Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-04-01-D-280 Tenofoviralafenamid

Stand: März 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Tenofovir **[Chronische Hepatitis B bei Erwachsenen]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Tenofovirdisoproxil Entecavir Adefovirdipivoxil Telbivudin Lamivudin Interferon alfa-2a Peginterferon alfa 2a rekombinantes Interferon alfa-2b
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Tenofoviralafenamid (fumarat)	Behandlung der chronischen Hepatitis B (CHB)-Infektion bei Erwachsenen
Tenofovirdisoproxil Viread® J05AF07	… Hepatitis-B-Infekt.: Erw. m. komp. Lebererkrank. (m. nachgew. aktiver viraler Replikat., dauerhaft erhöht. ALT-Werten im Serum u. histolog. Nachw. aktiver Entzünd. u./od. Fibrose) od. m. nachgew. Lamivudin-resistenten Hepatitis-B-Virus od. m. dekomp. Lebererkrank. Zur Behandl. chron. Hepatitis B bei Jugendl. im Alter v. 12 bis <18 J. m. komp. Lebererkrank. u. nachgew. immunaktiver Erkrank., d. h. aktiver viraler Replikat., dauerhaft erhöht. Serum-ALT-Werten u. histolog. Nachw. einer aktiven Entzünd. u./od. Fibrose.
Entecavir BARACLUDE® J05AF10	Zur Behandl. d. chron. Hepatitis-B-Virus-Infekt. (HBV) bei Erw. mit: kompens. Lebererkrank. u. nachgewies. aktiver Virusreplikation, persist. erhöhten Serumspiegeln d. ALT sowie mit einem histolog. Befund einer aktiven Entzünd. u./od. Fibrose; bei dekompens. Lebererkrank. Zur Behandl. d. chron. HBV-Infekt. bei Nukleosid-naiven Kdrn. u. Jugendl. von 2 bis < 18 J. mit kompens. Lebererkrank. u. nachgewies. akt. Virusreplikation, persist. erhöhten ALT-Serumspiegeln od. mit einem histolog. Befund einer mäßig bis schweren Entzünd. u./od. Fibrose.
Adefovirdipivoxil Hepsera® J05AF08	Behandl. d. chron. Hepatitis B b. Erw. m. komp. Lebererkrank. m. nachgewiesener aktiver Virusreplikat., kontinuierl. erhöht. Serum-Alanin-Aminotransferase-(ALT-)Werten sowie histolog. Nachweis einer aktiven Leberentzünd. u. Fibrose (d. Einleit. einer Ther. m. Hepsera sollte nur dann in Betracht gezogen werden, wenn ein alternativer antivir. Wirkst. m. einer höh. genet. Resistenz-Barriere nicht verfügbar od. nicht geeignet ist) od. m. dekomp. Lebererkrank. in Komb. m. einem zweiten Wirkst. o. Kreuzresistenz ggü. Hepsera.
Telbivudin Sebivo® J05AF11	Behandl. d. chron. Hepatitis B bei erw. Pat. mit kompensierter Lebererkrank. u. Nachweis viraler Replikation, anhaltend erhöhten Alanin-Aminotransferase-(ALT-)Spiegeln u. histolog. Nachweis einer aktiven Entzünd. u./od. Fibrose. Einleit. d. Ther. nur, wenn ein alternativer antiviraler Wirkst. m. einer höh. genet. Resistenz-Barriere nicht verfügbar od. geeign. ist.
Lamivudin Zeffix® J05AF05	Chron. Hepatitis B b. Erw. m. komp. Lebererkrank. m. Nachw. aktiver Virusreplikation, persist. Erhöh. d. ALT-Werte u. histolog. Nachw. aktiver Leberentzünd. u./od. Fibrose (Einleit. d. Behandl. nur in Betracht ziehen, wenn ein alternatives antivirales AM mit einer höh. genet. Barriere ggü. Resistenzen nicht verfügbar od. dessen Anw. nicht angemessen ist.), dekomp. Lebererkrank. in Komb. mit einem 2. AM, das keine Kreuzresistenz ggü. Lamivudin aufweist.
Interferon alfa-2a Roferon®- L03AB04	… Chron., histol. nachgewiesene Hepatitis B u. C b. erwachsenen Patienten…
Peginterferon alfa 2a Pegasys	Behandl. d. chron. Hepatitis B b.: erw. Pat. m. Serum-Markern f. HBV-Replikat. (Vorhandensein v. HVB-DNA) u. HBeAg, erhöht. ALT(GPT)-Werten u. histolog. nachgew. akt. Leberentzünd. u./od. Fibrose… Chron. Hepatitis B: Zur Behandl. d. HBeAg-pos. od. HBeAg-neg. chron. Hepatitis B b. Erw. m. kompens. Lebererkrank., m. Nachweis viraler Replikation,

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L03AB11	erhöht. GPT-Werten u. histolog. verifiz. Leberentz. u./od. -fibrose.
rekombinantes Interferon alfa-2b IntronA® L03AB05	Behandl. d. chron. Hepatitis B b.: erw. Pat. m. Serum-Markern f. HBV-Replikat. (Vorhandensein v. HVB-DNA) u. HBeAg, erhöht. ALT(GPT)-Werten u. histolog. nachgew. akt. Leberentzünd. u./od. Fibrose…

Quellen: AMIS-Datenbank, Fachinformationen,

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Tenofoviralafenamid
[chronische Hepatitis B bei Jugendlichen ab 12 Jahren und mit einem Körpergewicht von mindestens 35 kg]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Tabelle II. zugelassene Arzneimittel im Anwendungsgebiet.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Tenofovir-alafenamid AJ05AF13 Vemlidy®	Zur Behandlung der chronischen Hepatitis B (CHB)-Infektion bei Jugendlichen (ab 12 Jahren, mit einem Körpergewicht von mindestens 35 kg).
Tenofovirdisoproxil J05AF07 Viread®	Hepatitis-B-Infekt.: Viread 245 mg Filmtabletten werden angewendet für die Behandlung chronischer Hepatitis B bei Jugendlichen im Alter von 12 bis < 18 Jahren mit kompensierter Lebererkrankung und nachgewiesener immunaktiver Erkrankung, d. h. aktiver viraler Replikation, dauerhaft erhöhten Serum-ALT-Werten und histologischem Nachweis einer aktiven Entzündung und/oder Fibrose.
Entecavir J05AF10 Baraclude®	Baraclude ist auch indiziert zur Behandlung der chronischen HBV-Infektion bei Nukleosid-naiven Kindern und Jugendlichen von 2 bis < 18 Jahren mit kompensierter Lebererkrankung und nachgewiesener aktiver Virusreplikation, persistierend erhöhten ALT-Serumspiegeln oder mit einem histologischen Befund einer mäßigen bis schweren Entzündung und/oder Fibrose.

Quellen: AMIS-Datenbank, Fachinformationen,

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation chronische Hepatitis B durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.05.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 630 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 24 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung der chronischen Hepatitis B (CHB)-Infektion bei Erwachsenen

Berücksichtigte Wirkstoffe/Therapien:

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ADV	adefovir
ALT	alanine aminotransferase
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CHB	chronische hepatitis B
DAHTA	Deutsche Agentur für Health Technology Assessment
eGFR	renal function
EOF	End of follow-up
EOT	End of treatment
ETV	entecavir
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HBsAg	hepatitis B surface antigen
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LAM	Lamivudin
LdT	Telbivudine
NA	Nucleotide Analogs
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NOS	Newcastle-Ottawa Scale
PCR	polymerase chain reaction
PEG-IFNa	pegylated interferon alfa
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
TDF	Tenofovir
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG-Berichte/G-BA-Beschlüsse

Es wurden derzeit keine relevanten G-BA-Beschlüsse/IQWiG-Berichte identifiziert

Cochrane Reviews

Es wurden derzeit keine relevanten Cochrane Reviews identifiziert

Systematische Reviews

Bedre RH et al., 2016 [3]. Antiviral therapy with nucleotide/nucleoside analogues in chronic hepatitis B: A meta-analysis of prospective randomized trials	1. Fragestellung: To estimate the effect of antiviral drugs in chronic hepatitis B with compared to placebo.
	2. Methodik Population: Patients with chronisc hepatitis B Intervention: Antiviral drugs (siehe Ergebnisteil) Komparator: Placebo Endpunkte: Virological response, biochemical response, histological response, seroconversion of HBeAg, and loss of HBeAg, adverse events Suchzeitraum (Aktualität der Recherche): Literature search from 1990 to 2013. Hinweis: Search restricted only for placebo-controlled double blind or single blind study. Anzahl eingeschlossene Studien/Patienten (Gesamt): 1987 patients from 10 studies. All trials contain nucleotide/ nucleoside therapy as intervention treatment and placebo therapy as control treatments. Qualitätsbewertung der Studien: The heterogeneity was assessed with χ^2 and I^2 statistics. Publication bias was assessed by funnel plot. Keine weiteren Angaben zur Bewertung der Qualtät der Studien.
	3. Ergebnisdarstellung Wirksamkeit:

	Greater rates of improvement obtained in antiviral group for *virological response* [43.96 % vs. 3.15 %, RR= 0.57, 95 % CI = 0.54–0.61, p-value <0.00001], *biochemical response* [58.37 % vs. 21.87 %, RR= 0.52, 95 % CI = 0.48–0.56, p-value <0.00001], *histological response* [58.99 % vs. 27.13 %, RR = 0.56, 95 % CI = 0.50–0.63, p-value <0.0001], *seroconversion of HBeAg* [10.66 % vs. 5.56 %, RR= 0.94, 95 % CI = 0.91–0.97, p-value = 0.0005], and *HBeAg loss* [14.59 % vs. 9.64 %, RR=0.92, 95 % CI= 0.88–0.96, p-value=0.0002]. Sicherheit: No statistically significant differences.
	4. Fazit der Autoren: *In conclusion, the early initiation of adaptive nucleoside analogue drugs for antiviral therapy is the best available treatment in patients with HBeAg positive and HBeAg negative chronic hepatitis B without any significant adverse effects.*
Chan HL et al., 2016 [4] Renal Function in Nucleos(t)ide Analog-Treated Patients With Chronic Hepatitis B: A Systematic Literature Review and Network Meta-Analysis	1. Fragestellung This systematic literature review and network meta-analysis aimed to assess renal function associated with telbivudine treatment compared to other NAs in patients with CHB.
	2. Methodik Population: Patients with chronic hepatitis B Intervention/Komparator: adefovir, entecavir, lamivudine, telbivudine, tenofovir, and placebo Endpunkt: absolute change; percentage improvement from baseline Suchzeitraum (Aktualität der Recherche): bis Juli 2015. Network meta-analysis was performed to compare renal function with telbivudine treatment versus other NAs after 1 year of therapy → For the purpose of the present analysis, Bayesian models were used. Anzahl eingeschlossene Studien/Patienten (Gesamt): In total, 6 RCTs and 34 observational studies were included (17 retrospective studies, 12 prospective studies, three non-RCTs, and one case–control study and cross-sectional study each). Of the 40 included studies, 35 had an active control group, and in the remaining five studies, NAs were compared with untreated controls. Entecavir, telbivudine, and tenofovir were the most commonly reported treatments. Overall, 90% (36/40) of the studies were conducted in populations with

	mixed HBeAg status, whereas only three studies enrolled HBeAg-negative patients and one study enrolled HBeAg-positive patients. Qualitätsbewertung der Studien: Each included study was assessed for methodological quality (internal and external validity). RCTs that met the eligibility criteria for review were critically appraised for quality based on the NICE recommendations. All included observational studies were critically appraised for quality based on the Downs and Black checklist.
	3. Ergebnisdarstellung Studienqualität: Overall, the methodological quality of the included studies was adequate Hinweis: *The included studies were widely heterogeneous, and considering specific assumptions, an NMA was possible only in the non-RCTs. For eGFR changes from baseline at 1 year in the non-RCTs, it was possible to construct a network diagram for available evidence. The assumptions used to attempt the NMA were as follows: all non-RCTs were comparable in terms of baseline characteristics and missing SE was computed to be 10% of themean change in eGFR from baseline. For the purpose of analysis, the eGFR values from different equations were analyzed together.* Telbivudine consistently showed an improvement in renal function as measured by an estimated glomerular filtration rate (eGFR) over various time points regardless of the method of measurement. Changes in eGFR (mL/min) from baseline and corresponding 95% credible intervals with various NAs were as follows: • Monotherapies: telbivudine: 7.78 [6.91, 8.65], entecavir: -1.07 [-4.80, 2.62], lamivudine: -6.08 [-13.35, 1.15], tenofovir: -9.53 [-14.31, -4.89]) • Combination therapies: telbivudine + adefovir: 8.37 [-34.00, 50.34], telbivudine + tenofovir: 8.29 [-0.05, 16.64], entecavir + adefovir: 4.15 [-38.55, 46.37], telbivudine + lamivudine: 0.51 [-11.77, 12.96], and lamivudine + adefovir: -0.39 [-42.48, 41.21]). • At 1 year, the change in eGFR from baseline was significantly higher with telbivudine compared to other NAs.
	4. Fazit der Autoren: *This SLR and NMA provide evidence that telbivudine is associated with a significant improvement in renal function (eGFR) in patients with CHB, either alone or in*

	combination with other NAs. 5. Hinweise durch FB Med • Funding: Novartis Pharma AG • Limitation von Netzwerkmetaanalysen sind zu beachten
Chen L et al., 2016 [5] Efficacy of Tenofovir-Based Combination Therapy versus Tenofovir Monotherapy in Chronic Hepatitis B Patients Presenting with Suboptimal Responses to Pretreatment: A Meta-Analysis	1. Fragestellung The aim of this study was to compare the efficacy of the two regimens by performing a meta-analysis.
	2. Methodik Population: Patients with chronisc hepatitis B and suboptimal response on any previous NA other than TDF treatment and presenting with a suboptimal response to the prior NA treatment Intervention: TDF-based combination therapy Komparator: TDF Monotherapy Endpunkte: Virological response (HBV DNA levels), serological response (HBeAg and HBsAg loss or seroconversion), biochemical response (ALT normalization) Suchzeitraum (Aktualität der Recherche): March 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 9 eligible articles relating to a total of 1089 subjects (592 in combination therapy groups and 497 in monotherapy groups). 5 studies were RCTs and 4 were cohorts. Qualitätsbewertung der Studien: The quality of all included RCTs was assessed using the revised Jadad quality scale, which graded the quality of a study from 0 (lowest) to 7 (highest) by examining randomization, blinding, allocation concealment, and drop-out. For cohort designs, the quality was assessed using the Newcastle-Ottawa Scale (NOS) based on several standards including selection of cohorts, comparability of cohorts, and assessment of the outcomes.
	3. Ergebnisdarstellung All of the five RCTs receiving a Jadad score of at least 5 were considered of relatively high quality and all of the four cohort studies received NOS score of at least 5. Publication bias was not found in any outcome measure • The proportion of patients with undetectable HBV DNA at 24,

	48, and 96 weeks were similar between the two comparable groups • HBV DNA reduction, rates of ALT normalization, hepatitis B e antigen (HBeAg) loss, and HBeAg seroconversion were also similar between the two groups
	4. Fazit der Autoren: *In conclusion, based on the available data, our results indicate that TDF-based combination therapy did not show any significant advantage in those efficacy indicators nor did it result in any compromised safety when compared to TDF monotherapy. Further studies are needed to verify this comparison.* 5. Hinweise durch FB Med • Wenig Studien • Einige Studien keine RCTs inkl. retrospektivem Design
Liang X et al., 2016 [16] Effect of Telbivudine Versus Other Nucleos(t)ide Analogs on HBeAg Seroconversion and Other Outcomes in Patients with Chronic Hepatitis B: A Network Meta-Analysis	1. Fragestellung The aim of this NMA was to assess the efficacy of telbivudine versus adefovir, entecavir, lamivudine, and tenofovir in nucleos(t)ide-naive hepatitis B e antigen (HBeAg)-positive patients with CHB.
	2. Methodik Population: Patients with Chronic Hepatitis B Intervention/Komparator: Only those RCTs with interventions or comparators: adefovir, entecavir, lamivudine, telbivudine, tenofovir, and placebo Endpunkte: HBeAg seroconversion, HBeAg loss, HBV DNA levels, alanine aminotransferase (ALT), normalization, and hepatitis B surface antigen (HBsAg) loss and seroconversion Suchzeitraum (Aktualität der Recherche): 2004 to 2015 NMA was performed to compare the efficacy outcomes of telbivudine versus other approved NAs at 1- and 2-year time points. → For this analysis, Bayesian models were used. *Hinweis*: All RCTs with HBeAg-positive, nucleos(t)ide-naive patients with CHB were identified. RCTs reporting both HBeAg-positive and -negative patients were considered if subgroup data for HBeAg-positive patients were reported Anzahl eingeschlossene Studien/Patienten (Gesamt): 75 included studies. 9 (12%) studies in total were placebo controlled. Of the remaining 5 studies, 1 compared lamivudine

	with untreated controls and 4 were dose-ranging studies. *Hinweis*: In the included RCTs, lamivudine was the most commonly assessed comparator accounting for 24 studies. This was followed by placebo, which was the comparator in 12 of the included studies. NAs were assessed as monotherapy in 58 of the included studies. Qualitätsbewertung der Studien: The RCTs that met the inclusion criteria for the review were critically appraised for quality based on the recommendations by NICE
	3. Ergebnisdarstellung Studienqualität: Overall, 19% of the included studies may be at risk of bias. Analysis of Heterogeneity → None of the factors including study location, age, and baseline HBV DNA was found to affect the results. HBeAg Seroconversion: A total of 40 studies reported HBeAg seroconversion results. The relative efficacy of NAs at the 1-year time point demonstrated that telbivudine was superior to adefovir, entecavir, and lamivudine. The relative efficacy outcomes of telbivudine versus other NAs at the 2-year time point were not statistically significant. There were a relatively small number of studies (14 studies) which reported outcomes at the 2-year time point. HBeAg Loss: Thirty studies reported HBeAg loss results. The NMA on relative efficacy at the 1-year time point showed that telbivudine was superior to entecavir and lamivudine for HBeAg loss in patients with CHB. The relative efficacy of NAs at the 2-year time point yielded no statistically significant results. ALT Normalization: Thirty-two studies reported ALT normalization results. The NMA demonstrated that telbivudine was superior to lamivudine in ALT normalization at the 1-year time point. Undetectable HBV DNA: There were 34 studies that reported rates of undetectable HBV DNA at 1 year of treatment. At the 1-year time point telbivudine was superior to adefovir and lamivudine in suppressing HBV DNA levels. Tenofovir was superior to telbivudine in suppressing HBV DNA levels.
	4. Fazit der Autoren: *This SLR and NMA demonstrated that in nucleos(t)ide-naive HBeAg-positive patients with CHB, telbivudine was superior to adefovir, entecavir, and lamivudine*

	in HBeAg seroconversion, and to entecavir and lamivudine in HBeAg loss at 1 year of treatment. Telbivudine also showed a superior response as compared to lamivudine in ALT normalization and to adefovir and lamivudine in suppressing HBV DNA levels. 5. Hinweise durch FB Med/Autoren • Limitationenen einer Netzwerkmetaanalyse sind zu berücksichtigen → Indirekte Vergleiche • viral resistance and adverse events due to NA treatment were not assessed • The analysis mainly reported results from RCTs with 1-year of treatment. A limited number of studies reported outcomes at the 2-year time point
Zuo SR et al., 2015 [24] A Meta-Analysis Comparing the Efficacy of Entecavir and Tenofovir for the Treatment of Chronic Hepatitis B Infection	1. Fragestellung To address this issue, we conducted a metaanalysis based on a current review of the literature addressing the efficacy and safety of entecavir and tenofovir
	2. Methodik Population: patients with chronic HBV Intervention: Entecavir Komparator: Tenofovir Endpunkte: virological response, biochemical response, serological response, HBeAg seroconversion, or HBsAg loss and adverse reaction rate Suchzeitraum (Aktualität der Recherche): bis Juni 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): The final analysis group included 2 randomized controlled trials, 2 prospective cohort studies, and 7 casecontrol studies and comprised a total of 1,647 patients *Hinweis*: Eight studies included nucleos(t)ide-naïve chronic HBV patients and 3 studies included non-naïve chronic HBV patients. Qualitätsbewertung der Studien: The Newcastle–Ottawa Scale and 5-score Jadad Scale were used to assess the quality of non-randomized controlled studies and randomized studies in the metaanalysis.
	3. Ergebnisdarstellung

	In the entecavir group, 842 of 992 were nucleos(t)ide-naïve chronic HBV patients, and in the tenofovir group 481 of 664 were nucleos(t)ide-naïve. • The virological response to tenofovir was statistically significant superior to entecavir (RR: 0.82; 95%CI: 0.72–0.93), especially in nucleos(t)ide-naïve chronic HBV patients at 48 weeks (RR: 0.78; 95%CI: 0.65–0.92). • There was no difference between entecavir and tenofovir for virological response at 24 weeks. • The ALT normalization rate, serological response, and adverse event rate were also not significantly different between entecavir and tenofovir at 24 or 48 weeks after treatment.
	4. Fazit der Autoren: *In conclusion, the results of this meta-analysis indicated that tenofovir was superior to entecavir at inhibiting HBV replication in nucleos(t)ide-naïve patients at 48 weeks, and there was no difference in non-naïve patients at 24 or 48 weeks after treatment. In addition, there was no significant difference in the serological response and ALT normalization. Although HBV infection is a global problem, the largest infected populations are from Asia, especially from China. Our analysis provides novel insights for the treatment of chronic HBV infection in China.*
Kim V et al., 2016 [14] Pegylated interferon alfa for chronic hepatitis B: systematic review and meta-analysis	1. Fragestellung Here we performed a systematic review and meta-analysis evaluating all studies of pegylated interferon alfa (PEG-IFNa) treatment in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB.
	2. Methodik Population: hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB Intervention/Komparator: PEG-IFNa monotherapy or PEG-IFNa combination therapy, including in patients who had not previously received treatment or who had experienced treatment failure. Endpunkte: Virological response (primärer Endpunkt der Studie); biochemical response (normalization of ALT levels), HBeAg seroconversion (loss of HBeAg and presence of anti-HBe antibody) in HBeAg-positive patients and HBsAg seroconversion (loss of HBsAg and presence of anti-HBs antibody) in HBeAg-

	negative patients. Suchzeitraum (Aktualität der Recherche): between 1999 and September 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): We identified 14 studies involving 2829 patients. Qualitätsbewertung der Studien: We assessed the quality and the risk of bias in individual trials using Cochrane Collaboration's tool. Publication bias was evaluated using a funnel plot.
	3. Ergebnisdarstellung **Outcome evaluation: PEG-IFNa vs PEG-IFNa + LAM** <u>HBeAg-positive patients:</u> *Virological response* was reported by two studies. Response rates significantly differed between patients receiving PEG-IFNa + LAM combination therapy vs PEGIFNa monotherapy at the end of treatment (EOT) (57% vs 20%; RR, 0.35; 95% CI, 0.29–0.43; P < 0.00001; I^2 = 0%), but not at the end of follow-up (EOF) *Biochemical response* was reported by two studies. Analysis revealed significantly higher response rates for patients treated with PEG-IFNa + LAM vs PEGIFNa at EOT (48% vs 37%; RR, 0.78, 95% CI, 0.66–0.91; P = 0.002; I^2 = 36%), but not at EOF. *Serological response* was reported by two studies. Rates of HBeAg seroconversion did not significantly differ between PEG-IFNa and PEG-IFNa + LAM at EOT and at EOF. <u>HBeAg-negative patients:</u> *Virological response* was reported by four studies. The reported response rates significantly differed in favour of PEG-IFNa + LAM combination therapy over PEG-IFNa monotherapy at EOT (85% vs 65%; RR, 0.77; 95% CI, 0.69–0.85; P < 0.00001; I^2 = 25%), but not at EOF. *Biochemical response* was reported by four studies. Analysis revealed significantly ALT normalization with PEG-IFNa + LAM vs PEG-IFNa at EOT (50% vs 40%; RR, 0.81; 95% CI, 0.66–0.99; P = 0.04; I^2 = 0%), but not at EOF. *Serological response* was reported by two studies. Rates of HBsAg seroconversion did not significantly differ between PEG-IFNa and PEG-IFNa + LAM at EOF.

	Outcome evaluation: PEG-IFNa + LAM vs LAM HBeAg-positive patients Virological, biochemical and serological responses were reported by one study → keine Ergebnisse berichtet HBeAg-negative patients Virological, biochemical and serological responses were reported by one study → keine Ergebnisse berichtet **Outcome evaluation: PEG-IFNa vs PEG-IFNa + ADV** HBeAg-positive patients: No differences between the groups regarding virological and biochemical response. Serological response was reported by two studies. Analysis revealed that response rates were significantly higher for patients treated with PEG-IFNa + ADV vs with PEG-IFNa at EOT (51% vs 34.2%; RR, 0.67; 95% CI, 0.49–0.92; P = 0.01; I^2 = 0%) HBeAg-negative patients: Virological and biochemical responses were reported by one study → keine Ergebnisse berichtet **Outcome evaluation: PEG-IFNa + LAM vs PEGIFNa + ADV** HBeAg-positive patients: Virological response was reported by one study, which was unable to compare responses between PEGIFNa + LAM and PEG-IFNa + ADV therapies because all patients achieved HBV DNA of <50 IU/mL at 96 weeks, and none experienced virological rebound after EOT. Serological response was reported by one study → keine Ergebnisse berichtet **Outcome evaluation: PEG-IFNa + ETV vs ETV** HBeAg-positive patients Virological, biochemical and serological responses were reported by one study. → keine Ergebnisse berichtet **Outcome evaluation: PEG-IFNa vs first PEG-IFNa→ETV vs first ETV→PEG-IFNa** HBeAg-positive patients: PEG-IFNa vs first PEG-IFNa→ETV. Virological, biochemical and serological responses were reported by one study. → keine Ergebnisse berichtet PEG-IFNa vs first ETV→PEG-IFNa. Virological, biochemical

	and serological responses were reported by one study. → keine Ergebnisse berichtet First PEG-IFNa→ETV vs first ETV→PEG-IFNa. Virological, biochemical and serological responses were reported by one study. → keine Ergebnisse berichtet **Outcome evaluation: first PEG-IFNa→LdT vs first LdT→ PEG-IFNa** <u>HBeAg-negative patients</u> Virological and biochemical responses were reported by one study. **Outcome evaluation: PEG vs conventional IFNa** <u>HBeAg-positive patients:</u> Virological, biochemical and serological responses were reported by one study.
	4. Fazit der Autoren: *In conclusion, this is the first meta-analysis to compare the all treatments with PEG-IFNa in HBeAg-positive and HBeAg-negative patients with CHB. Our results demonstrated substantial virological, biochemical and serological responses following simultaneous treatments with PEG-IFNa and NAs (LAM and ADV) in comparison with PEG-IFNa or NA monotherapies. Our review has some limitations, such as the lack of RCTs of each treatment, the not exclusion of publication bias influence and the heterogeneity among trials. The development of new antiviral drugs to further improve treatment strategies for CHB remains an important goal.* 5. Hinweise durch FB Med • Unterschiedliche Dosierungen von PEG-IFNa2a and PEG-IFNa2b in den unterschiedlichen Studien
Zeng T et al., 2014 [23] Entecavir Plus Adefovir Combination Therapy Versus Lamivudine Add-On Adefovir for Lamivudine-Resistant Chronic Hepatitis B: A Meta-Analysis	1. Fragestellung To determine whether adefovir (ADV) in combination with entecavir (ETV) is more effective than with lamivudine (LAM) in patients with lamivudine resistant chronic HBV infection.
	2. Methodik Population: Patients with Lamivudine-Resistant Chronic Hepatitis B Intervention: Adefovir (ADV) + Entecavir (ETV) Komparator: Lamivudine (LAM) + ADV

	Endpunkte: Mean reduction of HBV DNA level; HBV-DNA undetectability(virologic response); virologic breakthrough; normalization of serum ALT Suchzeitraum (Aktualität der Recherche): bis März 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 studies were chosen for inclusion in the meta-analysis, which comprised a total of 323 patients. Qualitätsbewertung der Studien: The quality of each study was independently assessed by the same two authors according to the following high-quality features: (1) studies designed with case characteristics (clinical and/or demographic) matched to controls; and (2) presence of a definitive listing of inclusion and exclusion criteria for patients, along with clear definitions of treatment response. When there was disagreement between the two reviewers, a third party was consulted.
	3. Ergebnisdarstellung Two studies were randomized controlled trials and two were cohorts. → Keine weitere Beschreibung zur Qualität der eingeschlossenen Studien. Serum HBVDNA reductions after 3 and 6 months of treatment in the ETV+ADV group were greater than that of LAM+ADV group (mean difference (MD)=0.90, 95% CI: 0.74–1.07, P<0.00001 MD=0.81, 95% CI: 0.57–1.06, P<0.00001). The rate of 6 months HBV DANN undetectability with ETV+ADV was statistically significant higher than that of LAM+ADV (RR=1.63, 95%CI: 1.14–2.34, P<0.007). There were statistically significant higher rates of serum ALT normalization than those in LAM+ADV group after 6 months of treatment (RR=1.40, 95% CI: 1.11–1.77, P<0.005). The ETV+ADV group had statistically significant lower viral breakthrough and genotypic mutation rates than LAM+ADV group after 12 months of treatment (RR=0.24, 95% CI: 0.10–0.58, P=0.002).
	4. Fazit der Autoren: *In conclusion, compared to ADV add-on LAM combination therapy, ETV+ADV combination therapy had faster and significantly greater suppression of HBV DNA for patients with LAM-resistant HBV. A combination of ETV+ADV resulted in significantly better virologic response than the LAM+ADV combination ETV+ADV combination therapy is more effective in preventing development of resistance. The combination of ETV plus ADV is a better overall option*

	compared with ADV add-on LAM for patients with LAM-resistant HBV in these countries as china where TDF is too expensive for patients suffering from chronic hepatitis B.
Xie QL et al., 2015 [22] The Efficacy and Safety of Entecavir and Interferon Combination Therapy for Chronic Hepatitis B Virus Infection: A Meta-Analysis	1. Fragestellung The objective of this study was to evaluate the effectiveness and safety of entecavir (ETV) and interferon (IFN) combination therapy in the treatment of chronic hepatitis B (CHB) mono-infection via a meta-analysis of randomized controlled trials (RCTs).
	2. Methodik Population: Patients with HBV Intervention/Komparator: ETV + IFN Komparator: ETV or IFN monotherapy Endpunkte: • Wirksamkeit: Undetectable HBV DANN, ALT normalization, HBeAg seroconversion • Sicherheit: Side effects, laboratory abnormalities, hepatitis flares, death. Suchzeitraum (Aktualität der Recherche): Oktober 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 trials encompassing 1010 participants were included in this meta-analysis Qualitätsbewertung der Studien: The methodological quality of the trials was assessed based on sequence generation, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. We also used the Jadad scale to evaluate the quality of the RCTs.
	3. Ergebnisdarstellung Eleven eligible studies were RCTs. Five studies received Jadad scores of 5, and the others received scores of 2 or 3. • It showed that at 12 and > 96 weeks of therapy, the combination of ETV and IFN was not better than ETV in improving the undetectable HBV DNA and HBeAg seroconversion rates. • At 48 weeks of therapy and approximately 2 years of follow up, combination therapy was statistically significant superior

	to ETV in improving the undetectable HBV DNA (48 weeks: RR=1.46, 95% CI=1.13-1.90; follow up: RR=2.20, 95% CI=1.26-3.81, respectively) and HBeAg seroconversion rates (48 weeks: RR=1.82, 95% CI=1.44-2.30; follow up: RR=1.92, 95% CI=1.19-3.11, respectively). • When compared to IFN group, at 24 and 48 weeks of therapy, combination group showed a statistically significant greater undetectable HBV DNA (24 weeks: RR=2.14, 95% CI=1.59-2.89; 48 weeks: RR=2.28, 95% CI=1.54-3.37, respectively) and ALT normalization rate (24 weeks: RR=1.56, 95% CI= 1.24-1.96; 48 weeks: RR=1.55, 95% CI = 1.16-2.07, respectively). • At 48 weeks of therapy, combination group achieved a statistically significant greater HBeAg seroconversion rate than IFN (48 weeks: RR=1.58, 95% CI=1.24-2.00). • No significant differences were observed in the side effects of the three therapies.
	4. Fazit der Autoren: *Our meta-analysis indicated that ETV and IFN combination therapy is more effective than ETV or IFN mono-therapy in HBeAg-positive CHB treatment. The combination of the two is also safe in the treatment of CHB. However, there are still some limits to combination therapy: first, combination therapy is very expensive; second, a definite duration for combination therapy is unclear; and third, it is uncertain that whether an initial combination therapy approach or a sequential therapy approach is more suitable. Therefore, studies with much larger sample sizes are needed to explore the advantages of combination therapy.* 5. Hinweise durch FB Med • Nicht untersucht: differences between conventional IFN and pegylated IFN were not further / differences between the initial combination therapy and sequential combination therapy • Quality of some of the included trials was not high because details about the methods of randomization, allocation, concealment, and blinding were unclear.
Liu F et al., 2014 [17] Efficacy and resistance in de novo combination lamivudine and adefovir dipivoxil	1. Fragestellung The aim of this study was to evaluate the effectiveness and resistance of de novo combination of lamivudine (LAM) and adefovir dipivoxil (ADV) compared with entecavir (ETV) monotherapy for nucleos(t)ide–naive patients with CHB.
	2. Methodik Population: Nucleos(t)ide–naive patients with CHB

therapy versus entecavir monotherapy for the treatment-naive patients with chronic hepatitis B: a meta-analysis *siehe auch:* **Sheng YL et al., 2011 [19]:** Lamivudine plus adefovir combination therapy versus entecavir monotherapy for lamivudineresistant chronic hepatitis B: a systematic review and meta-analysis.	Intervention: Lamivudine (LAM) + adefovir dipivoxil (ADV) Komparator: Entecavir (ETV) monotherapy Endpunkte: • Primäre Wirksamkeitsendpunkte: Biochemical response, virologic response, and HBeAg seroconversion • Sekundäre Endpunkte: Emergence of viral resistance; safety profiles Suchzeitraum (Aktualität der Recherche): Bis Mai 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 studies (328 patients in total) Qualitätsbewertung der Studien: Quality of included study was assessed based on following criteria: (1) For RCT: Methodological quality was assessed using the Jadad quality scale. (2) For cohorts, the quality of studies was assessed by the Newcastle-Ottawa Scale (NOS)
	3. Ergebnisdarstellung *Studienqualität*: One study was an RCT and stated the method of randomization, withdrawal and allocation concealment, but did not describe the blinding. Accordingly, it received a Jadad score of 4. The other reports were on cohort studies with defined inclusion and exclusion criteria and definitions of the treatment responses. All study populations had comparable baseline characteristics between the LAM+ ADV and ETV groups. However, one study did not follow up long enough for outcomes to occur, so it received a score of 8. The others had scores of 9. Virologic response: Four studies reported virologic response rates after 12, 24, and 48 weeks. The results showed that the virologic response rates were obviously higher in the combination group than that of ETV monotherapy (53.6%, 72.1%, 90.0% vs. 47.6%, 64.8%, 78.9% at 12, 24, and 48 weeks, respectively). → No significant heterogeneity was found at virologic response between two groups at 12, and 24 weeks. However, at week 48, the differences in virologic response rates were statistically significant (RR = 1.14, 95% CI (1.03, 1.26), P =0.01). Only three studies reported virologic responses at 96 weeks → but with significant heterogeneity in virologic responses between the two groups (I^2 = 82%). Virologic response was higher in the combination therapy group than that in the ETV monotherapy

	group (96.2% vs. 82.8%). However, no significant differences were found. Biochemical responses: Four studies showed the biochemical response rates at weeks 12, and 24. → No heterogeneity. No statistically significant differences between the two groups. ALT normalization: Another four studies provided the rates of ALT normalization at 48 weeks treatment. → Heterogeneity was found between these studies (I^2 = 68%). There were no statistical significant differences between groups in terms of the ALT normalization rates at 12, 24, and 48 weeks after treatment, although the proportion in the combination group was lower than that of in the ETV monotherapy group after 12, 24 weeks post treatment (36.3% vs. 38.2%, and 67.6% vs. 71.8%, respectively), and was higher than that obtained in the monotherapy group at 48 weeks (91.4% vs. 81.6%). There were three studies that reported the ALT normalization rates at 96 weeks → no heterogeneity. ALT normalization rate in the combination group was statistically significant superior to ETV group (96.3% vs. 86.7%; RR = 1.11, 95% CI (1.02, 1.21), P =0.01). HBeAg seroconversion: Three studies provided the data regarding HBeAg seroconversion after 48 and 96 weeks of treatment. → no heterogeneity. No statistically significant differences between the two groups in week 48, however, with prolonged duration up to 96 weeks, the difference became statistically significant (RR = 2.00, 95% CI (1.26, 3.18), P =0.003). Viral breakthrough No viral breakthrough was reported in the combination group. However, six patients experienced viral breakthrough in ETV group. Sicherheit: Both groups were well tolerated.
	4. Fazit der Autoren: *In conclusion, de novo combination of LAM and ADV therapy for naïve treated patients was not superior to the ETV monotherapy in short duration; however, the combination therapy had higher biochemical response and HBeAg seroconversion rates compared with monotherapy when the therapy duration was prolonged up to 96 weeks. The rate of emergence of viral resistance in combination group was less than that in the ETV group. However, given the limited number*

	of studies included in the analysis, caution should be exercised in extrapolation of the conclusion to all patients infected with CHB. More high-quality, well-designed, randomized controlled, multicenter studies are clearly needed to confirm these observations.
Ke W et al., 2014 [13] Comparison of Efficacy and Safety of Tenofovir and Entecavir in Chronic Hepatitis B Virus Infection: A Systematic Review and Meta-Analysis	1. Fragestellung Tenofovir (TDF) and entecavir (ETV) are both potent antiviral agents for the treatment of chronic hepatitis B virus (HBV) infection. Multiple studies have compared efficacy and safety of these two agents, but yielded inconsistent results. Hence, we conducted a meta-analysis to discern comparative efficacy and safety.
	2. Methodik Population: Patients with chronic HBV Intervention: Tenofovir (TDF) Komparator: Entecavir (ETV) Endpunkte: Efficacy was considered for patients 24 and 48 weeks post therapy by considering the following: HBV-DNA level, ALT normalization rate, HBeAg seroconversion rate, and drug safety (adverse events, laboratory abnormalities, deaths, tolerability, etc). Suchzeitraum (Aktualität der Recherche): bis Juni 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 were selected involving 844 patients (378 treated with TDF monotherapy and 466 treated with ETV monotherapy). Of these studies, 2 were RCTs, 4 were cohort studies, and 1 was a case-cohort study. Qualitätsbewertung der Studien: The two reviewers also assessed methodological quality based on following criteria: (1) Randomized controlled trials (RCTs) were assessed using the QUOROM guidelines and the Jadad scale; (2) non-RCTs must have met the case matched by the patient's baseline data; (3) selected studies had defined inclusion and exclusion criteria for the study population and a clear definition of treatment responses. Reviewers resolved discrepancies through discussion.
	3. Ergebnisdarstellung <u>Studienqualität</u>: Two manuscripts were RCTs. One received

	Jadad scores of 5 and the other 3. For non-RCTs, all were wellmatched based on baseline characteristics and clear definition of treatment response. With exceptions of Gao et al. and Kurdas et al. non-RCTs had defined inclusion and exclusion criteria for patients. • Four and six articles included data for 24 and 48-week HBV DNA suppression rates, respectively, and no significant differences for the rates between the two drugs were found in chronic HBV patients. • For the ALT normalization rate (three studies for 24 weeks, four articles for 48 weeks) and HBeAg seroconversion rate (two and four studies for 24 weeks and 48 weeks, respectively), no difference was observed between TDF and ETV. • Additionally, no significant distinction in short term safety was found for CHB patients.
	4. Fazit der Autoren: *Our meta-analysis indicates that ETV and TDF are comparable in efficacy and safety to sustain HBV DNA suppression with limited side effects. However, in considering limited efficacy of ETV in patients with LAM resistance, TDF is an alternative agent against HBV infection. Nonetheless, long-term efficacy and safety of TDF and ETV should be monitored in prolonged therapy in well-designed prospective studies with large sample sizes.* 5. Hinweise durch FB Med • Majority of included studies were non-RCTs
Chen Y et al., 2012 [6] Comparative meta-analysis of adefovir dipivoxil monotherapy and combination therapy of adefovir dipivoxil and lamivudine for lamivudine-resistant chronic hepatitis B.	1. Fragestellung The aim of the current study was to compare the effectiveness of adefovir dipivoxil (ADV) monotherapy with that of combination ADV and lamivudine (LAM) therapy in the treatment of LAM resistant chronic hepatitis B (CHB).
	2. Methodik Population: Patients with lamivudine-resistant CHB Intervention: Defovir dipivoxil (ADV) monotherapy Komparator: Combination ADV and lamivudine (LAM) Endpunkte: Virological; biochemical response Suchzeitraum (Aktualität der Recherche): bis 2010

	Anzahl eingeschlossene Studien/Patienten (Gesamt): In total, 11 studies. 6 were RCTs and the remaining 5 were prospective cohort studies (all in English). Qualitätsbewertung der Studien: The quality of the studies was assessed using the following factors: (1) definite description of the methods employed, including the inclusion criteria for patients, grouping and treatment, follow-up treatments, end-points, and statistical analyses, and (2) concrete presentation of results. → Only those studies that fulfilled the above quality criteria were included in the meta-analysis.
	3. Ergebnisdarstellung <u>Biochemical response:</u> No significant difference was present between the monotherapy and combination therapy in terms of biochemical response after 3 and 6 months of therapy. However, prolonging the duration of therapy to >12 months revealed significant differences between the two therapies →<u>Zum Vorteil der Kombinationstherapie</u> (3.35; 95%CI: 1.96, 5.72; p<0.00001). <u>Virological response:</u> No significant differences were present between the monotherapy and combination therapy in terms of virological response after 3, 6, and 12 months of therapy. However, prolonging the therapy duration to >12 months revealed a significant difference between the two therapies →<u>Zum Vorteil der Kombinationstherapie</u> (OR: 1.87; 95%CI: 1.16, 3.02); p= 0.01). <u>Sensitivity analysis → RCTs only:</u> *Biochemical response*: The summary OR, 95% CI, and p values were 1.83 (1.06, 3.16), p = 0.03 at 3 months after therapy; 1.53 (0.97, 2.41), p = 0.07 at 6 months; 1.82 (1.12, 2.95), p = 0.02 at 12 months; and 4.39 (2.04, 9.46), p = 0.0002 at >12 months. → The combination therapy did not show any considerable advantage during the first year of therapy. However when the therapy duration was extended to ≥12 months, the combination therapy appeared to be much more effective than the monotherapy. *Virological response:* The summary OR, 95% CI, and pvalues were 1.46 (0.81, 2.62), p = 0.21 at 3 months; 0.96 (0.52, 1.78), p = 0.90 at 6 months; 1.46 (0.80, 2.63), p = 0.21 at 12 months; and 2.81 (1.49, 5.30), p = 0.001 at >12 months. → No significant differences were found between the two therapies during the first year. However, when the therapy duration was extended to

	>12 months, the combination therapy seemed to be much more effective than the monotherapy (OR: 1.87; 95%KI: 1.16-3.02; p=0.01; I^2= 28%).
	4. Fazit der Autoren: *In conclusion, the results show that the effectiveness of both therapies depends on the duration of therapy. In therapies of short duration, no considerable predominance was observed for either therapy. However, extending therapy to more than 12 months gave the combination therapy a greater advantage over monotherapy, both in terms of biochemical and virological response.*
Huang R et al., 2013 [10] Interferon-alpha plus adefovir combination therapy versus interferon-alpha monotherapy for chronic hepatitis B treatment: A meta-analysis	1. Fragestellung The therapeutic effect of interferon (IFN)-a plus adefovir (ADV) combination therapy versus IFN-a monotherapy in chronic hepatitis B (CHB) treatment remains under debate. The objective of the present study was to compare the efficacy between these two regimens in CHB treatment.
	2. Methodik Population: CHB Intervention: IFN-a plus ADV combination therapy Komparator: IFN-a monotherapy Endpunkte: Virological responses, HBeAg clearance, HBeAg seroconversion, Biochemical response, HBsAg loss, safety Suchzeitraum (Aktualität der Recherche): bis 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 studies. 498 CHB patients were included in the IFN-a plus ADV combination therapy group and 524 CHB patients were included in the IFN-a monotherapy group. Qualitätsbewertung der Studien: Quality of the trials was assessed using the Jadad scale.
	3. Ergebnisdarstellung Qualität der Studien: 10 Studien hatten einen Jadad Score von 2 und 2 Studien einen Score von 3. • Rate of undetectable serum hepatitis B virus (HBV) DNA was significantly higher in the IFN-a plus ADV combination group than in the IFN-a monotherapy group, both at 24 weeks (RR= 1.74, 95%C= 1.47–2.05, P < 0.00001) and 48 weeks (RR = 1.56, 95% CI= 1.35–1.80, P < 0.00001) of

	treatment and after treatment (RR = 1.35, 95% CI = 1.10–1.66, P = 0.004). • The serum HBeAg clearance rate was higher in the combination group than in the monotherapy group (91/168 vs 48/173, RR = 1.84, 95% CI = 1.37–2.46, P < 0.0001) and was similar at 48 weeks of treatment. Only two studies reported the serum HBeAg clearance rate after treatment → Heterogeneity: I^2 = 61%). The HBeAg clearance rate was higher in the combination group than in the monotherapy group (90/173 vs 48/173, RR = 1.88, 95% CI = 1.19–2.99, P = 0.007). • Five studies reported the serum HBeAg seroconversion rate at 24 weeks of treatment and showed a higher rate in the combination group (59/156 vs 42/189, RR = 1.70, 95% CI = 1.22–2.38, P = 0.002). The same results were observed for the five studies reporting the serum HBeAg seroconversion rate at 48 weeks of treatment (103/187 vs 70/210, RR = 1.56, 95% CI = 1.24–1.95, P = 0.0001). Identical results were obtained for the two studies that reported the serum HBeAg seroconversion rate after treatment (60/115 vs 42/118, RR = 1.47, 95% CI = 1.09–1.98, P = 0.01). • As compared with the monotherapy group, the ALT normalization rate was similar in the combination group at 24 weeks of treatment treatment (132/195 vs 99/202). In contrast, there was a higher ALT normalization rate at 48 weeks of treatment (175/217 vs 151/240, RR = 1.29, 95% CI = 1.15–1.45, P < 0.0001). Four studies reported the ALT normalization rate after treatment and it was higher in the combination group (173/238 vs 145/241, RR = 1.21, 95% CI = 1.07–1.37, P = 0.003). • A greater serum HBsAg loss rate was not found between patients in the combination group as compared with the monotherapy group. For the three trials that reported a serum HBsAg loss rate after treatment, similar serum results were found between the two groups. • Sicherheit: From the eight trials reporting the treatment safety, only two were included in the metaanalysis. No significant differences were found between patients in the combination and monotherapy groups for the clinical adverse rates.
	4. Fazit der Autoren: *In conclusion, IFN-a plus ADV combination therapy is superior to IFN-a monotherapy in decreasing serum HBV DNA, clearing HBeAg, favoring HBeAg seroconversion and normalizing ALT, both at 24 or 48 weeks of treatment and after the cessation of treatment. However, no superiority was found*

	over IFN-a monotherapy for clearing HBsAg, and 48 weeks of IFN-a plus ADV combination therapy was only associated with an improved ALT normalization rate when compared with 24 weeks of treatment. More high-quality, well-designed, longterm, randomized controlled, multicenter trails that are adequately powered are still needed to evaluate the real beneficial effects of the IFN-a and ADV combination therapy in CHB patients. 5. Hinweise durch FB Med • Methodology of the trials was limited by the small sample size • There were only four studies that reported the follow-up efficacy
Huang ZB et al., 2013 [11] Comparison of the efficacy of Lamivudine plus adefovir versus entecavir in the treatment of Lamivudine-resistant chronic hepatitis B: a systematic review and meta-analysis	1. Fragestellung The goal of this systematic study and meta-analysis was to assess the efficacy of lamivudine plus adefovir compared with entecavir for the treatment ofpatients with lamivudine-resistant CHB.
	2. Methodik Population: Patients with lamivudine-resistant CHB. Intervention: Lamivudine plus adefovir Komparator: Entecavir Endpunkte: Undetectable HBV-DNA rate,virologic breakthrough rate, ALT normalization rate, HBeAgloss rate,HBeAg seroconversion rate, and adverse reaction rate Suchzeitraum (Aktualität der Recherche): bis 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 Studien (N= 696 Patienten) Qualitätsbewertung der Studien: The Cochrane Collaboration's tool and Newcastle-Ottawa scales were used to assess the quality of the randomized controlled trials (RCTs) and the non-RCTs, respectively.
	3. Ergebnisdarstellung Studienqualität: Almost all studies have a low quality scored by Cochrane Collaboration's tool • Rates of undetectable HBV DNA levels; ALT normalization rates; HBeAg loss; HBeAg Seroconversion: All were not

	significantly different between the groups at week 48. • Virologic Breakthrough: At week 48 rate of virologic breakthrough was higher in the ETV group than in the LAM+ADV group at this time point (Risk ratio: 0.23 [0.09 – 0.59]; p=0,002; I^2=50%) • Sicherheit: Almost 13% of all patients in the LAM plus ADV group and 11.1% of all patients in the ETV group had adverse reactions in the 48 weeks of treatment. Adverse reactions include severe abdominal pain or discomfort, headache, nausea, cough, rash, diarrhea, increased blood urea nitrogen level, and fatigue
	4. Fazit der Autoren: *When compared with ETV monotherapy, LAM plus ADV combination therapy was a better option for these CHB patients with LAM resistance. Although HBV infection is a global issue, the main infection population is from Asia and most of the data are from Asian countries. Based on the study data,we believe that the treatment of CHB discussed in the present article would be instructive for HBV-infected patients from Western countries.* 5. Hinweise durch FB Med • Some studies had a small sample size and were not RCTs
Wiens A et al., 2013 [20] Comparative Efficacy of Oral Nucleoside or Nucleotide Analog Monotherapy Used in Chronic Hepatitis B: A Mixed-Treatment Comparison Meta-analysis	1. Fragestellung To compare the efficacy of nucleoside or nucleotide analog monotherapy for the treatment of chronic hepatitis virus B (HBV) with adefovir dipivoxil, entecavir, lamivudine, telbivudine, and tenofovir disoproxil fumarate.
	2. Methodik Population: Patients with chronic HBV Intervention/Komparator: RCTs that compared two nucleoside or nucleotide analogs—lamivudine, adefovir, entecavir, telbivudine, and tenofovir—used as monotherapy Endpunkte: reduction of HBV DNA to undetectable levels by polymerase chain reaction, normalization of serum ALT levels, and seroconversion of HBeAg Suchzeitraum (Aktualität der Recherche): bis 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): Mixed-treatment comparison meta-analysis of 9 RCTs (N= 3972 patients) → Hinweis: Because some studies showed patient

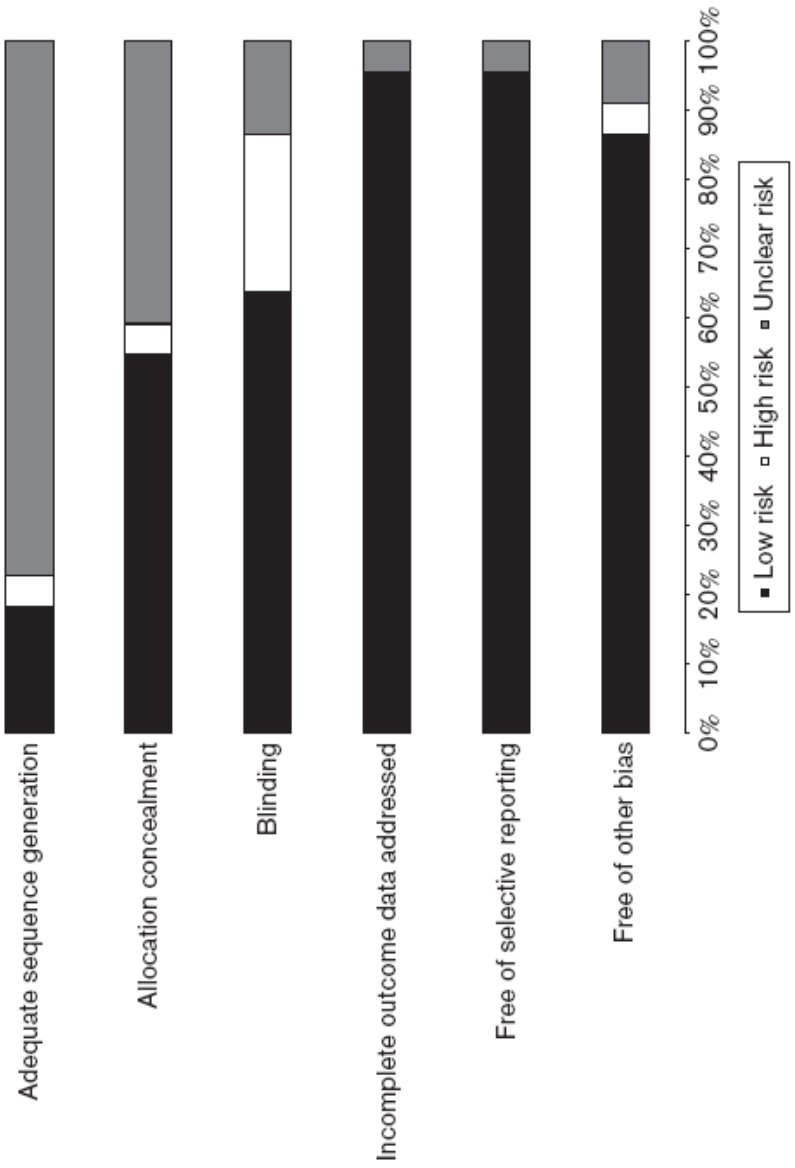
	data for individuals who were HBeAg positive and those who were HBeAg negative separately, they were added to the model as separate studies. Thus, we considered a total of 12 studies. Qualitätsbewertung der Studien: Methodologic quality of the study evaluated through the Jadad scale → Hinweis: studies with a Jadad score of less than 3 points were excluded (i.e., only high-quality studies were included).
	3. Ergebnisdarstellung The efficacy values extracted from the selected studies were combined into a mixed-treatment comparison using a random-effects model and Monte Carlo Markov chain. The network of evidence indicates that there are 10 possible comparisons, of which 6 have been studied directly in one or more trials. • In the mixed-treatment comparison, the OR was not significant for any of the comparisons with respect to the ALT level normalization and HBeAg seroconversion outcomes. • For the entecavir versus telbivudine, telbivudine versus adefovir, and adefovir versus lamivudine comparisons, the OR values for the HBV DNA level reduction were not statistically significant. • Regarding the HBV DNA reduction outcome, tenofovir demonstrated significantly higher efficacy than all of the other nucleoside or nucleotide analogs evaluated. Entecavir was statistically significantly superior to adefovir (OR 0.36; 95% credible interval (CrI) 0.15–0.85) and lamivudine (OR 4.13; 95% CrI 2.42–7.03), whereas telbivudine demonstrated superior efficacy compared with lamivudine (OR 0.37; 95% CrI 0.24–0.57). • Regarding the evaluated efficacy outcomes, tenofovir had the highest probability to be the first choice to reduce the HBV DNA levels, normalize ALT levels, and seroconvert HBeAg (100%, 50%, and 60%, respectively), whereas lamivudine had the highest probability to be the last choice for each of the three outcomes (83%, 79%, and 52%, respectively). • Regarding HBV DNA reduction, entecavir has the highest probability to be the second option after tenofovir, followed by telbivudine and adefovir. For the ALT level normalization and HBeAg seroconversion outcomes, adefovir has the highest probability to be the second choice, followed by entecavir and telbivudine.
	4. Fazit der Autoren: *Tenofovir demonstrated the highest probability of achieving HBV DNA level reduction, ALT level*

	normalization, and HbeAg seroconversion after 1 year of treatment. Tenofovir has potent antiviral activity, a favorable safety profile, and a higher barrier to the development of resistance. […] However, tenofovir is a new therapy, and further studies are needed to evaluate its long-term safety. When choosing among therapies, evaluating other outcomes, such as HBsAg seroconversion, cirrhosis progression, and histologic improvement, is also important. 5. Hinweise durch FB Med • Only few studies that directly compare only two drugs for the treatment of chronic hepatitis B. • Nucleosides or nucleotides can lead to a number of adverse effects, including the development of viral resistance that were not assessed in this study but are also important when selecting a particular therapy. • Only one of the studies included in our analysis was conducted in patients with lamivudineresistanct chronic hepatitis B. This can generate a bias in the evaluation of the efficacy of lamivudine compared with patients who did not show any resistance to nucleoside or nucleotide analogs. • The network analysis showed good consistency for most of the closed loops but not all. Some of the inconsistency can be explained by the inclusion of studies with different clinical profiles (HBeAg positive or negative status, different HBV genotypes) and different demographic factors (different ethnic groups) of the patients.
Liang J et al., 2012 [15] Entecavir versus lamivudine for the treatment of chronic hepatitis B: a systematic review	1. Fragestellung The aim of this study was to systematically review the efficacy and safety of entecavir versus lamivudine for the treatment of chronic hepatitis B (CHB).
	2. Methodik Population: Patients with CHB Intervention: Entecavir Komparator: Lamivudine Endpunkte: • <u>Primäre Endpunkte</u>: improvement of liver histology and loss of serum HBV DNA (as determined by polymerase chain reaction [PCR] assay). • <u>Sekundäre Endpunkte</u>: normalization of serum ALT, loss of

	serum HBeAg, HBeAg seroconversion, HBsAg loss and incidence of adverse events (including headache, common cold, upper respiratory tract infection, gastrointestinal disorders, fatigue, and increased ALT or AST during treatment and follow-up). Suchzeitraum (Aktualität der Recherche): 1978 bis 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs involved a total of 2178 patients with CHB, with 1119 receiving ETVand 1059 treated with LVD. Qualitätsbewertung der Studien: Methodological quality of the included RCTs was assessed using the criteria (randomization, allocation concealment, blinding, complete outcome data, selective outcome reporting, and other potential biases) described by Higgins et al. (2003) in the Cochrane Reviewers' Handbook 5.1.
	3. Ergebnisdarstellung Studienqualität: The quality of the evidence was classified as moderate for all the included RCTs. • Entecavir was associated with significantly improved liver histology, compared with lamivudine (RR 1.16, 95%CI: 1.07, 1.26, P= 0.0004). • Patients were significantly more likely to experience HBV-DNA loss and have normalized ALT levels when treated with entecavir versus lamivudine for either 48 or 96 weeks (RR 1.65, 95%CI: 1.37, 1.98, P< 0.00001; RR 1.15, 95%CI: 1.11, 1.20], P< 0.00001, respectively). • There were no statistically significant differences in the proportion of patients who achieved HBeAg loss or HBeAg seroconversion, or who developed adverse events between entecavir and lamivudine treatments.
	4. Fazit der Autoren: *Current clinical evidence suggests that despite of short- or long-term use; entecavir appears to be more effective than lamivudine in reducing serum HBV-DNA load, improving liver histology, and normalizing ALT in patients with CHB. However, the probability for patients to experience HBeAg loss or HBeAg seroconversion, or the risk for adverse events seems to be similar between entecavir and lamivudine regimens.* 5. Hinweise durch FB Med

	• Differences among the included RCTs, with respect to treatment duration, disease severity, and time points of and tools used for outcome assessment
Jiang H et al., 2013 [12] Lamivudine versus telbivudine in the treatment of chronic hepatitis B: a systematic review and meta-analysis	1. Fragestellung The purpose of this study was to evaluate the efficacy of lamivudine (LAM) versus telbivudine (LdT) in the treatment of chronic hepatitis B (CHB).
	2. Methodik Population: Patients with CHB Intervention: Lamivudine (LAM) Komparator: Telbivudine (LdT) Endpunkte: Biochemical response, HBeAg seroconversion, virological response, virologic breakthrough, therapeutic response, viral resistance Suchzeitraum (Aktualität der Recherche): 1990-2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs fulfilled the inclusion criteria and were subject to meta-analysis Qualitätsbewertung der Studien: Trial characteristics and outcomes were examined and recorded using a 10-point scoring system that had been used in a previously published meta-analysis to examine the reliability of RCTs. It included information such as allocation concealment, the randomization method, the inclusion and exclusion criteria, etc.
	3. Ergebnisdarstellung <u>Studienqualität</u>: The study quality was assessed for using the 10-point scale, the quality score ranged from 2 to 8, in which a higher score is associated with better quality. → 3 Studies had a score of 8; one study a score of 7; the rest of 5 or lower. *Virological response:* At the end of one-year treatment, statistical significant difference in favour of LdT vs. LAM (RR=1.43, 95%CI= 1.12–1.84, P=.005). *Viral breakthrough:* At the end of one-year treatment, statistical significant difference in favour of LAM vs. LdT (RR=0.34, 95%CI= 0.25–0.48, P<0.00001), viral resistance (RR=0.41, 95%CI= 0.28–0.58, P<0.00001)

	No statistically significant difference in the *biochemical response, HBeAg seroconversion, therapeutic response and adverse events.* The *creatine kinase (CK) elevation* occurred statistically significant more frequently in the LdT group than in LAM group (RR=2.43, 95%CI= 1.57–3.75, P<0.0001). When treatment prolonged to 2 years, LdT was statistically significant better than LAM at the *HBeAg seroconversion* (RR=1.29, 95%CI= 1.12–1.50, P=0.0007) and *therapeutic response* (RR= 1.34, 95% CI= 1.21–1.49, P<0.00001).
	4. Fazit der Autoren: *In summary, LdT was more effective in inhibiting HBV replication and promoting HBeAg seroconversion than LAM for CHB patients, for which adverse effects such as CK elevation must be paid attention to. Further, more high-quality, randomized controlled trails are clearly needed to guide the standards of treatment for CHB.*
Govan L et al., 2015 [9] Comparative effectiveness of antiviral treatment for hepatitis B: a systematic review and Bayesian network meta-analysis.	1. Fragestellung We update a recent meta-analysis to include additional trial evidence with the aim of determining which treatment is the most effective.
	2. Methodik Population: treatment-naive adults with HBeAg-positive or HBeAg-negative CHB Intervention/Komparator: combination of the following therapies (either as monotherapy or combination): placebo, lamivudine (LAM), pegylated interferon (PEG), adefovir (ADV), ETV, LdT, and TDF Endpunkte: Attainment of undetectable levels of HBV DNA, normalization of serum ALT levels, HBeAg seroconversion, HBeAg loss, HBsAg loss, histologic improvement of the liver Suchzeitraum (Aktualität der Recherche): The original review conducted their search up to 30 October 2009, and we included an overlap (from January 2009) in our search dates to capture any new articles published around the time of the original search. Anzahl eingeschlossene Studien/Patienten (Gesamt): 22 studies were identified (7508 patients): 12 studies analysed HBeAg-positive patients, six analysed HBeAg-negative patients, and

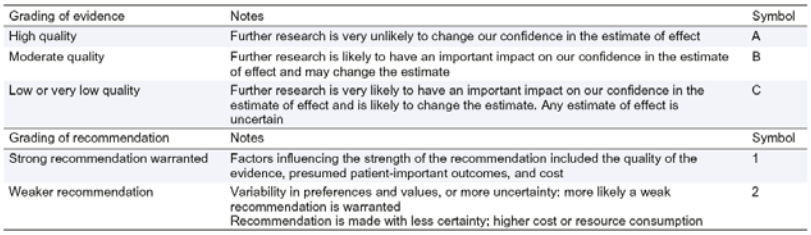
	four evaluated both HBeAg-positive and HBeAg-negative patients. We identified 15 trials that were multicentred, 14 of which were international trials. Qualitätsbewertung der Studien: The Cochrane risk of bias tool was used to assess study quality.
	3. Ergebnisdarstellung <u>Studienqualität:</u>  ➔ We used Bayesian random effects NMA to incorporate both direct and indirect evidence into our analysis. ➔ Twelve treatments were identified, including five combination therapies: LAM, PEG, ADV, ETV, LdT, TDF, PLA, LAM plus PEG, LAM plus LdT, LAM plus ADV, ETV plus TDF, and PEG plus ADV

	➔ 12 studies analysed HBeAg-positive patients, 6 analysed HBeAgnegative patients, and four evaluated both. **HBeAg-positive patients** • <u>For HBeAg-positive patients:</u> TDF had the highest rankings over key outcomes: highest probability of being ranked first for HBV DNA reduction (0.93) and ALT normalization (0.37); the highest probability of outcome in HBV DNA (0.92, 95% CrI 0.74–0.99); and significantly increased odds of reduction in HBV DNA compared with all other treatments (OR, 95% CrI of TDF vs. LAM (33.0, 6.99–292.7). • For HBV DNA outcome, PEG plus LAM had significantly increased odds of HBV DNA reduction compared with PEG or LAM alone (PEG: OR 3.13, 95% CrI 1.15–8.48; LAM: OR 5.86, 95% CrI 2.31–13.87). • ETV was ranked second for ALT normalization but the only significant difference in ORs was with LAM for the HBV DNA outcome. PLA ranked bottom for all outcomes and this was also reflected in the ORs, where PLA had reduced odds of HBV DNA reduction compared with all other treatments. ➔ *However, for the majority of treatment comparisons the associated CrIs are wide meaning large uncertainty in differences between treatments.* • For HBeAg-negative patients: The large network (seven therapies) ranked entecavir alone or in combination with tenofovir highly for reduction in HBV DNA and histologic improvement. In the smaller network (three therapies), tenofovir ranked first for undetectable HBV DNA and histologic improvement. No data existed to directly or indirectly compare these treatments. • For HBeAg-negative patients: Two disconnected networks were analysed. The larger network contained seven treatments: LAM, PEG, ETV, LdT, LAM plus PEG, PEG plus ADV and ETV plus TDF. o In this network, ETV and ETV plus TDF had the highest ranking overall. For HBV DNA, ETV plus TDF had the highest probability of being ranked first (0.54) and highest probability of an outcome (0.93, 95% CrI 0.49–0.99), followed by ETV alone (probability of being ranked first: 0.22; probability of an outcome: 0.90, 95% CrI 0.64–0.98). ETV was also ranked second for ALT normalization and first for histological improvement. o For all outcomes, there were no significant differences in ORs between any of the treatments comparisons. • The smaller network contained only three treatments: TDF,

	ADV, and PLA. TDF was ranked first for undetectable HBV DNA and histologic improvement, and second for ALT normalization. ADV was ranked first for ALT normalization and second in the other two outcomes. • Of all pairwise comparisons, the only significant difference was found between ADV versus PLA, and TDF versus PLA, where ADV and TDF were shown to be superior to PLA. For all outcomes, there was no significant difference between TDF and ADV in HBV DNA normalization; ALT normalization; histological improvement.
	4. Fazit der Autoren: *For HBeAg-positive patients tenofovir is the most effective at increasing efficacy, whereas for HBeAg-negative patients, either tenofovir or entecavir is most effective. Further research should focus on strengthening the network connections, in particular comparing tenofovir and entecavir in HBeAg-negative patients.* 5. Hinweise durch FB Med • Small numbers of studies available comparing particular treatments, and small numbers of participants and low event rate within those trials where data is available.

Leitlinien

EASL, 2012 [1] EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection	Fragestellung/Zielsetzung: The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection.
	Methodik These EASL CPGs represent an update of the last EASL HBV CPGs published in early 2009. They were developed by a CPG Panel of experts chosen by the EASL Governing Board, peer-reviewed by the experts of the 2009 HBV CPGs and approved by the EASL Governing Board. The CPGs have been based as far as possible on evidence from existing publications, and, if evidence was unavailable, on the experts' personal experience and opinion. Manuscripts and abstracts of important meetings published prior to September 2011 have been evaluated. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of

	underlying evidence.  **Empfehlungen:** Currently, there are two different treatment strategies for both HBeAg-positive and HBeAg-negative CHB patients: treatment of finite duration with (PEG-)IFN or a NA and long-term treatment with NA(s). The main theoretical advantages of (PEG-)IFN are the absence of resistance and the potential for immune-mediated control of HBV infection with an opportunity to obtain a sustained virological response off-treatment and a chance of HBsAg loss in patients who achieve and maintain undetectable HBV DNA. Frequent side effects and subcutaneous injection are the main disadvantages of (PEG-)IFN treatment. (PEG-)IFN is contraindicated in patients with decompensated HBV-related cirrhosis or autoimmune disease, in patients with uncontrolled severe depression or psychosis, and in female patients during pregnancy **(LoE: A1)**. Entecavir and tenofovir are potent HBV inhibitors with a high barrier to resistance. Thus, they can be confidently used as first-line monotherapies **(LoE: A1)**. The other three NAs may only be used in the treatment of CHB if more potent drugs with high barrier to resistance are not available or appropriate **(LoE: A1).** Lamivudine is an inexpensive agent, but engenders very high rates of resistance with long-term monotherapy. Adefovir is less efficacious and more expensive than tenofovir, engendering higher rates of resistance. Telbivudine is a potent inhibitor of HBV replication, but, due to a lower barrier to resistance, a high incidence of resistance has been observed in patients with high baseline HBV DANN levels and in those with detectable HBV DNA after 6 months of therapy; resistance rates to telbivudine are relatively low in patients with low baseline viremia (<2 x 10^8 IU/ml for HBeAg-positive and <2 x 10^6 IU/ml for HBeAg-negative patients) who achieve undetectable HBV DNA at 6 months of therapy. (1) <u>Treatment of finite duration with (PEG-)IFN or a NA. This strategy is intended to achieve a sustained off-treatment virological response **(LoE: A1).**</u>

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading of recommendation	**Notes**	**Symbol**
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption	2

	• PEG-IFN, if available, has replaced standard IFN in the treatment of CHB mostly due to its easier applicability (once weekly administration). It can also be used for HBeAg-negative patients, as it is practically the only option that may offer a chance for sustained off-treatment response after a finite duration of therapy. Full information about the advantages, adverse events and inconveniences of (PEG-)IFN versus Nas should be provided so the patient can participate in the decision **(LoE: A1).** • The combination of PEG-IFN with lamivudine showed a higher on-treatment virological response but did not show a higher rate of sustained off-treatment virological or serological response. The combination of PEG-IFN with telbivudine showed a potent antiviral effect, but it is prohibited because of a high risk of severe polyneuropathy. Thus, presently the combinations of PEG-IFN with lamivudine or telbivudine are not recommended **(LoE: A1)**. There is limited information on the efficacy and safety of combination of PEG-IFN with other NAs and presently this type of combination is not recommended. • Finite-duration treatment with a NA is achievable for HBeAg-positive patients who seroconvert to anti-HBe on treatment. However, treatment duration is unpredictable prior to therapy as it depends on the timing of anti-Habe seroconversion and the treatment continuation post anti-HBe seroconversion. Anti-HBe seroconversion may not be durable after NAs discontinuation, at least with less potent agents, in a substantial proportion of these patients requiring close virologic monitoring after treatment cessation. • An attempt for finite NA treatment should use the most potent agents with the highest barrier to resistance to rapidly reduce levels of viremia to undetectable levels and avoid breakthroughs due to HBV resistance **(LoE: A1)**. Once anti-HBe seroconversion occurs during NA administration, treatment should be prolonged for an additional 12 months; a durable off-treatment response (persistence of anti-HBe seroconversion) can be expected in 40–80% of these patients **(LoE: B1)**. <u>(2) Long-term treatment with NA(s).</u> This strategy is necessary for patients who are not expected or fail to achieve a sustained off-treatment virological response and require extended therapy, i.e. for HBeAg-positive patients who do not develop anti-Habe seroconversion and HBeAg-negative patients. This strategy is also recommended in patients with cirrhosis irrespective of HBeAg status or anti-HBe seroconversion on

	treatment **(LoE: C1).** The most potent drugs with the optimal resistance profile, i.e. tenofovir or entecavir, should be used as first-line monotherapies **(LoE: A1).** It is optimal to achieve and maintain undetectable HBV DANN level tested by real-time PCR, whatever the drug used **(LoE: B1)**. The long-term effects, safety and tolerability of entecavir and tenofovir are still unknown. Treatment with either tenofovir or entecavir monotherapy for P3 years achieves maintained virological remission in the vast majority of patients **(LoE: A1).** There are as yet no data to indicate an advantage of de novo combination treatment with NAs in NA naive patients receiving either entecavir or tenofovir **(LoE: C1).** <u>Treatment failure</u> It is important to distinguish between primary non-response, partial virological response and virological breakthrough *(1) Primary non-response.* Primary non-response is rarely observed with entecavir or tenofovir, telbivudine or lamivudine. In patients with primary non-response to any NA, it is important to check for compliance. In a compliant patient with a primary non-response, genotyping of HBV strains for identification of possible resistance mutations may help in formulating a rescue strategy that must reasonably be based on an early change to a more potent drug that is active against the resistant HBV variant **(LoE: B1).** Primary non-response seems to be more frequent with adefovir (approximately 10–20%) than with other NAs because of suboptimal antiviral efficacy. In NA(s) naive patients with primary non-response to adefovir, a rapid switch to tenofovir or entecavir is recommended **(LoE: B1)**. *(2) Partial virological response.* Partial virological response may be encountered with all available NAs. It is always important to check for compliance. In patients receiving lamivudine or telbivudine (drugs with a low genetic barrier to resistance) with a partial virological response at week 24 or in patients receiving adefovir (moderately potent drug that engenders relatively late emergence of resistance) with a partial response at week 48, change to a more potent drug (entecavir or tenofovir), preferentially without cross-resistance, is recommended **(LoE: A1).** The optimal management of patients with partial virological response under entecavir or tenofovir (highly potent drugs with a high genetic barrier to resistance) is currently debatable. In such patients with a partial virological response at week 48, the HBV DNA levels at week 48 and their kinetics must be taken into account. Patients with declining serum HBV DNA levels

	may continue treatment with the same agent (entecavir or tenofovir) given the rise in rates of virological response over time and the very low risk of resistance with long-term monotherapy with both these agents **(LoE: B1).** Some experts would suggest adding the other drug in order to prevent resistance in the long term, particularly in the rare patients without further HBV DNA decline despite drug compliance **(LoE: C2).** *(3) Virological breakthrough.* Virological breakthrough in compliant patients is related to the development of HBV drug resistance. Testing for genotypic resistance may be performed in compliant patients with confirmed virological breakthroughs, although it is not absolutely necessary for NA naive patients with confirmed virological breakthroughs under monotherapy with lamivudine or telbivudine **(LoE: B1)**. The rates of resistance at 5 years in NA naive patients are <1.5% and 0% for entecavir and tenofovir, respectively; thus, virological breakthroughs in NA naive patients receiving entecaviror tenofovir are usually due to poor drug compliance. In case of resistance […] • Lamivudine resistance: switch to tenofovir (add adefovir if tenofovir is not available) **(LoE: B1).** • Adefovir resistance: if the patient was NA naive before adefovir, switch to entecavir or tenofovir **(LoE: B1)**; entecavir may be preferred in such patients with high viraemia **(LoE: C2).** If the patient had prior lamivudine resistance, switch to tenofovir and add a nucleoside analogue **(LoE: C1)**. • Telbivudine resistance: switch to or add tenofovir (add adefovir if tenofovir is not available) **(LoE: C1).** • Entecavir resistance: switch to or add tenofovir (add adefovir if tenofovir is not available) **(LoE: C1)**. • Tenofovir resistance: tenofovir resistance has not been detected to date and therefore there is no experience, but it seems reasonable to add entecavir, telbivudine, lamivudine or emtricitabine if tenofovir resistance is confirmed **(LoE: C2)**. A switch to entecavir may be sufficient if the patient has not been treated with lamivudine in the past, while adding entecavir may be the preferred option for patients with prior lamivudine resistance **(LoE: C2)**.
KASL, 2016 [2]. KASL clinical practice guidelines: management of	Fragestellung/Zielsetzung: In 2015, the objective of this manuscript was to update the recommendations for management of CHB, including pidemiology, prevention, natural history, diagnosis, treatment, monitoring, drug resistance mutations and treatment of special populations discussed herein

chronic hepatitis B	based on current evidences or if, evidences lack, on expert opinions after deliberation.
	Methodik Grundlage der Leitlinie *Developer and funding:* The CHB Clinical Practice Guideline Revision Committee (CPGRC) comprising 17 hepatologists and 1 pediatrician was formed with support from the KASL. All of the required funding was provided by the KASL. Each member of the CHB-CPGRC collected and evaluated evidence, and contributed to writing the manuscript. Conflicts of interest of the CHB-CPGRC members are summarized in Conflicts of interest. *Evidence collection:* Relevant evidences obtained from a comprehensive literature search using MEDLINE (up to 2015) were systematically reviewed and selected. The languages were limited to English and Korean. *Levels of evidence and grades of recommendation:* The evidence and recommendations were graded according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system with minor modifications **Quality of evidence** / **Criteria** High (A) – Further research is unlikely to change confidence in the estimate of the clinical effect Moderate (B) – Further research may change confidence in the estimate of the clinical effect Low (C) – Further research is very likely to impact confidence on the estimate of clinical effect **Strength of recommendations** / **Criteria** Strong (1) – Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost Weak (2) – Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption NOTE. Of the quality levels of evidence, we excluded "very low quality (D)" from the guidelines for convenience. This was originally included in the GRADE system and indicates that the estimate of effect is highly uncertain.
	Empfehlungen **HBeAg-positive CHB** 1. HBeAg positive CHB patients with HBV DNA ≥ 20,000 IU/mL, plus serum AST or ALT ≥ 2 ULN or significant histologic changes such as inflammation or fibrosis (≥ moderate necroinflammation; ≥ periportal fibrosis) on biopsy should be considered for treatment. **(LoE: A1).** Treatment can be delayed for 3–6 months if spontaneous HBeAg seroconversion is expected **(LoE: B2).** However, patients with apparent or anticipated liver failure (i.e., those with jaundice, prolonged PT, hepatic encephalopathy, and ascites) should be treated promptly **(LoE: B1).** 2. For those with HBV DNA ≥ 20,000 IU/mL and serum AST or ALT < 2 ULN, observation or liver biopsy can be considered. Antiviral treatment is recommended for those showing subsequent elevation of serum ALT or AST, or significant

	histologic changes such as inflammation or fibrosis on biopsy **(LoE: A1).** 3. Monotherapy with tenofovir, entecavir, or peginterferon-α is preferred **(LoE: A1).** **HBeAg-negative CHB** 1. HBeAg negative CHB patients with HBV DNA ≥ 2,000 IU/mL plus serum AST or ALT ≥ 2 ULN or significant pathologic changes such as inflammation or fibrosis on biopsy should be considered for treatment **(LoE: A1).** 2. For those with HBV DNA ≥ 2,000 IU/mL and serum AST or ALT < 2 ULN, observation or liver biopsy can be considered. Antiviral treatment is recommended for those showing subsequent elevation of serum ALT or AST, or significant pathologic changes such as inflammation or fibrosis on biopsy **(LoE: A1).** 3. Monotherapy with tenofovir, entecavir, or peginterferon-α is preferred **(LoE: A1).**
Coffin CS et al., 2012 [7]. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines	Zielsetzung: The report presents the recommendations representing the best medical practice in the assessment and the management of chronic hepatitis B infection.
	Methodik The process used to arrive at consensus was as follows: An Organizing Committee was appointed by the CASL and the Canadian Liver foundation. This committee invited expert speakers to review the current literature on different topics. After the presentation, questions from the audience were addressed. A Writing Committee, selected by the Organizing Committee, assessed the information from the presentatios and from other sources, and prepared a document that was circulated to the speakers for comment. The strength of the recommendations and the evidence supporting the recommendations have been evaluated and graded according to the grading system adapted from the American College of Cardiology and the American Heart Association Practice Guidelines and the Grading of Recommendations Assessment Development and Evaluation (GRADE) system

	Adapted grading system for recommendations **Classification** **Description** **Class of evidence** Class 1 Strong recommendation There is high-quality evidence that supports the usefulness or efficacy of a given diagnostic test or treatment Class 2 On the balance of evidence and opinion, there is support in favour of the usefulness or efficacy of a given diagnostic test or treatment Class 2a Weight of evidence/opinion is in favour of usefulness/ efficacy Class 2b Usefulness/efficacy is less well established by evidence/ opinion Class 3 Cannot be recommended Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure or treatment is not useful or effective and in some cases may be harmful **Grade of evidence** Level A High-quality evidence from multiple randomized clinical trials or meta-analyses Level B Data from a single randomized trial, or nonrandomized studies Further information might have an impact on our confidence of the practice Level C Consensus opinion of experts, or case studies Further information is needed to support the practice
	Empfehlungen The consensus guideline committee has recommended that PEG IFN remain one of the first-line treatments for chronic hepatitis B **(Class 2a, Level A).** Tenofovir or entecavir is first-line therapy for treatment-naive HBV patients because they are the most potent agents available with no (tenofovir) or very low (entecavir) rates of antiviral resistance **(Class 1, Level A)**. Tenofovir is first-line therapy for lamivudine-resistant HBV. Entecavir should not be used in this setting due to the risk of development of entecavir resistance **(Class 1, Level A).** The treatment of choice for lamivudine-resistant HBV infection is tenofovir **(Class 2, Level A).**
WHO, 2015 [21]. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.	Zielsetzung: The present guidelines are the first WHO guidelines on the prevention, care and treatment of persons with chronic hepatitis B virus (HBV) infection – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. They provide a framework for the development or strengthening of hepatitis B treatment programmes in LMICs, but are also of relevance to some high-income countries.

	Methodik These WHO guidelines were developed following the recommendations for standard guidelines as described in the WHO Handbook for Guideline Development, 2012. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was followed for this process. A Guidelines Development Group was formed, ensuring representation from various stakeholder groups, including members of organizations that represent persons living with chronic hepatitis, advocacy groups, researchers, clinicians and programme managers. Geographical representation and gender balance were also considerations in selecting Group members. There was an initial scoping and planning process to formulate questions across the continuum of hepatitis B care and treatment most relevant to LMICs and determine patient-important outcomes. These questions were structured in PICO format (population, intervention, comparison, outcomes) and patient-important outcomes were identified for each research question. Systematic reviews and meta-analyses of the primary literature were commissioned externally to address the research questions and patient-important outcomes. Criteria for inclusion and exclusion of literature (e.g. study design, sample size, duration of follow up) for the reviews were based on the evidence needed and available to answer the research questions. The quality of the evidence was assessed and either rated down or rated up based on the following criteria: rated down based on (i) risk of bias (using the Cochrane Risk of Bias assessment tool), including publication bias; (ii) inconsistency or heterogeneity; (iii) indirectness (addressing a different population than the one under consideration); or (iv) imprecision. Conversely, the quality of the evidence was rated up if there was no reason to rate it down, and if it met any of the following three criteria: (i) large effect size; (ii) dose–response; or (iii) plausible residual confounders (i.e. when biases from a study might be reducing the estimated apparent intervention effect). Based on the rating of the available evidence, the quality of evidence was categorized as high, moderate, low or very low.

TABLE 2.1 GRADE categories of the quality of evidence (4–10)

Level of evidence	Rationale
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

TABLE 2.2 Key domains considered in determining the strength of recommendations

Domain	Rationale
Benefits and risks	Desirable effects (benefits) need to be weighed against undesirable effects (risks). The more that the benefits outweigh the risks, the more likely that a strong recommendation will be made.
Values and preferences (acceptability)	If the recommendation is likely to be widely accepted or highly valued, a strong recommendation will probably be made. If there are strong reasons that the recommended course of action is unlikely to be accepted, a conditional recommendation is more likely to be made.
Costs and financial implications (resource use)	Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness will more likely result in a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is more probable.

RECOMMENDATIONS: FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B:

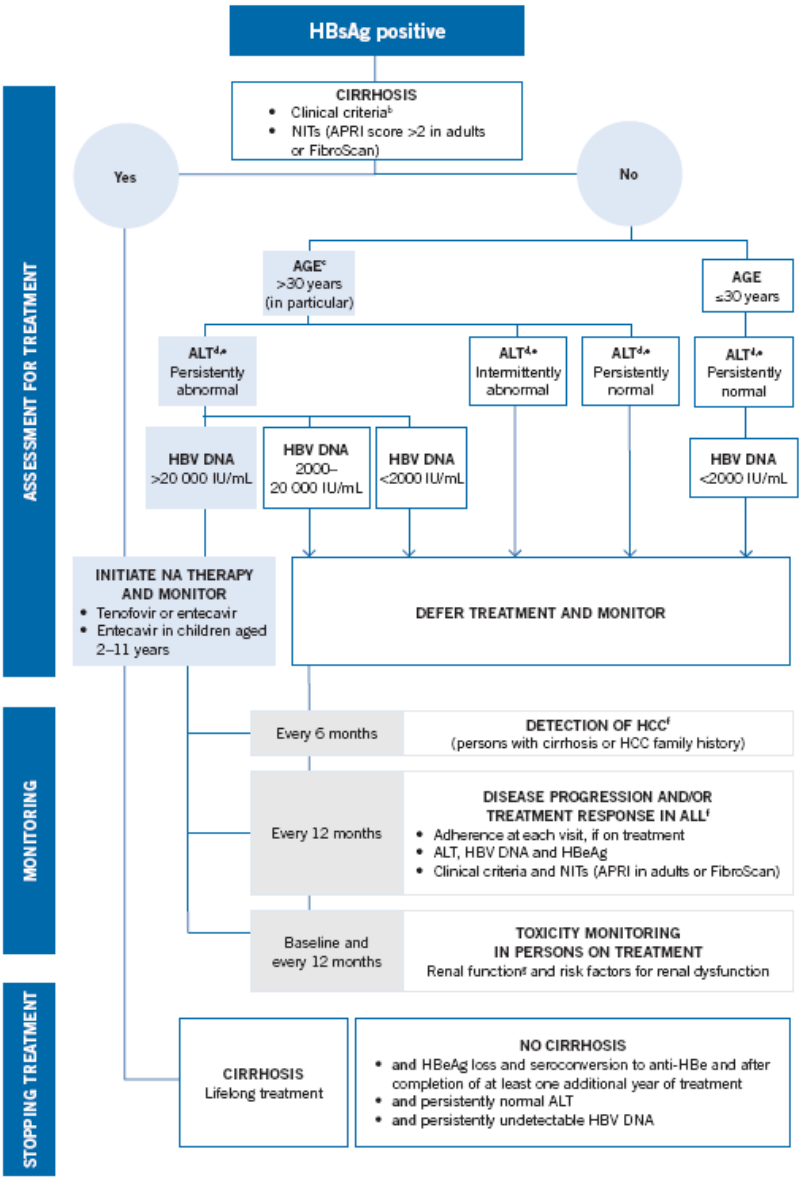
- In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. **(Strong recommendation, moderate quality of evidence)**
- NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. **(Strong recommendation, moderate quality of evidence)**

Existing recommendation for HBV/HIV coinfected persons[1]:

- In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. **(Strong recommendation, moderate quality of evidence)**

[1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013. These guidelines will be updated in 2015.

RECOMMENDATIONS: SECOND-LINE ANTIVIRAL THERAPIES FOR MANAGEMENT OF TREATMENT FAILURE

	• In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, entecavir, adefovird or telbivudine, a switch to tenofovire is recommended. *(Strong recommendation, low quality of evidence)* **ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]** 
NICE, 2013 [18]. Chronic hepatitis B	Zielsetzung: Guidance on chronic Hepatitis B
	Methodik Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informal) - eigene Checklisten - Anwendung von GRADE - GoR schlagen sich in den Formulierungen wider ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to

	recommendations.“
	Empfehlungen: • If you are starting drug treatment for the first time and your liver continues to work adequately (called compensated liver disease), you should be offered a drug called peginterferon alfa-2a as a first course of treatment. • You may need to change treatment if monitoring tests suggest this is needed. If so, your doctor will offer either tenofovir disoproxil or entecavir. • Alternatively, if your treatment is working well, your doctor may advise you to stop drug treatment altogether. • Once you have started antiviral treatment, you should not stop taking it without speaking to your doctor. […] You should not be offered treatment with either telbivudine or adefovir dipivoxil because more effective drugs are now available. If you are taking one of these drugs, you should discuss this with your doctor.
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS), 2011 [8]. Hepatitis-B-Virusinfektion: Prophylaxe, Diagnostik und Therapie	Zielsetzung: Management und die Therapie der chronischen HBV-Infektion
	Methodik Sonstige methodische Hinweise: Diese Leitlinie wurde >5 Jahre nicht akutalisiert und befindet sich derzeit in Überprüfung! Die Aktualisierung der Leitlinie erfolgte auf S3-Niveau auf Basis des Drei-Stufen-Konzepts: Eine Literaturrecherche nach bestmöglicher Evidenz und ein formaler Konsensus-Prozess waren die Kernpunkte bei der Leitlinienerstellung. Detaillierte Informationen finden Sie hierzu in einem separaten Methodenreport ((Leitlinienregister der AWMF, www.awmf.org). ➔ Die Aktualisierung der Leitlinie beinhaltet eine kritische Würdigung der klinischen, histologischen und virologischen Diagnostik, eine transparente Stadieneinteilung und Risikobewertung sowie die Empfehlung einer risikoadaptierten antiviralen Therapie. Die aktuelle Datenlage wurde zu allen Fragestellungen eingearbeitet. Durchführung einer Konsensuskonferenz

Tab. F Definition der Konsensstärke.

Konsensstärke	Zustimmung
Starker Konsens	>95 %
Konsens	>75 – 95 %
Mehrheitsentscheidung	>50 – 75 %

Tab. G Einteilung der Empfehlungsgrade.

Empfehlungs-grad[1]	Erläuterung
A	konsistent Studien mit Evidenzgrad I vorhanden
B	konsistent Studien mit Evidenzgrad II oder III bzw. Extra-polationen von Studien mit Evidenzgrad I vorhanden
C	Studien mit Evidenzgrad IV oder Extrapolationen von Studien mit Evidenzgrad II oder III

[1] Modifiziert nach „Scottish Intercollegiate Guidelines Network (SIGN)", www.sign.ac.uk. Der Empfehlungsgrad „D" inkonsistente bzw. nicht schlüssige Studien jedes Evidenzgrades oder Expertenmeinung" wurde nicht vergeben.

Empfehlungen:

<u>Welche grundsätzlichen Fragen sind bei der Therapieplanung der Hepatitis B zu berücksichtigen?</u>

- Bei der Auswahl der Medikamente zur Therapie der Hepatitis B soll zunächst geprüft werden, ob eine Alpha-Interferontherapie möglich und sinnvoll ist (**LoE: A**).
- Die Auswahl von Nukleos(t)id-Analoga sollte das Stadium der Lebererkrankung, die Höhe der HBV-Virämie sowie evtl. Vortherapien berücksichtigen (**LoE: B**). Liegt eine Leberzirrhose oder eine Viruslast von > 106 IU/ml vor, sollte primär eine Substanz mit hoher genetischer Resistenzbarriere eingesetzt werden (**LoE: B**).
  Abstimmung: 100% (starker Konsens)

Interferon-alpha-basierte Therapie

<u>Bei welchen Patienten soll eine Behandlung mit Interferon alpha erwogen werden?</u>

- (PEG)-Interferon alpha ist wirksam bei HBeAg-positiven und HBeAg-negativen Patienten mit chronischer Hepatitis B und kompensierter Lebererkrankung (maximal Child-Pugh A Leberzirrhose). Nebenwirkungen und Kontraindikationen einer Therapie mit Interferon alpha sind zu beachten.
- Der Einsatz von (PEG)-Interferon alpha soll bei allen Patienten geprüft werden (**LoE: A**).
- Aufgrund der mindestens äquivalenten Ansprechraten, aber einer patientenfreundlicheren Applikation einmal pro Woche

ist die Therapie mit PEG-Interferon alpha empfehlenswerter als Standard-Interferon alpha (**LoE: C**).
Abstimmung: 100% (starker Konsens)

Therapie der chronischen Hepatitis B mit Nukleosid-Analoga oder Nukleotid-Analoga

Bei nicht ausreichendem Therapieansprechen oder Resistenz soll die Therapie angepasst werden (**LoE: A**).

- Wurde ein Nukleosid-Analogon (Lamivudin, Entecavir, Telbivudin) eingesetzt, soll eine Therapieumstellung auf Tenofovir erfolgen (**LoE: A**).
- Wurde Adefovir eingesetzt, sollte eine Therapieumstellung auf Entecavir oder Tenofovir erfolgen (**LoE: B**).
- Wurde Tenofovir eingesetzt, kann eine Therapieumstellung auf Entecavir erfolgen oder ein Nukleosid-Analogon zusätzlich gegeben werden (**LoE: C**).
  Abstimmung: 96% (starker Konsens, abgestimmt durch eine zweite Delphi-Umfrage)

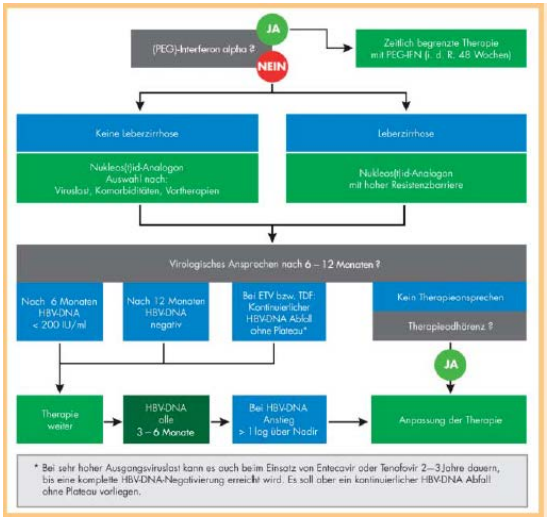


Abb. 2 Behandlungsalgorithmus zur Therapie der chronischen Hepatitis B.

Tab. 13 Vorschläge zur Therapieanpassung bei nicht ausreichendem virologischem Ansprechen oder Resistenzentwicklung unter einer Nukleos(t)id-Analoga-Monotherapie.

nicht ausreichendes Therapieansprechen/Resistenz	Therapieoption[1]
Lamivudin	Wechsel auf Tenofovir (A) (Wechsel auf Entecavir)[2]
Adefovir[3]	*Wechsel auf Entecavir (B)* *Wechsel auf Tenofovir (B)*
Entecavir	Wechsel auf Tenofovir (A)
Telbivudin	Wechsel auf Tenofovir (A) (Wechsel auf Entecavir)[2]
Tenofovir[4]	Wechsel auf Entecavir, oder zusätzliche Gabe von Lamivudin, Telbivudin oder Entecavir (C)

[1] Diese Vorschläge sind nicht in allen Fällen durch kontrollierte Studien belegt.

[2] Entecavir kann eingesetzt werden, wenn das Vorhandensein von Varianten, die mit einer Resistenz gegen Entecavir assoziiert sind, ausgeschlossen wurde und ein Einsatz von Tenofovir aus anderen Gründen nicht möglich/sinnvoll ist.

[3] Adefovir wird nicht mehr als Primärtherapie empfohlen. Im Falle einer Therapieanpassung ist eine mögliche Vorbehandlung mit Lamivudin und das Vorliegen einer gesicherten Resistenz zu berücksichtigen.

[4] Bei Patienten wurden bislang keine HBV-Polymersemutanten, die mit einer Tenofovir-Resistenz einhergehen, im Verlauf einer Tenofovir-Therapie nachgewiesen.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 19.05.2016**

#	Suchfrage
1	MeSH descriptor: [Hepatitis B] explode all trees
2	(chronic and hepatitis and b):ti,ab,kw (Word variations have been searched)
3	(hbv or chb):ti,ab,kw (Word variations have been searched)
4	#1 or #2 or #3
5	#1 or #2 or #3 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 19.05.2016

#	Suchfrage
1	hepatitis b, chronic[MeSH Terms]
2	(((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND b[Title/Abstract])
3	((hbv[Title/Abstract]) OR chb[Title/Abstract])
4	(#1 OR #2 OR #3)
5	((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract])
6	(#4) AND #5
7	("Hepatitis B, Chronic/diet therapy"[Mesh] OR "Hepatitis B, Chronic/drug therapy"[Mesh] OR "Hepatitis B, Chronic/radiotherapy"[Mesh] OR "Hepatitis B, Chronic/surgery"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh])
8	(#6) OR #7
9	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
10	(((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
11	(#9) OR #10
12	(#8) AND #11
13	(#12) AND ("2011/05/01"[PDAT] : "2016/05/19"[PDAT])

Leitlinien in Medline (PubMed) am 19.05.2016

#	Suchfrage
1	hepatitis b[MeSH Terms]
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND b[Title/Abstract]
3	(hepatitis[Title]) AND b[Title]
4	(hbv[Title/Abstract]) OR chb[Title/Abstract]
5	(((#1) OR #2) OR #3) OR #4
6	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
7	(#5) AND #6
8	(#7) AND ("2011/05/01"[PDAT] : "2016/05/19"[PDAT])

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Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation *Chronische Hepatitis B* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.03.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 863 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 5 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation

Zur Behandlung der chronischen Hepatitis B (CHB)-Infektion bei Jugendlichen (von 12 bis <18 Jahren mit einem Körpergewicht von mind. 35 kg).

Berücksichtigte Wirkstoffe/Therapien

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CHB	chronische hepatitis B
DAHTA	Deutsche Agentur für Health Technology Assessment
EASL	European Association for the Study of the Liver
ETV	entecavir
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	chronic hepatitis B viral infection
HCC	hepatocellular carcinoma
IFN	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KASL	Korean Association for the Study of the Liver
NA	Nucleotide Analogs
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
TDF	Tenofovir
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG-Berichte/G-BA-Beschlüsse

Es wurden derzeit keine relevanten G-BA-Beschlüsse/IQWiG-Berichte identifiziert

Cochrane Reviews

Es wurden derzeit keine relevanten Cochrane Reviews identifiziert

Systematische Reviews

Jonas MM et al., 2016 [3]. Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis	1. Fragestellung: We conducted this systematic review and meta-analysis to synthesize existing evidence about effectiveness of antiviral therapy in the management of chronic HBV infection in children.
	2. Methodik Population: Children (<18 years) with chronic hepatitis B Intervention: Antiviral drugs (siehe Ergebnisteil) Komparator: Placebo Endpunkte: cirrhosis, decompensated liver disease, HCC, ALT normalization, HBV DNA suppression, HBeAg/HBsAg seroconversion, and HBeAg/HBsAg loss Suchzeitraum (Aktualität der Recherche): Literature search from January 1988 to December 2014. Hinweis: Due to the anticipated limited number of randomized controlled trials (RCTs) evaluating patient-important (clinical) outcomes, we included observational studies that evaluated such outcomes. Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 studies that enrolled 1425 children. Two studies evaluated the clinical (patient-important) outcomes of death, cirrhosis, and HCC and 12 studies reported intermediate outcomes. Hinweis: 1 RCT zu tenofovir (n=106) (Murray et al. 2012) und 1 RCT zu entecavir (n=180) (Jonas et al. 2015)

	Qualitätsbewertung der Studien: To measure the overall heterogeneity across the included studies, we calculated the I^2 statistic, with I^2 >50% suggesting high heterogeneity. Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane risk of bias tool and the Newcastle-Ottawa Scale for RCTs and observational studies. Quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity), and publication bias.
	3. Ergebnisdarstellung Wirksamkeit: One RCT (Murray 2012) compared *tenofovir* to placebo treatment. After 72 weeks of treatment, tenofovir demonstrated significantly higher rates of ALT normalization (RR= 2, 95% CI 1.4-2.9) and HBV DNA suppression (RR= 92.4, 95% CI 5.8-146.7) but no statistically significant effect on HBeAg clearance/loss. The quality of evidence was moderate to low due to indirectness and imprecision. In one RCT (Jonas 2015), *entecavir* compared to placebo was associated with significantly higher ALT normalization (RR= 2.9, 95% CI 1.8-4.7), HBV DNA suppression (RR= 14.8, 95% CI 3.7-58.3), and HBeAg seroconversion (RR= 2.4, 95% CI 1.1-5.5) at 48 weeks. Longer duration of treatment (96 weeks) resulted in persistently statistically significant HBeAg seroconversion (RR= 1.8, 95% CI 1.0-3.4) but not ALT normalization and HBV DNA suppression. The quality of evidence was limited due to the use of surrogate outcomes. Sicherheit: Transient effects on body weight and growth have been observed; but no long-term safety issues have been identified. Quellen: Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. HEPATOLOGY 2012;56:2018-2026. Jonas MM, Chang M-H, Sokal E, Schwarz KB, Kelly D, Kim KM, et al. Randomized controlled trial of entecavir versus placebo in children with HBeAg-positive chronic hepatitis B. HEPATOLOGY 2015; doi: 10.1002/hep.28015.
	4. Fazit der Autoren:

	Therapeutic choices for children with chronic hepatitis B have been limited but expanding as entecavir has recently been shown to be safe and effective in this population and data regarding pegylated IFN and tenofovir use in children are expected soon.

Leitlinien

KASL, 2016 [2]. KASL clinical practice guidelines: management of chronic hepatitis B	Fragestellung/Zielsetzung: In 2015, the objective of this manuscript was to update the recommendations for management of CHB, including epidemiology, prevention, natural history, diagnosis, treatment, monitoring, drug resistance mutations and treatment of special populations discussed herein based on current evidences or if, evidences lack, on expert opinions after deliberation.
	Methodik Grundlage der Leitlinie Aktualisierung der Leitlinie aus 2011, Gremium aus 17 Heptaologen und 1 Kinderarzt, systematische Recherche in Medline, formale Konsensusprozesse und externer Peer-Review, Interessenskonflikte offengelegt Suchzeitraum (Aktualität der Recherche): up to 2015. The languages were limited to English and Korean. LoE/GoR nach Grade: **Quality of evidence** / **Criteria** High (A) – Further research is unlikely to change confidence in the estimate of the clinical effect Moderate (B) – Further research may change confidence in the estimate of the clinical effect Low (C) – Further research is very likely to impact confidence on the estimate of clinical effect **Strength of recommendations** / **Criteria** Strong (1) – Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost Weak (2) – Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption NOTE. Of the quality levels of evidence, we excluded "very low quality (D)" from the guidelines for convenience. This was originally included in the GRADE system and indicates that the estimate of effect is highly uncertain.
	Empfehlungen <u>What is the optimal management of CHB in children?</u> 1. HBeAg-positive CHB children with an HBV DNA level >20,000 IU/mL and HBeAg-negative CHB children with an HBV DNA level >2,000 IU/mL should be considered for treatment when the AST or ALT level is > 2 ULN for at least 6 months, or moderate-to-severe necroinflammation or periportal fibrosis is evident in a liver biopsy. **(A1)** 2. Tenofovir, entecavir or interferon-α is the first-line therapy in children with CHB. **(B1)** Data on peginterferon are currently

<table>
<tr><td></td><td>scarce, but its use in children can be based on the results of studies involving adults. (C1)

3. If antiviral resistance develops, it should be treated in accordance with the guidelines for antiviral resistance management in adults. (B1)</td></tr>
<tr><td rowspan="3">WHO, 2015 [5]. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection.</td><td>Zielsetzung: The present guidelines are the first WHO guidelines on the prevention, care and treatment of persons with chronic hepatitis B virus (HBV) infection – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more.</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie

Systematische Recherche und Aufbereitung, Konsensusprozesse, externs Peer-Review-Verfahren, weitere Methodik in Handbuch beschrieben, Interessenskonflikte offengelegt

Suchzeitraum (Aktualität der Recherche): nicht beschrieben

LoE/GoR nach GRADE

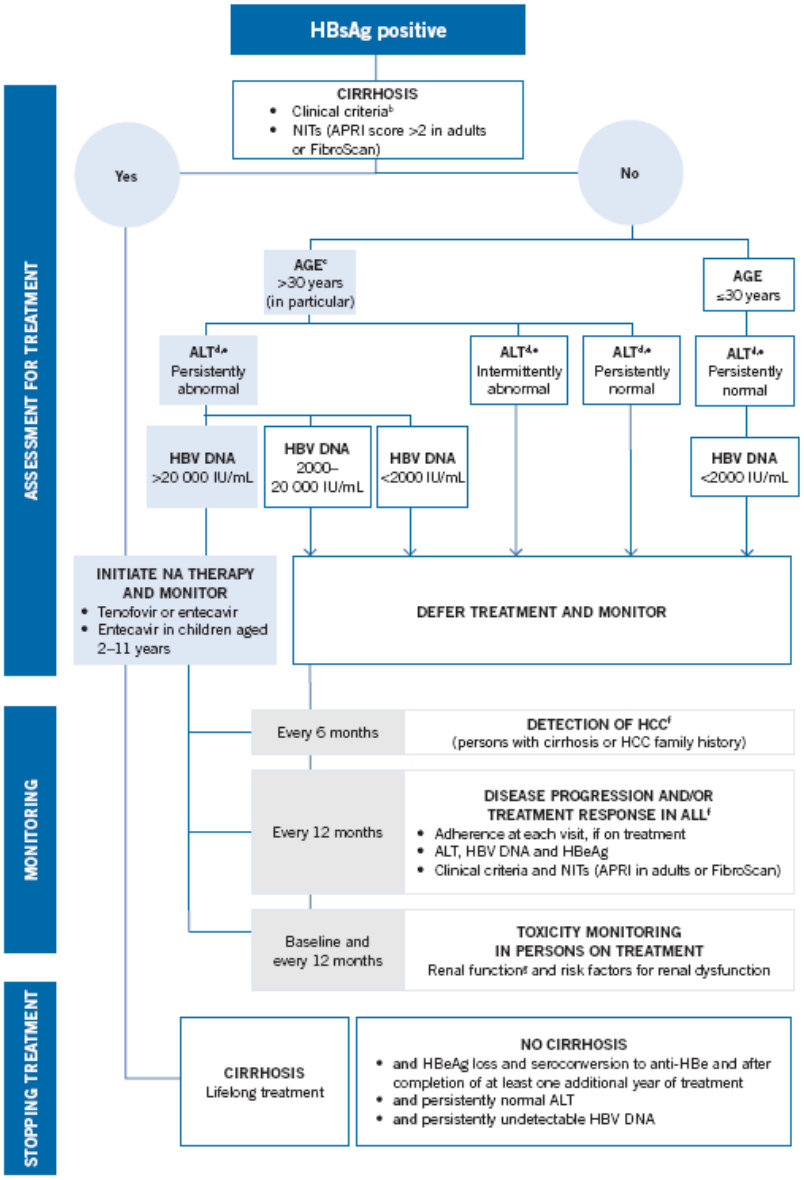
TABLE 2.1 GRADE categories of the quality of evidence (4–10)

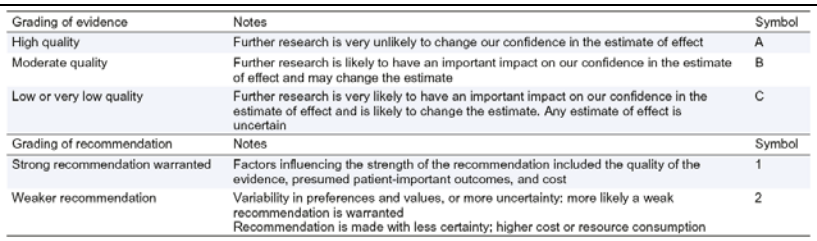
<table><tr><th>Level of evidence</th><th>Rationale</th></tr><tr><td>High</td><td>Further research is very unlikely to change our confidence in the estimate of effect.</td></tr><tr><td>Moderate</td><td>Further research is likely to have an important impact on our confidence in the effect.</td></tr><tr><td>Low</td><td>Further research is very likely to have an estimate of effect and is likely to change the estimate.</td></tr><tr><td>Very low</td><td>Any estimate of effect is very uncertain.</td></tr></table>
TABLE 2.2 Key domains considered in determining the strength of recommendations

<table><tr><th>Domain</th><th>Rationale</th></tr><tr><td>Benefits and risks</td><td>Desirable effects (benefits) need to be weighed against undesirable effects (risks). The more that the benefits outweigh the risks, the more likely that a strong recommendation will be made.</td></tr><tr><td>Values and preferences (acceptability)</td><td>If the recommendation is likely to be widely accepted or highly valued, a strong recommendation will probably be made. If there are strong reasons that the recommended course of action is unlikely to be accepted, a conditional recommendation is more likely to be made.</td></tr><tr><td>Costs and financial implications (resource use)</td><td>Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness will more likely result in a strong recommendation.</td></tr><tr><td>Feasibility</td><td>If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is more probable.</td></tr></table></td></tr>
<tr><td>RECOMMENDATIONS: FIRST-LINE ANTIVIRAL THERAPIES FOR CHRONIC HEPATITIS B:

• In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide</td></tr>
</table>

	analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. Entecavir is recommended in children aged 2–11 years. **(Strong recommendation, moderate quality of evidence)** • NAs with a low barrier to resistance (lamivudine, adefovir or telbivudine) can lead to drug resistance and are not recommended. **(Strong recommendation, moderate quality of evidence)** Existing recommendation for HBV/HIV coinfected persons[1]: • In HBV/HIV-coinfected adults, adolescents and children aged 3 years or older, tenofovir + lamivudine (or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART. **(Strong recommendation, moderate quality of evidence***)* [1] Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: World Health Organization; 2013. These guidelines will be updated in 2015.

	ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a] 
EASL, 2012 [1] EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection	Fragestellung/Zielsetzung: The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection.
	Methodik Grundlage der Leitlinie Aktualisierung der Leitlinie aus 2009, systematische Rechereche und Aufbereitung der Literatur, informelle Konsensusprozesse, externer Peer-Review, Interessenskonflikte offengelegt Suchzeitraum (Aktualität der Recherche): bis September 2011 LoE/GoR nach GRADE:

	 Grading of evidence / Notes / Symbol High quality — Further research is very unlikely to change our confidence in the estimate of effect — A Moderate quality — Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate — B Low or very low quality — Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain — C Grading of recommendation / Notes / Symbol Strong recommendation warranted — Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost — 1 Weaker recommendation — Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption — 2
	Empfehlungen: Chronic hepatitis B runs an asymptomatic course in most children, in whom treatment indications should be very carefully evaluated. In general, a conservative approach is warranted **(A1)**. Only conventional IFN, lamivudine and adefovir have been evaluated for safety and efficacy, which were comparable to adults. There are ongoing studies with other NAs in children to better define treatment strategies for children. (Hinweis: nicht in Deutschland zugelassen)
NICE, 2013 [4]. Chronic hepatitis B – Information for the public	Zielsetzung: Guidance on chronic Hepatitis B
	Methodik Grundlage der Leitlinie Systematische Recherche und Evidenzaufbereitung, Konsensusprozesse (je nach Bedarf fomal oder informal) Suchzeitraum (Aktualität der Recherche): nicht beschrieben LoE/GoR GoR schlagen sich in den Formulierungen nieder ""To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."
	Empfehlungen: • If you are a child or young person with chronic hepatitis B, you should be offered drug treatment if you have significant liver disease (called fibrosis or cirrhosis), or if your liver tests are abnormal (called abnormal liver function). • If your liver continues to work adequately (called compensated liver disease) and you have not taken drug treatment before, you may be offered peginterferon alfa-2a (Hinweis: nicht in Deutschland zugelassen). This treatment is usually taken for 48 weeks. You will be monitored once treatment starts and you may be offered a different treatment if monitoring tests suggest this is needed.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 21.03.2017

#	Suchfrage
1	MeSH descriptor: [Hepatitis B, Chronic] explode all trees
2	(chronic and hepatitis and b):ti,ab,kw
3	(hbv or chb):ti,ab,kw
4	#1 or #2 or #3
5	#4 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 22.03.2017

#	Suchfrage
1	"Hepatitis B, Chronic/diet therapy"[Mesh] OR "Hepatitis B, Chronic/drug therapy"[Mesh] OR "Hepatitis B, Chronic/radiotherapy"[Mesh] OR "Hepatitis B, Chronic/surgery"[Mesh] OR "Hepatitis B, Chronic/therapy"[Mesh]
2	(((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND b[Title/Abstract])
3	((hbv[Title/Abstract]) OR chb[Title/Abstract])
4	#2 OR #3
5	(#4) AND ((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract])
6	#1 OR (#4)
7	(#6) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
8	((#7) AND ("2012/03/01"[PDAT] : "2017/03/31"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 22.03.2017

#	Suchfrage
1	hepatitis b[MeSH]
2	((chronic[Title/Abstract]) AND hepatitis[Title/Abstract]) AND b[Title/Abstract]
3	(hepatitis[Title]) AND b[Title]
4	(hbv[Title/Abstract]) OR chb[Title/Abstract]
5	(((#1) OR #2) OR #3) OR #4

	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[Title])*
6	(((#N) AND ("2012/03/01"[PDAT] : "2017/03/31"[PDAT])) NOT ((comment[Publication Type]) OR letter[Publication Type])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Literatur

1. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57(1):167-185.

2. KASL clinical practice guidelines: management of chronic hepatitis B. Clin Mol Hepatol 2016;22(1):18-75.

3. **Jonas MM, Lok AS, McMahon BJ, Brown RS, Jr., Wong JB, Ahmed AT, et al.** Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis. Hepatology 2016;63(1):307-318.

4. **National Institute for Health and Care Excellence (NICE).** Hepatitis B (Chronic): Diagnosis and Management of Chronic Hepatitis B in Children, Young People and Adults [online]. London (GBR): NICE; 2013. [Zugriff: 27.03.2017]. (Clinical guideline; Band 165). URL: https://www.nice.org.uk/guidance/cg165/resources/chronic-hepatitisb-246463447237.

5. **World Health Organization (WHO).** Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection [online]. Genf (SUI): 2015. [Zugriff: 22.03.2017]. URL: http://www.who.int/hepatitis/publications/hepatitis-b-guidelines/en/.