthermore, recent studies suggest that on-treatment viral markers, in particular
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22 quantitative HBV DNA and HBsAg, may be applied to identify patients who are unlikely
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24 to benefit from PEG-IFN early during the treatment course, thereby avoiding
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26 unnecessary treatment. Patients who are not eligible for PEG-IFN or who have a low
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28 probability of response to PEG-IFN based on baseline or on-treatment factors should be
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30 advised to initiate or switch to NA therapy.
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Table 1. Overview of response rates in HBeAg-positive and HBeAg-negative patients after 1 year of antiviral therapy.

Agent	HBeAg positive			HBeAg negative	
	HBeAg seroconversion	HBV DNA undetectability	Normal ALT	HBV DNA undetectability	Normal ALT
Peginterferon	22-27%	10-25%	34-39%	63%	38%
Lamivudine	18%	36%	60%	72%	71%
Adefovir	12%	21%	48%	51%	72%
Telbivudine	23%	60%	77%	88%	74%
Entecavir	21%	67%	68%	90%	78%
Tenofovir	21%	76%	68%	93%	76%

These trials were not head-to-head comparisons and different virologic assays were used. HBV DNA undetectability: HBV DNA <300 – 400 copies/mL.

Table 2. Pros and cons of nucleos(t)ide analogues versus peginterferon for the treatment of chronic hepatitis B.

Nucleos(t)ide analogues	Peginterferon
Daily oral dosing	Weekly subcutaneous injection
Well tolerated in the medium term	Frequent side-effects
Potent HBV DNA suppression	Modest HBV DNA suppression
Limited increase in rate of HBsAg loss	Increase in rate of HBsAg loss
Response hardly durable after therapy	Response durable after therapy
Risk of antiviral resistance	Absence of antiviral resistance
Long-term or indefinite therapy may be required	Finite duration of therapy
Less expensive during first year, possibly equally or more costly after long-term therapy	Expensive

Table 3. Baseline predictors of response to peginterferon therapy.

HBeAg-positive patients	HBeAg-negative patients
Older age	Younger age
Female sex	Female sex
Lower HBV DNA level (≤ 9 log copies/mL)	Lower HBV DNA level
Higher ALT level ($\geq 2 \times$ ULN)	Higher ALT level
HBV genotype A	

Baseline parameters associated with higher response rates to 1 year of peginterferon therapy. Data for HBeAg-negative patients are from single studies and are unconfirmed.

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Table 4. Recommendations for considering HBeAg-positive patients for peginterferon.

HBV genotype	Consider peginterferon in HBeAg-positive patients with:
A	Either high ALT ($\geq 2 \times$ ULN) or low HBV DNA (≤ 9 log copies/mL)
B or C	Both high ALT ($\geq 2 \times$ ULN) and low HBV DNA (≤ 9 log copies/mL)
D	Peginterferon generally not recommended

Recommendations are based on an average probability of a sustained off-treatment response (HBeAg loss and HBV DNA < 2000 IU/mL 6 months after treatment) of more than 30%. Probabilities for individual patients may vary, and other characteristics (including age and sex) should be taken into consideration.

For Peer Review

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7 **Figure 1.** Rates of antiviral resistance in nucleos(t)ide analogue naïve patients treated
8 with the 5 registered nucleos(t)ide analogues within randomized controlled trials and
9 subsequent follow-up studies. The bars represent years of therapy. These trials used
10 different virologic assays and were not head-to-head comparisons for all the agents.
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18 **Figure 2A.** Flowchart showing the chance of a sustained off-treatment response (HBeAg
19 negativity and HBV DNA <10,000 copies/mL 26 weeks after treatment) based on the
20 presence of any HBsAg decline at week 12 of peginterferon alfa-2b therapy for 52 weeks
21 in HBeAg-positive patients.⁷⁴ *SR: sustained response.
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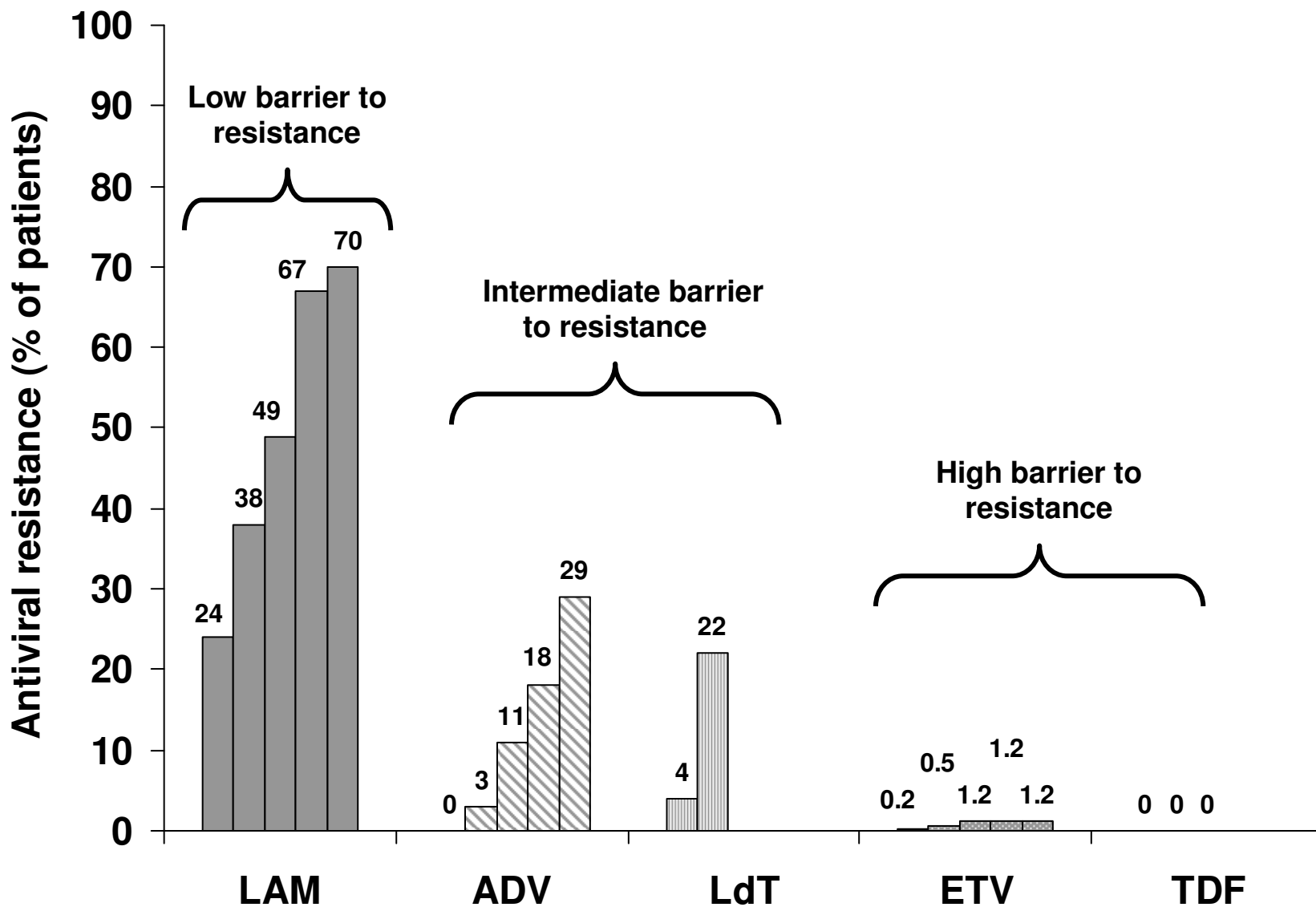
28 **Figure 2B.** Flowchart for the probability of a sustained off-treatment response (HBV
29 DNA <10,000 copies/mL and normal ALT 24 weeks after treatment) based on (1) the
30 presence of any HBsAg decline and (2) HBV DNA decline ≥ 2 log at week 12 of
31 peginterferon alfa-2a therapy for 48 weeks in HBeAg-negative patients.⁷⁶ *SR: sustained
32 response.
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Statement of interests

Vincent Rijckborst and Milan J. Sonneveld have nothing to disclose. Prof. H.L.A. Janssen received grants from and is a consultant for: Bristol Myers Squibb, Gilead Sciences, Novartis, Roche, Merck (Schering Plough).

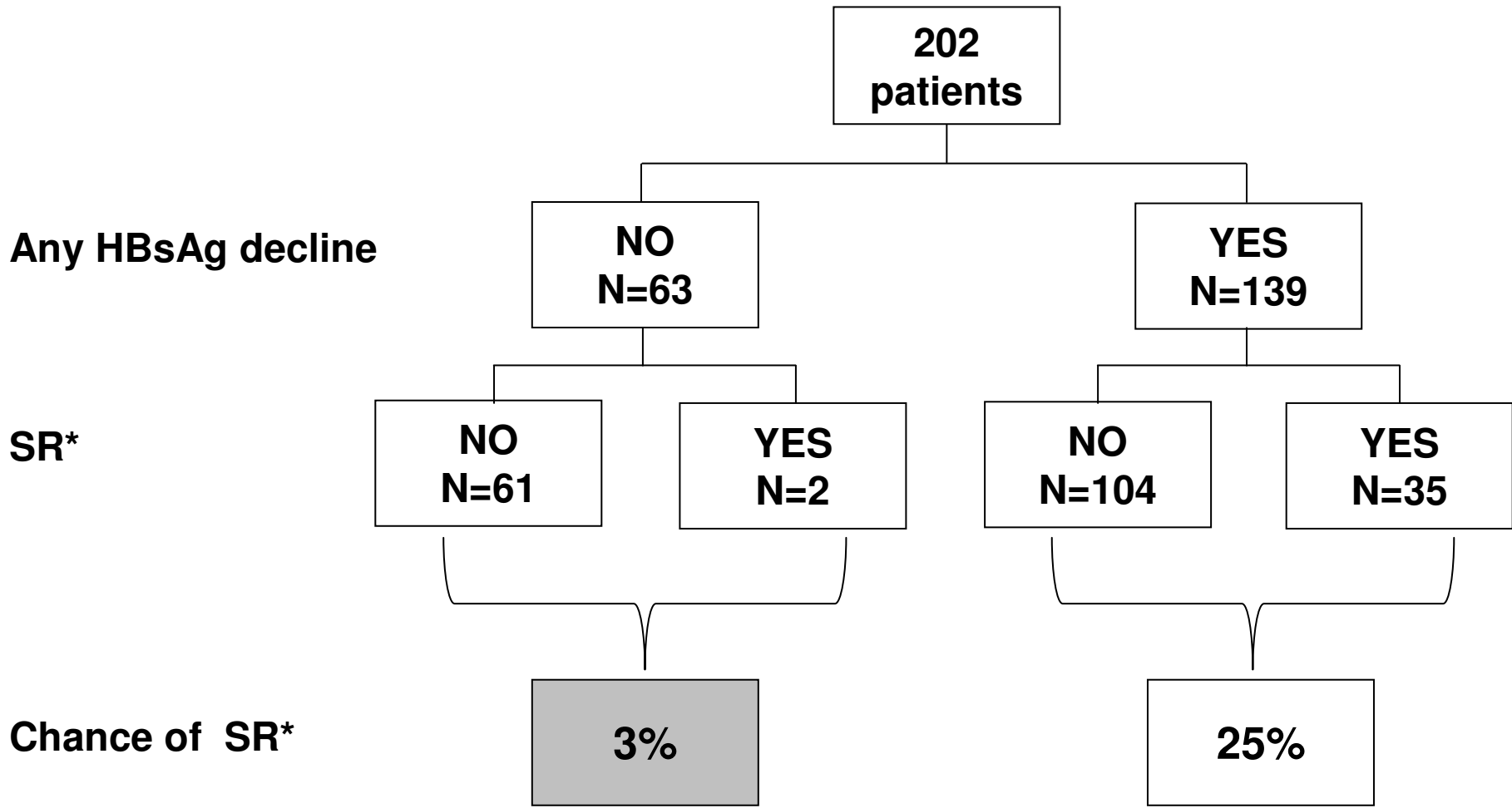
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