Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-016 Tenofoviralafenamid

Stand: März 2018

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

Tenofoviralafenamid [Chronische Hepatitis B] **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 unter 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	2017-04-01-D-208 Tenofoviralafenamid (Beschluss vom 21.09.2017)
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 J05AF13 Vemlidy®	Vemlidy wird bei Erwachsenen und Jugendlichen (ab 12 Jahren, mit einem Körpergewicht von mindestens 35 kg) zur Behandlung chronischer Hepatitis B angewendet (siehe Abschnitt 5.1).
Lamivudin Zeffix® J05AF05	Zeffix ist angezeigt zur Behandlung der chronischen Hepatitis B bei Erwachsenen mit: • kompensierter Lebererkrankung mit Nachweis aktiver Virusreplikation, persistierender Erhöhung der Serum-Alanin-Aminotransferase (ALT [GPT])-Werte und histologischem Nachweis aktiver Leberentzündung und/oder Fibrose. Eine Einleitung der Lamivudin-Behandlung sollte nur dann in Betracht gezogen werden, wenn ein alternatives antivirales Arzneimittel mit einer höheren genetischen Barriere gegenüber Resistenzen nicht verfügbar oder dessen Anwendung nicht angemessen ist (siehe Abschnitt 5.1). • dekompensierter Lebererkrankung in Kombination mit einem zweiten Arzneimittel, das keine Kreuzresistenz gegenüber Lamivudin aufweist (siehe Abschnitt 4.2).
Tenofovirdisoproxil Viread® J05AF07	Viread 245 mg Filmtabletten werden angewendet für die Behandlung chronischer Hepatitis B bei Erwachsenen mit: • kompensierter Lebererkrankung mit nachgewiesener aktiver viraler Replikation, dauerhaft erhöhten Alaninaminotransferase-(ALT-)Werten im Serum und histologischem Nachweis einer aktiven Entzündung und/oder Fibrose (siehe Abschnitt 5.1). • nachgewiesenem Lamivudin-resistenten Hepatitis-B-Virus (siehe Abschnitte 4.8 und 5.1). • dekompensierter Lebererkrankung (siehe Abschnitte 4.4, 4.8 und 5.1). 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 (siehe Abschnitte 4.4, 4.8 und 5.1).
Adefovirdipivoxil Hepsera® J05AF08	Hepsera wird für die Behandlung der chronischen Hepatitis B angewendet bei Erwachsenen mit: • kompensierter Lebererkrankung mit nachgewiesener aktiver Virusreplikation, kontinuierlich erhöhten Serum-Alanin-Aminotransferase-(ALT)-Werten sowie histologischem Nachweis einer aktiven Leberentzündung und Fibrose. Die Einleitung einer Therapie mit Hepsera sollte nur dann in Betracht gezogen werden, wenn ein alternativer antiviraler Wirkstoff mit einer höheren genetischen Resistenz-Barriere nicht verfügbar oder nicht geeignet ist. (siehe Abschnitt 5.1). • dekompensierter Lebererkrankung in Kombination mit einem zweiten Wirkstoff ohne Kreuzresistenz gegenüber Hepsera.
Entecavir Baraclude® J05AF10	Baraclude ist indiziert zur Behandlung der chronischen Hepatitis-B-Virus-Infektion (HBV) (siehe Abschnitt 5.1) bei Erwachsenen mit: • kompensierter Lebererkrankung und nachgewiesener aktiver Virusreplikation, persistierend erhöhten Serumspiegeln der Alaninaminotransferase (ALT) sowie mit einem histologischen Befund einer aktiven Entzündung und/oder Fibrose. • dekompensierter Lebererkrankung (siehe Abschnitt 4.4)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Sowohl für die kompensierte als auch für die dekompensierte Lebererkrankung basiert diese Indikation auf Daten aus klinischen Studien mit Nukleosid-naiven Patienten (d. h. solchen, die nicht mit Nukleosidanaloga vorbehandelt waren) mit HBeAg-positiver und HBeAg-negativer HBV-Infektion. Hinsichtlich Patienten mit einer Lamivudinrefraktären Hepatitis B siehe Abschnitte 4.2, 4.4 und 5.1. 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. Hinsichtlich der Entscheidung eine Behandlung bei Kindern und Jugendlichen zu initiieren siehe Abschnitte 4.2, 4.4 und 5.1.
Telbivudin Sebivo® J05AF11	Sebivo ist für die Behandlung der chronischen Hepatitis B bei erwachsenen Patienten mit kompensierter Lebererkrankung und Nachweis viraler Replikation, anhaltend erhöhten Alanin-Aminotransferase-(ALT-)Spiegeln und histologischem Nachweis einer aktiven Entzündung und/oder Fibrose indiziert. Die Einleitung einer Therapie mit Sebivo sollte nur dann in Betracht gezogen werden, wenn ein alternativer antiviraler Wirkstoff mit einer höheren genetischen Resistenz-Barriere nicht verfügbar oder nicht geeignet ist.
Interferon alfa-2a Roferon®-A L03AB04	Histologisch nachgewiesene chronische Hepatitis B bei erwachsenen Patienten, bei denen Marker für die Virusreplikation, d. h. positive Nachweise von HBV-DNS oder HBe-Antigen, vorliegen.
Peginterferon alfa-2a Pegasys® L03AB11	Pegasys ist indiziert zur Behandlung der Hepatitis-B-Envelope-Antigen (HBeAg)-positiven und HBeAg-negativen chronischen Hepatitis B (CHB) bei erwachsenen Patienten mit kompensierter Lebererkrankung, mit Nachweis viraler Replikation, erhöhten Alaninaminotransferase (ALT)-Werten und histologisch verifizierter Leberentzündung und/oder -fibrose (siehe Abschnitte 4.4 und 5.1). Pegasys ist indiziert zur Behandlung der HBeAg-positiven CHB bei Kindern und Jugendlichen ab 3 Jahren ohne Leberzirrhose mit Nachweis viraler Replikation und dauerhaft erhöhten ALT-Serumwerten. Bezüglich einer Therapieentscheidung für eine Behandlung bei Kindern und Jugendlichen siehe Abschnitte 4.2, 4.4 und 5.1.
Interferon alfa-2b IntronA® L03AB05	Behandlung von erwachsenen Patienten mit chronischer Hepatitis B, die im Serum Marker für eine Hepatitis-B-Virus-Replikation (Vorhandensein von Hepatitis-B-Virus-DNA [HBV-DNA] und Hepatitis-B-Antigen [HBeAg]), erhöhte Alanin-Aminotransferase-Werte (ALT[GPT]-Werte) und eine histologisch nachgewiesene aktive Leberentzündung und/oder Fibrose aufweisen.

Quellen: AMIS-Datenbank, Fachinformationen, Stand 03/2018

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-016 (Tenofoviralafenamid)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	19.03.2018

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 22.02.2018 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 879 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 34 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Indikation der Synopse: zur Behandlung der chronischen Hepatitis B (CHB)-Infektion

Indikation laut Zulassung: Behandlung der chronischen Hepatitis B (CHB)-Infektion bei Erwachsenen und Jugendlichen (ab 12 Jahren, mit einem Körpergewicht von mindestens 35 kg)

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ADV	adefovir
ALT	alanine aminotransferase
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CHB	chronische hepatitis B
CHB	Chronic hepatitis B
CI	confidence interval
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
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
INF	interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LAM	Lamivudin
LdT	Telbivudine
NA	Nucleotide Analogs
NA	nucleos(t)ide analogue
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NOS	Newcastle-Ottawa Scale
NOS	Newcastle-Ottawa Scale
PCR	polymerase chain reaction
PEG-IFNa	pegylated interferon alfa
RCT	randomized controlled trial
RCT	Randomized controlled trial
RR	Relative risk
SIGN	Scottish Intercollegiate Guidelines Network
TDF	Tenofovir
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG-Berichte/G-BA-Beschlüsse

G-BA, 2017 [7]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Tenofoviralafenamid Vom September 2017 Siehe auch: **IQWiG, 2017 [12].**	**Anwendungsgebiet (laut Zulassung vom 9. Januar 2017):** Vemlidy wird bei Erwachsenen und Jugendlichen (ab 12 Jahren, mit einem Körpergewicht von mindestens 35 kg) zur Behandlung chronischer Hepatitis B angewendet (siehe Abschnitt 5.1 der Fachinformation). **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) therapienaive erwachsene Patienten mit chronischer Hepatitis B **Zweckmäßige Vergleichstherapie:** (PEG-)Interferon alfa oder Tenofovirdisoproxil oder Entecavir **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein** Zusatznutzen ist nicht belegt. b) therapieerfahrene erwachsene Patienten mit chronischer Hepatitis B **Zweckmäßige Vergleichstherapie:** eine patientenindividuelle antivirale Therapie in Abhängigkeit der Vortherapie(n) und unter Berücksichtigung des Grundes für den Therapiewechsel, insbesondere Therapieversagen aufgrund eines virologischen Versagens und etwaig einhergehender Resistenzbildung oder aufgrund von Nebenwirkungen. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. c) therapienaive jugendliche Patienten ab 12 Jahren mit chronischer Hepatitis B **Zweckmäßige Vergleichstherapie:** Tenofovirdisoproxil oder Entecavir **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. d) therapieerfahrene jugendliche Patienten ab 12 Jahren mit chronischer Hepatitis B **Zweckmäßige Vergleichstherapie:** Tenofovirdisoproxil **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.

Cochrane Reviews

Es wurden derzeit keine relevanten Cochrane Reviews identifiziert

Systematische Reviews

Han Y et al., 2017 [9]. The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: A systematic review and Meta-analysis	1. Fragestellung to assess the efficacy and safety between tenofovir and entecavir in the treatment of CHB and HBV related cirrhosis through Metaanalysis
	2. Methodik Population: CHB patients Intervention: ETV Komparator: TDF Endpunkte: the numbers of patientswho reached the normalized serum alanine aminotransferase levels (ALT norm) after treatment as the primary outcome to combine; the occurrence rate of patientswho reached the undetectable levels of HBV-DNA as the secondary outcome to combine. Recherche: PubMed, the Cochrane Library, Nature, CNKI and WanFang data / up to May 12, 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 20 articles were included into Metaanalysis (12 articles compared the efficacy of TDF and ETV in CHB patients; 4 articles provided the comparison of TDF and ETV in HBV related liver cirrhosis patients; and 5 articles were included in safety assessment model). Qualitätsbewertung der Studien: We used the Cochrane Risk of Bias assessment tool for RCTs, and the Newcastle-Ottawa Scale (NOS) for cohort studies for the assessment of each study's quality.
	3. Ergebnisdarstellung Qualität der Studien: NOS Score between 6-8

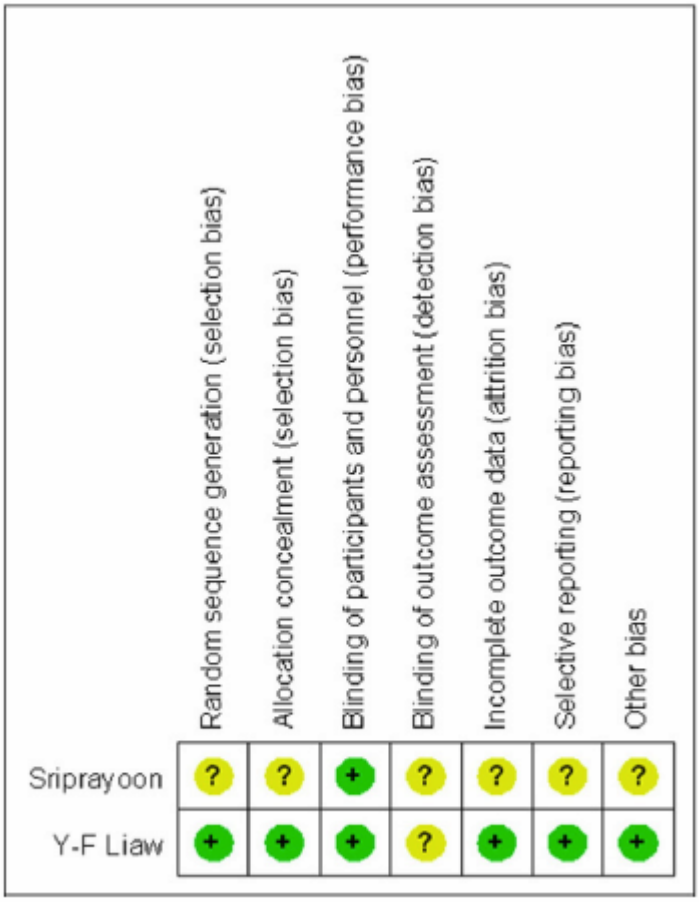


Fig. 2. Risk of bias of RCT studies.

- There was significant difference of ALT norm level in the short-term period of 3 months (RR = 1.43, 95%CI: 1.06–1.94, P< 0.017) and 6 months (RR = 0.89, 95%CI: 0.81–0.97, P < 0.017), and significant difference of undetectable HBV-DNA only in 3 months follow-up period (RR=1.59, 95%CI: 1.04–2.42, P< 0.017) between TDF and ETV, but no significant difference in the long-term period
- There is significant difference between TDF and ETV in eGFR level (RR = 1.601, 95%CI: 1.035–2.478, P = 0.0034) and hypophosphatemia incidence (RR = 4.008, 95%CI: 1.485–10.820, P = 0.006).

4. Fazit der Autoren: TDF has a better efficacy than ETV in 3 months treatment duration, but intriguingly, TDF might not better than ETV during the 6 months treatment period in the viral suppression and liver function improvement. There is no significant difference between TDF and ETV in the long-term treatment duration and in the treatment of HBV related liver cirrhosis. Both TDF and ETV could influence renal function but patients under TDF therapy may have more risk to suffer from renal damage and hypophosphatemia.

Chen J et al., 2017 [4].

Comparison of the

1. Fragestellung

to compare the efficacy between tenofovir disoproxil fumarate (TDF)

Efficacy of Tenofovir Versus Tenofovir plus Entecavir in the Treatment of Chronic Hepatitis B in Patients With Poor Efficacy of Entecavir: A Systematic Review and Meta-analysis.	and TDF plus entecavir (ETV) combination therapy in patients with chronic hepatitis B (CHB) with a poor response to ETV.
	2. Methodik Population: patients with CHB → *Hinweis*: Patients with coinfection (hepatitis C virus, hepatitis D virus, or HIV), decompensated liver diseases, hepatocellular carcinoma, liver failure, or previous liver transplant were excluded. Intervention / Komparator: with the intervention therapies of TDF monotherapy versus TDF plus ETV combination Endpunkte: k.A. (siehe Ergebnisteil) Recherche: the China National Knowledge Infrastructure (CNKI), PubMed, EMBASE, and SCOPE libraries / for citations dated between September 2012 and October 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): Five studies (from CNKI and PubMed) with a total of 408 patients met the inclusion criteria: 212 patients in the TDF group and 196 patients in the TDF plus ETV group. Qualitätsbewertung der Studien: The quality of the RCTs and non-RCTs were assessed by using the Cochrane tool and the New-castle-Ottawa scale, respectively
	3. Ergebnisdarstellung Qualität der Studien: The percentages of low risk of detection bias, incomplete outcome data, and selective reporting were all >50% according to the description of each study.The percentages of low risk of selection bias and other biases were approximately 50%.The percentages of high risk of bias performance were <50%. Generally, the outcome of risk of bias graph indicated that there was a low risk of bias of the 2 randomized studies in this meta-analysis. • The rates of viral suppression between the 2 groups were comparable at weeks 24 and 48 of treatment (P = 0.546 vs P = 0.818). • In addition, the sub analysis revealed that no significant differences were observed in the rates of viral suppression between the 2 groups at week 24 (subgroup 1 [partial response to ETV]: P= 0.822; subgroup 2 [resistance to ETV]: P= 0.294) and week 48 (subgroup1: P= 0.797; subgroup 2: P= 0.545). • No significant differences were found in alanine aminotransferase normalization, hepatitis B antigen loss, hepatitis B antigen seroconversion, virologic breakthrough, and tolerability between the 2 groups at weeks 24 and 48. Therefore, the results suggest that TDF monotherapy should be chosen for patients with CHB with a

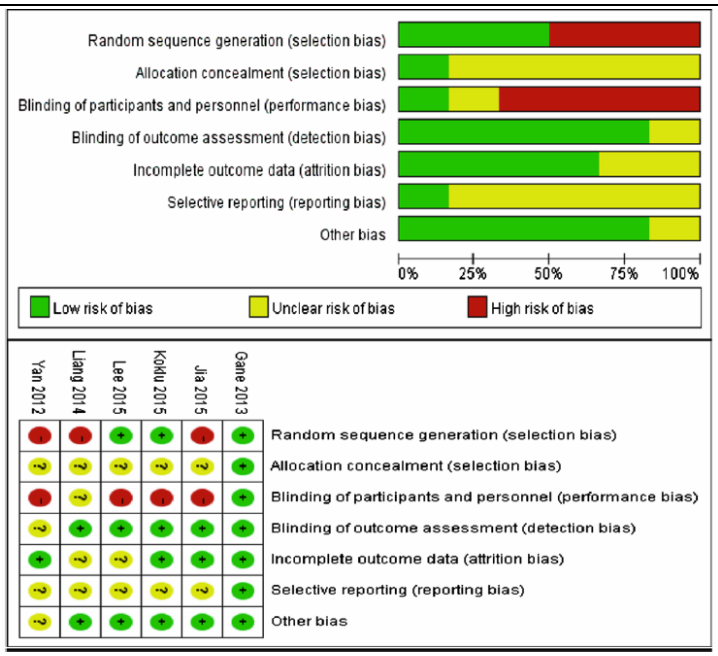
	poor response to ETV for reasons of economy and convenience.
	4. Fazit der Autoren: Our meta-analysis found that TDF monotherapy at weeks 24 and 48 was comparable to TDF plus ETV combination therapy for patients with a poor response to ETV.Therefore, TDF monotherapy may be a better choice for these patients when considering economic benefit and convenience. However, because of the limited sample sizes, larger and longer RCTs and additional studies should be conducted to verify the result.
Zhou J et al., 2016 [33]. A Meta-Analysis of the Efficacy of Interferon Monotherapy or Combined with Different Nucleos(t)ide Analogues for Chronic Hepatitis B	1. Fragestellung to compare the efficacy of interferon (IFN) with or without different nucleos(t)ide analogues (NAs).
	2. Methodik Population: HBeAg-positive and/or negative adult CHB patients Intervention/Komparator: IFN combination with NAs (LAM, ADV or ETV) and IFN monotherapy Endpunkte: • Primäre Endpunkte: virological and serological responses at the end of at least 24 weeks of follow-up • Sekundäre Endpunkte: virological and serological response at week 24 and 48 treatment respectively Recherche: The PubMed, Wan Fang and CNKI databases were searched to identify relevant trials up to May 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Fifty-six studies fulfilled the criteria for the meta-analysis Qualitätsbewertung der Studien: The quality of all included RCTs was assessed using the Modified 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
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: five studies were considered to be of good overall quality, eighteen were assessed to be of fair quality, whilst the remainder were considered poor. • Compared with IFN monotherapy, combination therapy were superior in HBV DNA undetectable rate (Risk Ratio (RR) = 1.55, 95% confidence interval (CI): 1.44–1.66, p < 0.00001), HBeAg and HBsAg loss rate (RR = 1.38, 95% CI: 1.22–1.56, p < 0.00001; RR = 1.69, 95% CI: 1.03–2.78, p = 0.04, respectively) at the end of week 48 treatment. • Sub-analysis showed the RRs of virological response for entecavir

	(ETV), adefovir (ADV), and lamivudine (LAM) were 1.64, 1.61 and 1.52, respectively; RRs of HBeAg loss rate were 1.34, 1.71 and 1.34, respectively. • However, at the end of follow-up, IFN plus NAs therapy was better than IFN monotherapy only in terms of HBV DNA undetectable rate (p = 0.0007).
	4. Fazit der Autoren: This meta-analysis demonstrated that a better efficacy of NAs combination therapy than IFN monotherapy in virological and serological responses at the end of treatment. However, at the end of follow-up, only HBV DNA undetectable rate was superior in combination therapy. Therefore, in clinically practice, the benefits of combination therapy should be weighed against the higher cost. 5. Kommentare zum Review • limited randomized controlled trial studies which included ETV combination therapy only the virological and serological responses were analyzed in this meta-analysis, because most studies had not reported histological improvement. • only a few studies included in the current meta-analysis were of high quality, although the publication bias was minimal
Wang HL et al., 2016 [25]. Antiviral Therapy in Lamivudine-Resistant Chronic Hepatitis B Patients: A Systematic Review and Network Meta-Analysis	1. Fragestellung Direct und network meta-analysis with updated evidence to evaluate effects of different rescue strategies including TDF, ETV, LAM/ADV, and ADV in the treatment of LAM-R patients.
	2. Methodik Population: CHB patients with LAM resistance Intervention/Komparator: TDF, ETV or ADV, or LAM plus ADV therapy Endpunkte: rates of undetectable HBV DNA (<400 copies/mL), ALT normalization, (<40 IU/mL), HBeAg loss, and virological breakthrough for patients 24, 48, and 96 weeks after therapy Recherche: We searched PUBMED, MEDLINE, EMBASE, and CNKI databases up to February 15, 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): nine studies met the inclusion criteria for this review, including 764 patients with LAM-R. Among nine studies, two studies compared TDF versus LAM/ADV and one study compared TDF versus ETV or ADV, respectively, six studies compared ETV versus LAM/ETV, and two studies compared ADV versus LAM/ADV Qualitätsbewertung der Studien: Cochrane Collaboration’s tool

	3. Ergebnisdarstellung Qualität der Studien: The percentages of low risk of selection bias, performance bias, and the detection bias were less than 50% according to the description of each study. The percentages of low risk of bias of incomplete outcome data, selective reporting, and other bias were all more than 50%. The outcome of risk of bias graph showed that there was low risk of bias in this meta-analysis. *Direct Meta-Analysis:* • TDF showed a stronger antiviral effect than any one of ETV, LAM/ADV, and ADV against LAM-R hepatitis B virus. • LAM/ADV therapy was superior to ADV in suppressing viral replication. • ETV achieved similar rate of HBV DNA undetectable compared to ADV or LAM/ADV. *Network meta-analysis:* • TDF had higher rates of HBV DNA undetectable compared to ETV (OR, 24.69; 95% CrI: 5.36–113.66), ADV (OR, 37.28; 95% CrI: 9.73–142.92), or LAM/ADV (OR, 21.05; 95% CrI: 5.70–77.80). • However, among ETV, ADV, and LAM/ADV, no drug was clearly superior to others in HBV DNA undetectable rate. • Moreover, no significant difference in the rate of ALT normalization or HBeAg loss was observed compared the four rescue strategies with each other. • TDF appears to be a more effective rescue therapy than LAM/ADV, ETV, or ADV. LAMplus ADV therapy was a better treatment option than ETV or ADV alone for patients with LAMR.
	4. Fazit der Autoren: In conclusion, TDF monotherapy appears to be a more effective rescue therapy than LAM/ADV, ETV, or ADV for patients with LAM-R. LAM and ADV combination therapy was a better treatment option than ETV or ADV alone. ETV or ADV monotherapy is not a reasonable therapeutic option for CHB patients with LAM-R. 5. Kommentare zum Review • Some studies had a small sample size and some of the reports' experimental controls were not very balanced. • long-term outcomes of TDF in treatment of LAM-R patients were not adequately assessed owing to limited published studies in this area.
Wang HL et al., 2016 [24]. Efficacy of tenofovir-based rescue therapy	1. Fragestellung to compare the efficacy between TDF and TDF-based combination therapy against LAM-R HBV in CHB patients
	2. Methodik

in patients with lamivudine-resistant hepatitis B virus: A systematic review and meta-analysis	Population: CHB patients who had failed inprevious LAM monotherapy and/or combination therapyof LAM and ADV because of the development of LAM-R Intervention / Komparator: monotherapy vs. TDF-based combination therapy Endpunkte: Efficacy was considered for patients' 24, 48 weeks post-therapy by considering the following: HBV-DNA level (< 400copies/ml), ALT normalization rate (< 40 IU/ml), HBeAg loss rate. Recherche: Pubmed, Medline, EMBASE, China NationalKnowledge Infrastructure (CNKI), the VIP database, the Wan-fang database up to June 15, 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): Five articles (683 patients in total) met entry criteria Qualitätsbewertung der Studien: Cochrane Collaboration's tool
	3. Ergebnisdarstellung Qualität der Studien: The percentages of low risk ofselection bias, performance bias and the detection bias wereless than 50% according to the description of each study. Thepercentages of low risk of bias of incomplete outcome data,selective reporting and other bias were all more than 50%.The outcome of risk of bias graph showed that there was lowrisk of bias in this meta-analysis. • The overall efficacy of tenofovir based combination therapy was not significantly better with regard to the rates of virological response, ALT normalization and HBeAg loss compared with TDF monotherapy through 48-week treatment. • Additionally, subgroup analysis showed that no significant difference was determined as TDF group compared to TDF-based group at 48 weeks, in terms of rates of HBV DNA undetectability, ALT normalization and HBeAg loss in the treatment of LAM-R patients with prior failure of LAM monotherapy. • Moreover, the rates of HBV DNA suppression between groups were similar through 24 or 48 weeks of treatment in LAM-R patients with prior failure of LAM/ADV therapy.
	4. Fazit der Autoren: In conclusion, our meta-analysis results demonstrated that TDF monotherapy was as effective as TDF-based combination therapy in maintaining viral suppression in LAM-R patients with prior failure of LAM and a suboptimal responseto (or failure of) ADV therapy. Nonetheless, more double blinding and large-scale randomized control trials should be carried out to remedy aboveshortcomings, and to elucidate the relationship between theantiviral efficacy of TDF and ADV-R mutations in

	treatmentfor CHB patients with LAM-R HBV infection. 5. Kommentare zum Review • among tenofovir-based combination therapies,three studies used TDF-LAM, one used TDF-FTC and one used TDF-NA which might affect the consistency of the results • rate of safety could not be conducted because only two of the enrolled studies provided the data which were not in the same period of time
Wu X et al., 2016 [28]. Potential effects of telbivudine and entecavir on renal function: a systematic review and meta-analysis	1. Fragestellung to assess the potential effects of telbivudine (LdT) and entecavir (ETV) on renal function in patients with chronic hepatitis B (CHB), we performed a meta-analysis of the relevant data available on these agents to evaluate their effects on the estimated glomerular filtration rate (eGFR) during treatment.
	2. Methodik Population: CHB patients Intervention/Komparator: The study interventions were at least one of LdT and ETV Endpunkte: change in eGFR from baseline to 1 year after the start of treatment; factors associated with renal damage Recherche: PubMed, EMBASE, Scopus, CNKI (China National Knowledge Infrastructure), Cochrane Library, and WanFang databases were searched for relevant articles appearing in the literature up to July 1, 2015. Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 6 studies (1960 CHB patients) with 1-year eGFR outcomes were retrieved and analyzed. Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien:</u>

	 **Fig. 5** Risk of bias in the 6 studies included in the analysis • Generally, the results of the 6 studies analyzed showed that eGFR was improved after LdT treatment, but was decreased after ETV treatment. Using a fixed-effects approach, the change in eGFR was found to be significantly different between LdT and ETV treatment (Z = 3.64; P = 0.0003). • Whereas the eGFR was slightly decreased with ETV compared with baseline (−1.45 mL/min/1.73 m2), the eGFR was improved with LdT (2.99 mL/min/1.73 m2) after 1 year of treatment. • An overall test of effect in the meta-analysis showed that the eGFR in LdT-treated patients was significantly improved after 1-year of treatment (Z = 3.71; P = 0.0002).
	4. Fazit der Autoren: In conclusion, this meta-analysis provides evidence that LdT has a renal protective effect whereas ETV does not. However, the mechanism of the renal protective effect of LdT is not clear, and nor is it clear whether the benefits of LdT on renal function outweigh its lower barrier to resistance in specific clinical situations. Additionally, when and how the dosage of ETV should be modified during long-term treatment in patients with renal impairment, especially those with co-existing hypertension and diabetes, are other unanswered questions. These questions need to be addressed in well-designed clinical trials to explore and thus potentially modify the existing guideline recommendations.
Singal AK et al., 2013 [21]. Meta-analysis: the impact of oral anti-viral	1. Fragestellung to determine the efficacy of oral anti-viral agents in reducing HCC risk in relationship with other known factors.
	2. Methodik Population: patient population – adult patients with chronic HBV

agents on the incidence of hepatocellular carcinoma in chronic hepatitis B	(treatment naive as well as treatment experienced) Intervention / Komparator: single or combination oral nucleos(t)ide analogues Endpunkte: incidence of HCC during follow-up Recherche: Electronic databases (Medline, Cochrane reviews and EMBASE, ISI Web of science) from 1995 to 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 49 studies Qualitätsbewertung der Studien: based on the following binomial parameters: randomisation, blinding, control group or not, prospective or retrospective, defined inclusion criteria, defined intervention, defined outcome, similar baseline characteristics, intention-to-treat analysis and follow-up on drop outs or deaths. Each parameter was given a numerical score of 0 or 1 with an overall quality score ranging from 0 to 10. Studies with a quality score of <5 were rated as poor, while those ≥5 were rated as high.
	3. Ergebnisdarstellung <u>Qualität der Studien:</u> • 17 Studies with Lamivudine = diese Studien hatten einen durschnittlichen Score von 5,3. • 16 Studies with Adefovir = diese Studien hatten einen durchschnittlichen Score von 5,7. • 10 Studies with ETV, TBV, TDF = diese Studien hatten einen durchschnittlichen Score von 6,8. • 6 Studies of LAM with an untreated control group: diese Studien hatten einen durchschnittlichen Score zwischen 5-10 Pooled homogeneous data from six studies showed lamivudine (LAM) treatment (n = 3306) to reduce HCC risk by 51% compared with no treatment (n = 3585) (3.3 vs. 9.7 per 100 person years, P < 0.0001). Pooled data from 49 studies (23 with LAM; 16 with adefovir; and 10 with entecavir, tenofovir or telbivudine) of 10 025 treated patients showed HCC incidence of 1.3 per 100 person years, independent of the agent used. Patient age >50 years and hepatitis B virus-DNA detectability at HCC diagnosis increased risk of HCC by twofold with a 10-fold higher risk among patients with cirrhosis compared with chronic hepatitis. Meta-regression showed patient age, study location (Eastern vs. Western) and type of study (randomized or not) contributed to heterogeneity.
	4. Fazit der Autoren: In summary, our meta-analysis demonstrates that LAM therapy is associated with a 56% reduction in the incidence of HCC among chronic HBV patients compared with no treatment. In addition, among patients receiving an oral anti-viral agent, subject age, the presence of cirrhosis and method of HCC

	detection all significantly impact the incidence of HCC. Finally, although we did not observe a difference in the incidence of HCC based on the individual agent prescribed, additional prospective studies are needed that control for the confounders of subject age, gender, cirrhosis and HCC detection method to better estimate the risk of developing HCC among those receiving the newer anti-viral agents. 5. Kommentare zum Review • Substantial heterogeneity among the studies when pooled together. Our meta-regression suggests that the heterogeneity was, in part, due to age of the patient at enrolment, study design and study location (Eastern or Western hemisphere)
Lok AS et al., 2016 [19]. Antiviral Therapy for Chronic Hepatitis B Viral Infection in Adults: A Systematic Review and Meta-Analysis	1. Fragestellung to help providers determine when treatment should be initiated, which medication is most appropriate, and when treatment can safely be stopped.
	2. Methodik Population: adults ≥18 years old diagnosed with chronic HBV infection who received antiviral therapy Intervention / Komparator: siehe supplementary table 1 im Anhang Endpunkt: siehe supplementary table 1 im Anhang Recherche: Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus from early 1988 to September 16, 2014. Anzahl eingeschlossene Studien/Patienten (Gesamt): 73 studies were included Qualitätsbewertung der Studien: Cochrane Risk of Bias assessment tool and modified Newcastle-Ottawa Scale to assess the risk of bias in RCTs and observational studies, respectively. 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 Qualität der Studien: Risk of bias assessment for RCTs was low to moderate as two of the included RCTs reported the randomization method, two reported use of allocation concealment, and six reported

	the blinding method used. Most of the observational studies were at high risk of bias due to lack of clear description of the selection process of the population and inadequate exposure and outcome ascertainment. Siehe für weitere Informationen auch supplementary table 4 im Anhang. *Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic Hepatitis B Infection:* Among 42 studies comparing antiviral therapy versus control in 62,731 patients, 16 studies compared IFN versus no treatment, 16 studies compared lamivudine versus no treatment, seven studies compared entecavir versus no treatment, one study each compared telbivudine and tenofovir versus placebo, and three studies compared a variety of oral antiviral versus no treatment. • In seven RCTs involving 3463 subjects with a mean follow-up of 28 months, antiviral therapy versus control significantly decreased the overall risk of decompensated liver disease (one RCT, RR= 0.4, 95% CI 0.3-0.7) and cirrhosis (one RCT, RR= 0.4, 95% CI 0.2-0.8). No significant differences were found in all-cause mortality or HCC incidence. • One RCT examined adverse events including death and decompensation as outcomes, but no events were observed in either the intervention or the control group. • In 35 observational studies involving 59,201 patients with a mean follow-up of 60 months, meta-analysis showed that antiviral therapy versus control decreased the risk of HCC (23 studies, RR= 0.5, 95% CI 0.4-0.7, I2 = 87.4%), all-cause mortality (23 studies, RR= 0.6, 95% CI 0.5-0.8, I2 = 92.3%), and cirrhosis (four studies, RR= 0.6, 95% CI 0.4-0.8, I2 = 0%) but did not significantly reduce the risk of decompensated liver disease (six studies, RR= 0.7, 95% CI 0.3-1.9, I2 = 96.5%) when compared to untreated controls. *Effectiveness of antiviral therapy compared to control in the subgroup with stable chronic hepatitis B:* • 21 studies that enrolled patients with stable chronic hepatitis B, 0%-91% of the 54,719 patients included had compensated cirrhosis. Reduction in risk of decompensated cirrhosis was shown in only one RCT and reduction in HCC in 11 observational studies. No studies demonstrated reduction in allcause mortality *Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection and Compensated Cirrhosis:* • In one RCT enrolling 222 patients with cirrhosis and a follow-up of 53 months, lamivudine versus control reduced all-cause mortality (RR= 0.1, 95% CI 0.1-0.3, moderatequality evidence). • In 10 observational studies involving patients with compensated cirrhosis (mean follow-up 60 months), antiviral therapy decreased

	the risk of HCC (10 studies, RR= 0.6, 95% CI 0.4-0.8, I2 = 36.3%), decompensated liver disease (two studies, RR = 0.5, 95% CI 0.2-0.9, I2 = 67.2%), and all-cause mortality (three studies, RR = 0.5, 95% CI 0.4-0.6, I2 = 0%). • In five observational studies with a mean follow-up of 84 months, IFN-a compared to no treatment significantly decreased the risk of HCC (five studies, RR = 0.6, 95% CI 0.4-0.9, I2 =0%) but not of all-cause mortality or decompensated liver disease. • In four observational studies with a mean follow-up of 45 months, lamivudine versus no treatment significantly reduced the risk of HCC (four studies, RR = 0.6, 95% CI 0.4-0.96, I2 = 49.9%), allcause mortality (one study, RR = 0.4, 95% CI 0.3-0.6), and decompensated liver disease (one study, RR = 0.3, 95% CI 0.3-0.5). • In one cohort study of 1980 patients with cirrhosis followed for a mean of 52 months, entecavir versus control reduced the risk of HCC (RR = 0.3, 95% CI 0.1-0.5) and death (RR = 0.6, 95% CI 0.3-0.98). *Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection and Decompensated Cirrhosis:* • In two observational studies with follow-up of 29 months, lamivudine versus control reduced all-cause mortality (two studies, RR = 0.5, 95% CI 0.3-0.8, I2 = 0%). *Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection Experiencing Acute on Chronic Liver Failure:* • In one RCT involving 26 patients followed for 1 year, tenofovir reduced all-cause mortality (RR = 0.5, 95% CI 0.3-0.99, moderate-quality evidence). • In four observational studies with a mean follow-up of 26 months, antiviral therapy versus no therapy reduced allcause mortality (RR = 0.7, 95% CI 0.6-0.8, I2 = 5.4%). Similarly, reduced mortality was also found in studies evaluating individual therapies including lamivudine (RR = 0.8, 95% CI 0.7-0.9, I2 = 50.2%), entecavir (RR = 0.7, 95% CI 0.6-0.8, I2 = 0%), and telbivudine (RR =0.4, 95% CI 0.2-0.9). *Effectiveness of Antiviral Therapy Compared to Control in Patients With Chronic HBV Infection With Severe Acute Exacerbations:* • In three observational studies with more than 12-month mean follow-up, meta-analysis of antiviral therapy versus control showed no statistically significant reduction in allcause mortality (RR = 0.9, 95% CI 0.5-1.5, I2 = 54.5%), which was consistent with studies evaluating the effect of individual agents: lamivudine (RR = 0.5, 95% CI 0.2-1.7) and entecavir (RR = 0.9, 95% CI 0.5-1.9, I2 =

	71.3%). *Head-to-Head Studies Comparing Individual Antiviral Agents:* • We included eight RCTs enrolling 2318 patients and 10 observational studies enrolling 6737 patients that compared one antiviral agent with another. • Only 1 study showed a significant difference in outcome with reduction in all-cause mortality in patients who received entecavir versus lamivudine (one study, RR 5 0.4, 95% CI 0.3-0.6, very low-quality evidence). • Four studies enrolled 607 patients with chronic HBV infection and decompensated cirrhosis (mean follow-up 28 months). Reduction in risk of HCC was observed in the RCT57 comparing entecavir versus adefovir (RR = 0.4, 95% CI 0.2-0.8), and reduction in all-cause mortality was observed in the cohort study comparing entecavir versus lamivudine (RR = 0.4, 95% CI 0.3-0.7) in patients who received entecavir. • Three cohort studies that enrolled 508 patients with acute on chronic liver failure and compared entecavir to lamivudine (mean follow-up 32 months) showed no significant effect on all-cause mortality. • Two cohort studies that compared entecavir versus lamivudine in 320 patients with severe acute exacerbation of chronic hepatitis B (mean follow-up 32 months) showed no significant effect on mortality. *Effectiveness of Antiviral Therapy in Patients With Immune-Tolerant Chronic HBV Infection:* • One RCT compared tenofovir (64 patients) to a combination of tenofovir and emtricitabine (62 patients) for 192 weeks. Although no long-term clinical outcomes were reported, tenofovir and emtricitabine versus tenofovir showed a statistically significant increase in viral suppression (RR = 1.4, 95% CI 1.1-1.8, moderate-quality evidence) but no statistically significant increase in HBeAg loss, HBeAg seroconversion, or HBsAg clearance. *Safety of Entecavir Compared to Tenofovir:* • Eleven studies (one RCT and 10 observational studies) compared entecavir versus tenofovir in 1300 patients with a mean follow-up of 18.6 months. • Meta-analysis of the studies included showed no statistically significant difference between entecavir and tenofovir in renal safety profiles or hypophosphatemia, but duration of observation was short. No studies reported on bone density. *Adding a Second Antiviral Agent Compared to Continuing Monotherapy (Entecavir or Tenofovir) in Patients With Chronic HBV Infection and*

	Persistent Viremia: • We were unable to identify comparative studies for this question. Uncontrolled studies and indirect evidence (Supporting Information) showed little to no benefit in adding a second antiviral agent compared to continuing monotherapy with entecavir or tenofovir
	4. Fazit der Autoren: Most of the current literature focuses on the immune active phases of chronic HBV infection; decision-making in other commonly encountered and challenging clinical settings depends on indirect evidence.
Zhang X et al., 2015 [32]. The efficacy and safety of entecavir in patients with chronic hepatitis B-associated Uver failure: a meta-analysis	1. Fragestellung to investigate the rescuing efficacy and safety of ETV in patients with CHB-associated tiver failure
	2. Methodik Population: patients with CHB-associated liver failure Intervention: ETV (0.5 mg/d) combined with routine comprehensive treatment Komparator: routine comprehensive treatment Endpunkte: • Primars endpoint: survival rate • Secondary endpoints: HBV DNA negative change rate, TBEL and PTA changes; safety Recherche: Pubmed, MEDLINE, EMBASE, Cochrane Library, the Chinese BioMedical Uterature (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Technological Journal of Database (VIP) and Wanfang databases for eligible articles published up to December 2013 without language and publication restrictions. Anzahl eingeschlossene Studien/Patienten (Gesamt): Six randomized controlled trials Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung <u>Qualität der Studien</u>: The overall quality of the studies included in this meta-analysis was suboptimal. Each ofthe six studies was a RCT, ofwhich four did not report how the allocation sequences were generated. Five studies did not report the methods of the allocation concealment, and one study took an open random allocation schedule. Five studies did not report the blinding of the study participants and personnel. Because different follow-up tünes and different outcomes were reported, often without full statistical details, it was not possible to meta-analyze all the data. • The overall analysis revealed FTV significantly improved survivat at

	4 weeks (RR: 1. 35; 95%CI: 1. 16, 1.57; p<0.0001) 8 weeks (RR= 1.33; 95% CI: 1.07, 1. 64; p =0.009), 12 weeks (RR= 1. 68; 95% CI: 1.24, 2. 28; p = 0.0008). • Pooled data also showed beneficial effects of antiviral therapy compared with control for HBV DNA negative change (RR = 5. 35; 95% CI: 2. 06, 13. 88; p = 0. 0006), TBIL and PTA jmprovement (TBIL: MD= -69.36; 95% CI: -134.37, -4.36; p =0.04 / PTA; MD = 16.26; 95% CI: 8. 59, 23.94; p < 0.0001). • No adverse effect was identified in the examined studies.
	4. Fazit der Autoren: Our results showed that antiviral therapy with ETV improved the short-term survival of patients with CHB-associated tiver failure. In addition, ETV was well tolerated during the treatment period. Further studies are still needed to strengthen these results. 5. Kommentare zum Review • All selected studies originated froca inainland China and were published in Chinese! (Übertragbarkeit Versorgungskontext)
Bedre RH et al., 2016 [1]. 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. <u>Hinweis</u>: 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 <u>Wirksamkeit</u>:

	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 [3]. 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. Kommentare zum Review • Funding: Novartis Pharma AG • Die Limitationen von Netzwerkmetaanalysen sind zu beachten
Chen L et al., 2016 [5]. Efficacy of Tenofovir-Based Combination Therapy versus Tenofovir Monotherapy in Chronic Hepatitis B	1. Fragestellung 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

Patients Presenting with Suboptimal Responses to Pretreatment: A Meta-Analysis	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 <u>Qualität der Studien</u>: 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. Kommentare zum Review • Wenig Studien

	• Einige Studien keine RCTs inkl. retrospektivem Design
Liang X et al., 2016 [17]. 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 Siehe auch: **Wang H et al., 2015 [23]**	1. Fragestellung 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 Qualität der Studien: 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. Kommentare zum Review • 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 [34]. A Meta-Analysis Comparing the Efficacy of Entecavir and Tenofovir for the Treatment of Chronic Hepatitis B	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

Infection	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 Qualität de Studien: • Bewertet anhand NOS: N= 9 Studien mit Score ≥6 • Bewertet anhand Jadad-Scale: N= 2 Studien mit Score 3 und 5 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 [15]. Pegylated interferon alfa for chronic hepatitis B: systematic review and meta-analysis	1. Fragestellung 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 <u>Qualität der Studien:</u>

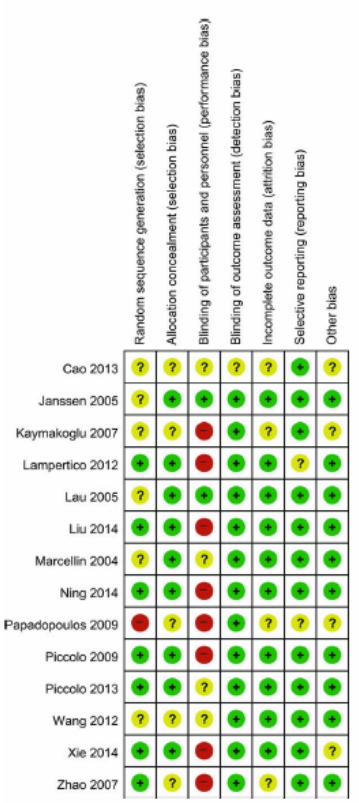


Fig. 2 Judgments of each risk of bias item for each included study.

Outcome evaluation: PEG-IFNa vs PEG-IFNa + LAM

HBeAg-positive patients:

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.

HBeAg-negative patients:

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** HBeAg-negative patients Virological and biochemical responses were reported by one study. **Outcome evaluation: PEG vs conventional IFNa** HBeAg-positive patients: 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. Kommentare zum Review • Unterschiedliche Dosierungen von PEG-IFNa2a and PEG-IFNa2b in den unterschiedlichen Studien
Zeng T et al., 2014 [30]. Entecavir Plus Adefovir Combination Therapy Versus Lamivudine Add-On Adefovir for Lamivudine-Resistant Chronic Hepatitis B:	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)

A Meta-Analysis	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 [29]. The Efficacy and Safety of Entecavir and Interferon Combination Therapy for Chronic Hepatitis B Virus Infection: A Meta-Analysis	1. Fragestellung 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 Qualität der Studien: 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. Kommentare zum Review • 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 [18]. Efficacy and resistance in de novo combination lamivudine and adefovir dipivoxil therapy versus entecavir monotherapy for the treatment-naive patients with chronic hepatitis B: a meta-analysis	1. Fragestellung 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 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 [14]. 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 Studienqualität: 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. Kommentare zum Review • Majority of included studies were non-RCTs

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 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 Jadad 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. Kommentare zum Review • 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	1. Fragestellung 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

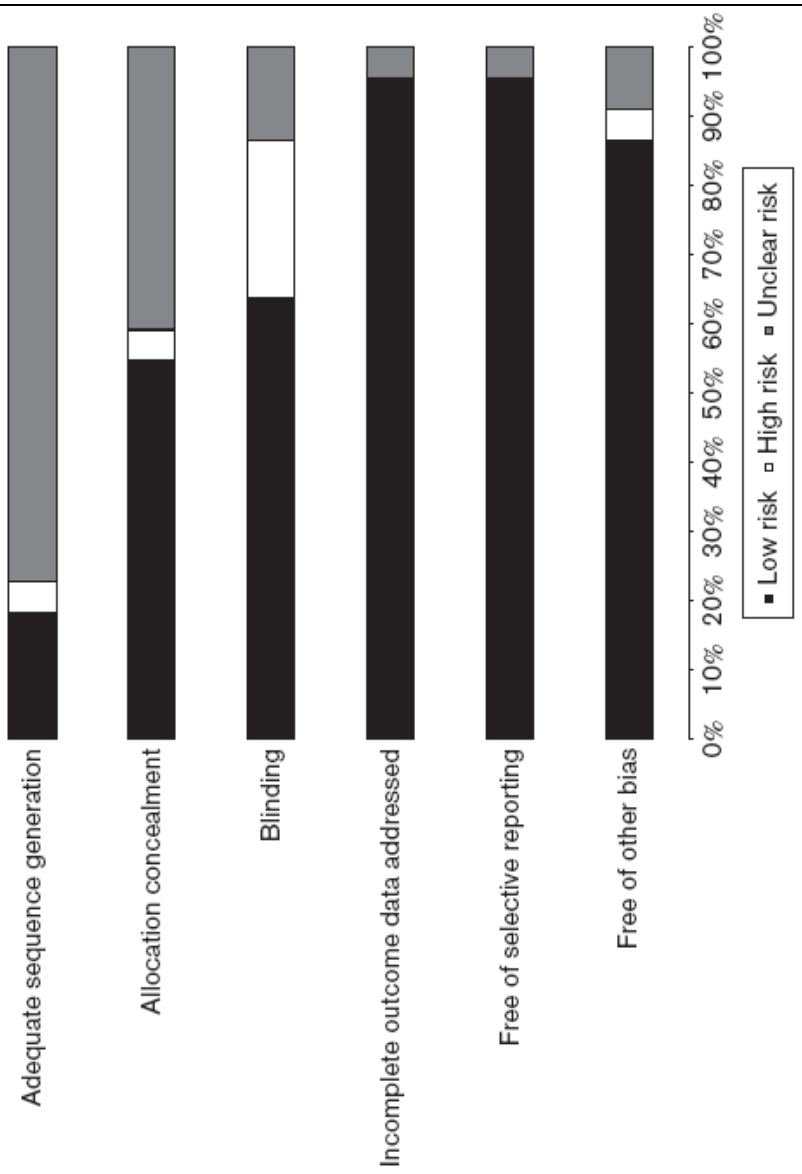
systematic review and meta-analysis	Endpunkte: Undetectable HBV-DNA rate,virologic breakthrough rate, ALT normalization rate, HBeAgloss rate,HBeAg seroconversion rate, and adverse reaction rate Suchzeitraum (Aktualität der Recherche): bis 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 Studien (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. Kommentare zum Review • Some studies had a small sample size and were not RCTs
Wiens A et al., 2013 [26]. Comparative Efficacy of Oral Nucleoside or Nucleotide Analog Monotherapy	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

Used in Chronic Hepatitis B: A Mixed-Treatment Comparison Meta-analysis	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. Kommentare zum Review • 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.
Zhang X et al., 2014 [31]. Entecavir versus Lamivudine therapy for patients with chronic hepatitis B-associated	1. Fragestellung to compare the efficacy and safety of ETV and LAM in patients with chronic hepatitis B (CHB)-associated liver failure.
	2. Methodik Population: patients with CHB-associated liver failure

liver failure: a meta-analysis	Intervention: Entecavir Komparator: Lamivudine Endpunkte: • Primäre Endpunkte: Survival rate • Sekundäre Endpunkte: TBIL, PTA changes and HBV DNA negative change, safety Suchzeitraum (Aktualität der Recherche): PubMed, EMBASE, Scopus, Web of science, Cochrane Library, Chinese BioMedical Literature (CBM), Chinese National Knowledge Infrastructure (CNKI), Chinese Technological Journal of Database (VIP) and Wanfang databases until January 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): Four randomized controlled trials and nine retrospective cohort studies comprising a total of 1549 patients. Qualitätsbewertung der Studien: Cochrane risk of bias tool (RCTs) / For observational cohort studies, methodological quality was assessed using the Newcastle-Ottawa Scale (NOS)
	3. Ergebnisdarstellung Studienqualität: The overall quality of included RCTs in this meta-analysis was suboptimal. None of four RCTs reported how the allocation sequences were generated. Three studies did not report the methods of allocation concealment, and one study (18) took an open random allocation schedule. None of the trials referred to blinding method. Quality of included observational cohort studies was assessed, and each of the studies had at least six stars. Two studies did not describe the comparability of ETV and LAM groups. One study recruited hepatitis B e antigen (HBeAg) negative patients with ACLF but not HBeAg positive patients, thus limiting the representative capacity of this study. • Overall analysis revealed comparable survival rates between patients received ETV and those received LAM. • After 24 weeks of treatment, patients treated with ETV had a significantly lower TBIL levels (MD = -37.34, 95% CI [-63.57, -11.11], P = 0.005), higher PTA levels (MD = 11.10, 95% CI [2.47, 19.73], P = 0.01) and higher HBV DNA negative rates (RR = 2.76, 95% CI [1.69, 4.51], P < 0.0001) than those treated with LAM. • In addition, no drug related adverse effects were observed in the two treatment groups
	4. Fazit der Autoren: ETV and LAM treatments had similar effects to

	improve 24 weeks survival rate of patients with CHB-associated liver failure, but ETV was associated with greater clinical improvement. Both drugs were tolerated well during the treatment. It is suggested to perform further studies to verify the results
Govan L et al., 2015 [8]. 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

- For HBeAg-positive patients: 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.
Jonas MM et al., 2016 [13]. Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis	1. Fragestellung: 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

Terrault NA et al.,	Fragestellung/Zielsetzung:

2016 [22]. **American Association for the Study of Liver Diseases (AASLD)** AASLD guidelines for treatment of chronic hepatitis B.	1. Should adults with immune active CHB be treated with antiviral therapy to decrease liverrelated complications? 2. Should adults with immune-tolerant infection be treated with antiviral therapy to decrease liverrelated complications? 3. Should antiviral therapy be discontinued in hepatitis B e antigen (HBeAg)-positive persons who have developed HBeAg seroconversion on therapy? 4. Should antiviral therapy be discontinued in persons with HBeAg-negative infection with sustained HBV DNA suppression on therapy? 5. In HBV-monoinfected persons, does entecavir therapy, when compared to tenofovir therapy, have a different impact on renal and bone health? 6. Is there a benefit to adding a second antiviral agent in persons with persistent low levels of viremia while being treated with either tenofovir or entecavir? 7. Should persons with compensated cirrhosis and low levels of viremia be treated with antiviral agents? 8. Should pregnant women who are hepatitis B surface antigen (HBsAg) positive with high viral load receive antiviral treatment in the third trimester to prevent perinatal transmission of HBV? 9. Should children with HBeAg-positive CHB be treated with antiviral therapy to decrease liverrelated complications?
	Methodik Grundlage der Leitlinie Multiple systematic reviews of the literature were conducted to support the recommendations in this practice guideline. An enhanced understanding of this guideline will be obtained by reading the applicable portions of the systematic reviews. *Kommentare zur Leitlinie*: this guideline was developed in compliance with the Institute of Medicine standards for trustworthy practice guidelines and uses the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach (siehe weitere Details in der LL unter Punkt *''Methods of Guideline Development''*
	Empfehlungen <u>Treatment of Persons With Immune-Active CHB</u> Recommendations 1A. The AASLD recommends antiviral therapy for adults with immune-active CHB (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications. *Quality/Certainty of Evidence: Moderate / Strength of Recommendation: Strong* 1B. The AASLD recommends Peg-IFN, entecavir, or tenofovir as preferred

	initial therapy for adults with immune-active CHB. *Quality/Certainly of Evidence: Low / Strength of Recommendation: Strong* Treatment of Adults With Immune-Tolerant CHB Recommendations 2A. The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB. *Quality/Certainly of Evidence: Moderate / Strength of Recommendation: Strong* 2B. The AASLD suggests that ALT levels be tested at least every 6 months for adults with immunetolerant CHB to monitor for potential transition to immune-active or -inactive CHB. *Quality/Certainly of Evidence: Very low / Strength of Recommendation: Conditional* 2C. The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy showing significant necroinflammation or fibrosis. *Quality/Certainly of Evidence: Very low / Strength of Recommendation: Conditional* Treatment of HBeAg Positive Immune-Active Chronic Hepatitis Persons Who Seroconvert to Anti-HBe on NA Therapy Recommendations 3A. The AASLD suggests that HBeAg-positive adults without cirrhosis with CHB who seroconvert to anti-HBe on therapy discontinue NAs after a period of treatment consolidation. *Quality/Certainty of Evidence: Very Low / Strength of Recommendation: Conditional* 3B. The AASLD suggests indefinite antiviral therapy for HBeAg-positive adults with cirrhosis with CHB who seroconvert to anti-HBe on NA therapy, based on concerns for potential clinical decompensation and death, unless there is a strong competing rationale for treatment discontinuation. *Quality/Certainty of Evidence: Very Low / Strength of Recommendation: Conditional* Management of Persons With Persistent Low-Level Viremia on NA Therapy Recommendations 6A. The AASLD suggests that persons with persistent low-level viremia (<2,000 IU/mL) on entecavir or tenofovir monotherapy continue monotherapy, regardless of ALT. *Quality/Certainty of Evidence: Very Low / Strength of Recommendation:*

	Conditional 6B. The AASLD suggests one of two strategies in persons with virological breakthrough on entecavir or tenofovir monotherapy: either switch to another antiviral monotherapy with high barrier to resistance or add a second antiviral drug that lacks crossresistance. *Quality/Certainty of Evidence: Very Low / Strength of Recommendation: Conditional* <u>Treatment of CHB in Children</u> Recommendations 9A. The AASLD suggests antiviral therapy in HBeAgpositive children (ages 2 to <18 years) with both elevated ALT and measurable HBV DNA levels, with the goal of achieving sustained HBeAg *seroconversion.* *Quality/Certainty of Evidence: Moderate / Strength of Recommendation: Conditional* 9B. The AASLD recommends against use of antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with persistently normal ALT, regardless of HBV DNA level. *Quality/Certainty of Evidence: Very Low / Strength of Recommendation: Strong*
Brook G et al., 2016 [2]. United Kingdom National Guideline on the Management of the viral hepatitides A, B and C 2015	Fragestellung/Zielsetzung: to help improve the sexual health of individuals attending sexual health clinics by encouraging high standards of care. The guideline offers recommendations on best practice regarding viral hepatitis for both men and women, including adolescents.
	Methodik Grundlage der Leitlinie This guideline is an update of a previous version published in 2008. In this version, we have significantly changed the sections on management of hepatitis B and C in line with new evidence and national guidelines, including those produced by NICE; other sections have been updated to reflect new evidence and practice. LoE/GoR: The recommendations/evidence are graded using the GRADE system
	Empfehlungen <u>3.8.4 Treatment of chronic infection</u> • Arrange screening for hepatitis C, hepatitis D and hepatitis A immunity (1D). • Vaccinate against hepatitis A if non-immune (1D).

	• Refer all HBsAgþve patients to a specialist experienced in the management of viral hepatitis (1D). • The decision to treat depends on pattern of disease, HBV DNA level and presence or absence of significant necro-inflammation and hepatic fibrosis. Treatment is usually given to adults with an HBV DNA >2000 IU/ml with evidence of necro-inflammation and/or fibrosis. • Treatment options are tenofovir, entecavir or pegylated interferon (1A). Treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer. • All patients should have an HIV test prior to starting HBV therapy because of the similar risks of acquisition, the different treatment strategies required in HIV co-infection and the significant risk of antiretroviral-resistant HIV developing if lamivudine, tenofovir or entecavir are used as monotherapy (1A). • Lamivudine, emtricitabine and tenofovir will suppress hepatitis B viral replication during therapy of HIV, and will prevent HBV-associated liver damage if given as part of triple ART (1B). • Lamivudine and emtricitabine should only be given to HIVþ patients in combination with tenofovir as part of highly active antiretroviral therapy (HAART) because of the rapid high rate of resistancethat occurs to these drugs if given as the only HBV-active agent (IA). Entecavir should not beused in HIVþ patients without adequately suppressed HIV as it causes the M184V-(lamivudine/emtricitabine) resistant mutation. • Active surveillance by a hepatologist of patients with significant fibrosis/cirrhosis for hepatocellular carcinoma (HCC) with ultrasound and alpha-feto proteinis recommended 6–12 monthly (1B). • In the context of HBV, there is a high risk of HCC development in some groups of non-cirrhotic patients. This includes African patients over the age of 20, Asian males over 40, Asian females over 50 and patients with a family history of HCC. HBVinfected patients meeting these criteria should be offered HCC screening in the hepatology clinic.
EASL, 2017 [6]. 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. The objective of this manuscript is to update the recommendations for the optimal management of HBV infection. In order to keep the manuscript and particularly the reference list within a reasonable length, only references

published after 2012 have been considered, since the readers can find the older supportive references in the 2012 EASL HBV CPGs.

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.

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

<u>NAs for naïve CHB patients</u>

- The long-term administration of a potent NA with high barrier to resistance is the treatment of choice regardless of the severity of liver disease (Evidence level I, grade of recommendation 1).
- The preferred regimens are ETV, TDF and TAF as monotherapies (Evidence level I, grade of recommendation 1).
- LAM, ADV and TBV are not recommended in the treatment of CHB (Evidence level I, grade of recommendation 1).

Monitoring of patients treated with ETV, TDF or TAF
Recommendations

- All patients treated with NA should be followed with periodical assessments including ALT and serum HBV DNA (Evidence level I, grade of recommendation 1).
- Patients at risk of renal disease treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodical renal monitoring including at least estimated glomerular filtration rate (eGFR) and serum phosphate levels (Evidence level II-2, grade of recommendation 1).
- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure (Evidence level II-2/I, grade of recommendation 1).

<u>Long-term outcome during NA</u>

- Patients under effective long-term NA therapy should remain under

	surveillance for HCC (Evidence level II-2, grade of recommendation 1). • HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores at the onset of NA therapy (Evidence level II-2, grade of recommendation 1). <u>NA discontinuation</u> • NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1). • NAs can be discontinued in non-cirrhotic HBeAgpositive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2). • Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved longterm (P3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2). <u>Management of patients with NA failure</u> • Prevention of resistance should rely on the use of first line therapy with high barrier to resistance NAs (Evidence level I, grade of recommendation 1). • Compliance to NA therapy should be checked in all cases of treatment failure (Evidence level II-1, grade of recommendation 1). • Management of treatment failure should be based on NAs cross-resistance data (Evidence level II-2, grade of recommendation 1). • Treatment adaptation should be performed as soon as virologic failure under NAs is confirmed (Evidence level II-1, grade of recommendation 1). <u>PegIFNa monotherapy for CHB patients</u> • PegIFNa can be considered as an initial treatment option for patients with mild to moderate HBeAgpositive or -negative CHB (Evidence level I, grade of recommendation 2). • The standard duration of PegIFNa therapy is 48 weeks (Evidence level I, grade of recommendation 1). • The extension of the duration of PegIFNa therapy beyond week 48 may be beneficial in selected HBeAgnegative CHB patients (Evidence level II-1, grade of recommendation 2).

Monitoring of patients treated with PegIFNα
Recommendations

- All CHB patients treated with PegIFNα should be followed with periodical assessments of at least full blood count, ALT, TSH, serum HBV DNA and HBsAg levels (Evidence level I/II-2, grade of recommendation 1).
- HBeAg-positive CHB patients treated with PegIFNα should be also followed with periodical assessments of HBeAg and anti-HBe (Evidence level I, grade of recommendation 1).
- CHB patients with virological response after PegIFNα therapy should remain under long-term follow-up because of the risk of relapse (Evidence level II-2, grade of recommendation 1).

Predictors of PegIFNα response and stopping rules
Recommendations

- In HBeAg-positive CHB patients, HBsAg levels >20,000 IU/ml for genotype B and C, or no decline of HBsAg levels for genotype A and D, at 12 weeks of PegIFNα therapy are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 2).
- In HBeAg-positive CHB patients with genotype A-D, HBsAg levels >20,000 IU/ml at 24 weeks of PegIFNα therapy are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 2).
- In HBeAg-negative CHB patients with genotype D, a combination of no decrease in HBsAg levels and $<2\ \log_{10}$ IU/ml reduction in serum HBV DNA levels at 12 weeks of PegIFNα therapy predicts no response and should be used as PegIFNα stopping rules (Evidence level II-2, grade of recommendation 1).

Long-term outcome after PegIFNa

- Patients with sustained responses after PegIFNa therapy and high baseline HCC risk should remain under surveillance for HCC even if they achieve HBsAg loss (Evidence level III, grade of recommendation 1).

Combination therapy for CHB: NA plus NA

- De novo combination therapy with two NAs with high barrier to resistance

	(ETV, TDF, TAF) is not recommended (Evidence level I, grade of recommendation 1). • In treatment-adherent patients with incomplete suppression of HBV replication reaching a plateau during either ETV or TDF/TAF long-term therapy, a switch to the other drug or combining both drugs may be considered (Evidence level III, grade of recommendation 2). <u>NA plus PegIFNa</u> • De novo combination of NA and PegIFNa is not recommended (Evidence level I, grade of recommendation 1). • In treatment naïve HBeAg-positive patients, short-term pretreatment with a NA before PegIFNa is not recommended (Evidence level II, grade of recommendation 1). • In long-term NA suppressed CHB patients, adding PegIFNa or switching to PegIFNa is not recommended (Evidence level II, grade of recommendation 1). <u>Treatment of patients with decompensated cirrhosis</u> • Patients with decompensated cirrhosis should be immediately treated with a NA with high barrier to resistance, irrespective of the level of HBV replication, and should be assessed for liver transplantation (Evidence level II-1, grade of recommendation 1). • PegIFNa is contraindicated in patients with decompensated cirrhosis (Evidence level II-1, grade of recommendation 1). • Patients should be closely monitored for tolerability of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction (Evidence level II-2, grade of recommendation 1).

Prevention of HBV recurrence after liver transplantation

Recommendations

- All patients on the transplant waiting list with HBV related liver disease should be treated with NA (Evidence level II, grade of recommendation 1).
- Combination of hepatitis B immunoglobulin (HBIG) and a potent NA is recommended after liver transplantation for the prevention of HBV recurrence (Evidence level II-1, grade of recommendation 1).
- Patients with a low risk of recurrence can discontinue HBIG but need continued monoprophylaxis with a potent NA (Evidence level II-1, grade of recommendation 2).
- HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA (Evidence level II-2, grade of recommendation 1).

Treatment in special patient groups with HBV infection

HIV co-infected patients

Recommendations

- All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count (Evidence level II-2, grade of recommendation 1).
- HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen (Evidence level I for TDF, II-1 for TAF, grade of recommendation 1).

	HDV co-infected patients **Recommendations** • PegIFNα for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease (Evidence level I, grade of recommendation 1). • In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1). • PegIFNα treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated (Evidence level II-2, grade of recommendation 2). *HCV co-infected patients* **Recommendations** • Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment (Evidence level II, grade of recommendation 1). • HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely (Evidence level II-2, grade of recommendation 2). • HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation (Evidence level II, grade of recommendation 1). **Children** • In children, the course of the disease is generally mild, and most of the children do not meet standard treatment indications. Thus, treatment should be considered with caution (Evidence level II-3, grade of recommendation 1). • In children or adolescents who meet treatment criteria, ETV, TDF, TAF, and PegIFNa can be used in this population (Evidence level II-2, grade of recommendation 2).
KASL, 2016 [16]. KASL clinical practice guidelines:	Fragestellung/Zielsetzung: 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

management of chronic hepatitis B	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).** <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 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)**
WHO, 2015 [27]. 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.

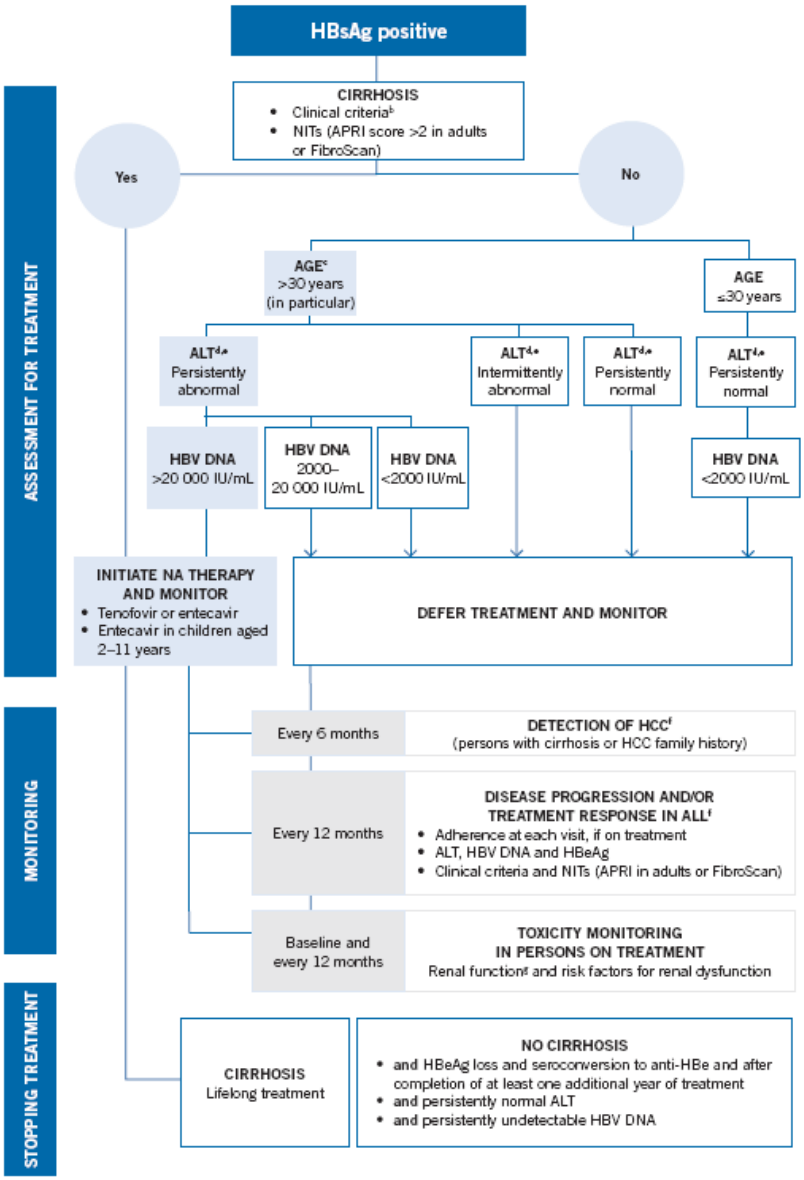
TABLE 2.2 Key domains considered in determining the strength of recommendations

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 tenofovir 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 [20]. 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.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 21.02.2018

#	Suchfrage
1	MeSH descriptor: [Hepatitis B] explode all trees
2	(chronic and (hepatitis or hepatitides) and b):ti,ab,kw (Word variations have been searched)
3	((hepatitis or hepatitides) and b):ti (Word variations have been searched)
4	(hbv or chb):ti,ab,kw (Word variations have been searched)
5	#1 or #2 or #3 or #4
6	#5 Publication Year from 2013 to 2018, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 21.02.2018

#	Suchfrage
1	hepatitis b[MeSH Terms]
2	((chronic[Title/Abstract]) AND ((hepatitis[Title/Abstract]) OR hepatitides[Title/Abstract])) AND b[Title/Abstract]
3	(((hepatitis[Title]) OR hepatitides[Title])) AND b[Title]
4	(hbv[Title/Abstract]) OR chb[Title/Abstract]
5	(#1 OR #2 OR #3 OR #4)
6	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	((((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	(#6 OR #7)
9	(#5 AND #8)
10	(#9) AND ("2013/02/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 21.02.2018

#	Suchfrage
1	hepatitis b[MeSH Terms]
2	((chronic[Title/Abstract]) AND ((hepatitis[Title/Abstract]) OR hepatitides[Title/Abstract])) AND b[Title/Abstract]
3	(((hepatitis[Title]) OR hepatitides[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 ("2013/02/01"[PDAT] : "3000"[PDAT])

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Anhang

Quelle: Lok AS et al., 2016 [19]

Supplemental Table 1: Inclusion and exclusion criteria for each key question

Definition of disease	Chronic HBV infection in adults ≥ 18 year old (detectable HBsAg in serum for >6 months)						
	Q1	Q2	Q3	Q4	Q5	Q6	Q7
Population	Immunoactive chronic HBV infection	Immunotolerant chronic HBV infection	Seroconverted from HBeAg to anti-HBe	HBeAg negative	HBV mono-infected population	HBV infection with persistent viral load under entecavir or tenofovir treatment	HBV infection and compensated cirrhosis with low level viremia (<2000 IU/ml)
Interventions and comparisons	Antiviral therapy		Stopped antiviral therapy compared to continued therapy		Entecavir compared to tenofovir	Adding 2nd antiviral drug compared to continued monotherapy	Antiviral therapy
Outcomes	Q1-2: Clinical outcomes: Cirrhosis, decompensated liver disease, HCC and death Intermediate outcomes (if evidence on clinical outcomes is limited or unavailable): HBsAg loss, HBeAg seroconversion and HBeAg loss Q3-4: Cirrhosis, decompensated liver disease, HCC, relapse (viral and clinical) and HBsAg loss Q5: Renal function, hypophosphatemia and bone density Q6: Resistance, flare/decompensation and HBeAg loss Q7: Clinical outcomes: Cirrhosis, decompensated liver disease, HCC and death						
Study design	RCT and controlled observational studies						
Exclusions	Acute HBV infection, children and pregnant women, HIV (+), HCV (+) or HDV (+) persons or other special populations such as hemodialysis, transplant, and treatment failure populations. Co treatment with steroids and uncontrolled studies.						

Supplemental Table 4: Summary of evidence:

Intervention (mean follow up)		Outcome	(No. of studies/ design)	Quality of the evidence (GRADE)	Relative effect (95% CI)
Question 1: Effectiveness of antiviral therapy in patients with immune active chronic HBV infection:					
Any Antiviral vs None (28 months for RCTs, 60 months for observational studies)		All-cause mortality	(4 RCTs)	⊕◯◯◯[1,2,4] VERY LOW	RR 0.45 (0.16 to 1.29)
		HCC	(3 RCTs)	⊕⊕⊕◯[4] MODERATE	RR 0.59 (0.32 to 1.11)
		Decompensated liver disease	(1 RCT)	⊕⊕⊕◯[1] MODERATE	RR 0.44 (0.29 to 0.68)
		Cirrhosis	(1 RCT)	⊕⊕⊕◯[1] MODERATE	RR 0.37 (0.19 to 0.71)
		All-cause mortality	(23 observational studies)	⊕◯◯◯[2] VERY LOW	RR 0.61 (0.46 to 0.81)
		HCC	(23 observational studies)	⊕◯◯◯[2] VERY LOW	RR 0.50 (0.0.35 to 0.73)
		Decompensated liver disease	(6 observational studies)	⊕◯◯◯[1,2,4] VERY LOW	RR 0.72 (0.28 to 1.89)
		Cirrhosis	(4 observational studies)	⊕◯◯◯[1] VERY LOW	RR 0.55 (0.38 to 0.78)
		HBsAg loss or seroconversion **	(11 RCTs)	⊕⊕⊕◯ MODERATE	RR 2.4 (1.2-4.9)
Q1.1: Antiviral therapy vs. no treatment, stratified based on the disease status:					
Compensated Cirrhosis	Any Antiviral vs. None	All-cause mortality	(3 observational studies)	⊕◯◯◯[1,2,4] VERY LOW	RR 0.48 (0.38 to 0.61)
		HCC	(10 observational studies)	⊕◯◯◯[1] VERY LOW	RR 0.57 (0.42 to 0.77)
		Decompensated liver disease	(2 observational studies)	⊕◯◯◯[2] VERY LOW	RR 0.45 (0.22 to 0.89)
Compensated Cirrhosis	IFN vs. None	All-cause mortality	(1 observational study)	⊕◯◯◯[1,2,4] VERY LOW	RR 0.71 (0.33 to 1.53)
		HCC	(5 observational studies)	⊕◯◯◯[1] VERY LOW	RR 0.64 (0.43 to 0.94)
		Decompensated liver disease	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.70 (0.33 to 1.48)
	Lamivudine vs. None	All-cause mortality	(1RCT)	⊕⊕⊕◯[1] MODERATE	RR 0.14 (0.06-0.34)
		All-cause mortality	(1 observational study)	⊕⊕◯◯ LOW	RR 0.44 (0.35 to 0.58)
		HCC	(4 observational studies)	⊕◯◯◯[2] VERY LOW	RR 0.61 (0.39 to 0.96)
		Decompensated liver disease	(1 observational study)	⊕⊕◯◯ LOW	RR 0.34 (0.25 to 0.46)
	Entecavir vs. None	All-cause mortality	(1 observational study)	⊕⊕◯◯ LOW	RR 0.55 (0.31 to 0.98)
		HCC	(1 observational study)	⊕⊕◯◯ LOW	RR 0.26 (0.13 to 0.53)
Decompensated	Lamivudine vs.	All-cause mortality	(2 observational	⊕◯◯◯[1]	RR 0.46

Cirrhosis	Control		studies)	VERY LOW	(0.27-0.76)
Acute on chronic liver failure	Any Antiviral vs. None	All-cause mortality	(1 RCT)	⊕⊕⊕◯[3] MODERATE	RR 0.51 (0.27 to 0.99)
		All-cause mortality	(4 observational studies)	⊕◯◯◯[3] VERY LOW	RR 0.72 (0.64 to 0.81)
	Lamivudine vs. None	All-cause mortality	(3 observational studies)	⊕⊕◯◯ LOW	RR 0.77 (0.68 to 0.88)
	Entecavir vs. None	All-cause mortality	(3 observational studies)	⊕⊕◯◯ LOW	RR 0.66 (0.55 to 0.79)
	Tenofovir vs. None	All-cause mortality	(1 RCT)	⊕⊕⊕◯[3] MODERATE	RR 0.51 (0.27 to 0.99)
	Telbivudine vs. None	All-cause mortality	(1 observational study)	⊕◯◯◯[3] VERY LOW	RR 0.37 (0.16 to 0.89)
Severe acute exacerbation of chronic hepatitis	Antiviral vs. Control	All-cause mortality	(3 observational study)	⊕◯◯◯[2,4] VERY LOW	RR 0.85 (0.48-1.5)
	Lamivudine vs. Control	All-cause mortality	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.51 (0.16-1.66)
	Entecavir vs. Control	All-cause mortality	(2 observational study)	⊕◯◯◯[2,4] VERY LOW	RR 0.94 (0.47-1.88)
Q1.2: Head to head studies comparing individual antiviral agents (stratified based on disease status):					
Compensated Cirrhosis	Adefovir vs. Lamivudine	HCC (48)	(1 RCT)	⊕⊕◯◯[4] LOW	RR 1.02 (0.26 to 3.97)
		All-cause mortality (96)	(1 RCT)	⊕⊕◯◯[4] LOW	RR 0.94 (0.14 to 6.24)
	Entecavir vs. Adefovir	All-cause mortality (96)	(1 RCT)	⊕⊕◯◯[4] LOW	RR 0.72 (0.45 to 1.15)
		Liver transplant (96)	(1 RCT)	⊕⊕◯◯[4] LOW	RR 3.34 (0.96 to 11.58)
		HCC (221)	(1 RCT)	⊕⊕⊕◯[3] MODERATE	RR 0.42 (0.22 to 0.8)
Compensated Cirrhosis	Entecavir vs. Lamivudine	All-cause mortality (48)	(1 observational study)	⊕◯◯◯[3] VERY LOW	RR 0.42 (0.31-0.57)
		HCC (12-60)	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 1.01 (0.8 to 1.27)
Compensated Cirrhosis	Entecavir vs. Telbivudine	HCC (156)	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.73 (0.31-1.72)
		All-cause mortality (160)	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.2 (0.01 to 4.11)
	Lamivudine vs. Tenofovir	All-cause mortality (26)	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.86 (0.27 to 2.68)
		HCC (26)	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 0.34 (0.07 to 1.64)
		Liver transplant (26)	(1 observational study)	⊕◯◯◯[4] VERY LOW	RR 1.03 (0.07 to 16.12)
	Telbivudine vs. Lamivudine	HCC (104)	(1 RCT)	⊕⊕⊕◯[3] MODERATE	RR 0.94 (0.51 to 1.74)
		All-cause mortality (120)	(1 RCT)	⊕⊕⊕◯[3] MODERATE	RR 0.68 (0.37 to 1.25)
Acute on chronic liver failure	Entecavir vs. Lamivudine	All-cause mortality (48)	(5 observational studies)	⊕◯◯◯[4] VERY LOW	RR 1.31 (0.72 to 2.39)

Question 2. Effectiveness of antiviral therapy in patients with immune-tolerant chronic HBV infection:				
Peg IFN + Adefovir vs. Control	HBeAg loss	(1 observational study)	⊕◯◯◯[1,3,4] VERY LOW	RR 20.29 (1.22 to 337.68)
	HBeAg seroconversion	(1 observational study)	⊕◯◯◯[1,3,4] VERY LOW	RR 41.77 (2.62 to 666.87)
Tenofovir + Emtricitabine vs. Tenofovir	HBV DNA suppression	(1 RCT)	⊕⊕⊕◯[3] MODERATE	RR 1.4 (1.1 to 1.8)
	HBeAg loss	(1 RCT)	⊕⊕◯◯[3,4] LOW	RR 0.3 (0.03- 2.2)
	HBeAg seroconversion	(1 RCT)	⊕⊕◯◯[3,4] LOW	RR 0.14 (0.01-2.8)
	HBsAg clearance	(1 RCT)	⊕⊕◯◯[3,4] LOW	RR 1 (0.3-3.9)
Question 3: Discontinuing vs. continuing antiviral therapy in HBeAg positive patients who seroconverted from HBeAg to anti-HBe:				
Stopped vs. Continued therapy	Recurrent viremia	(2 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 94.4 (13.3-670.7)
	ALT Flares□	(2 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 6.35 (0.36 to 112.47)
Question 5. Safety of entecavir compared to tenofovir:				
Tenofovir vs. Entecavir	Increase in Creatinine ≥ 0.5 mg/dl from baseline	(1 RCT)	⊕⊕◯◯[3,4] LOW	RR 1.96 (0.23 to 16.48)
	Confirmed phosphorus <2.0 mg/dl	(1 RCT)	⊕⊕◯◯[3,4] LOW	RR 1.5 (0.06 to 35.4)
	Increase in Creatinine of ≥ 0.5 mg/dl from baseline	(2 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 0.85 (0.07 to 9.979)
	Decrease of eGFR >20 ml/min	(2 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 0.93 (0.65 to 1.32)
	eGFR < 50-60 ml/min	(3 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 1.79 (0.85 to 3.80)
	Renal impairment	(1 observational study)	⊕◯◯◯[1,3,4] VERY LOW	RR 3.33 (0.14 to 79.9)
	Hypophosphatemia	(3 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 3.51 (0.99 to 12.40)
	Increase in creatinine kinase	(2 observational studies)	⊕◯◯◯[1,3,4] VERY LOW	RR 0.95 (0.12 to 7.59)

Footnotes:

1. Increased risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision

eGFR: estimated glomerular filtration rate

** Chou R, Dana T, Bougatsos C, Blazina I, Khangura J, Zakher B. Screening for hepatitis B virus infection in adolescents and adults: a systematic review to update the U.S. Preventive Services Task Force recommendation. Annals of Internal Medicine 2014;161:31-45.