Antiviral Therapy for Chronic Hepatitis B Virus Infection in Adults:

A Systematic Review and Meta-Analysis

Authors:

Anna SF Lok, MD[1]
aslok@umich.edu
Brian J. McMahon, MD[2]
bdm9@cdc.gov
Robert S. Brown, Jr., MD, MPH[3]
rsb2005@med.cornell.edu
John B. Wong, MD[4]
jwong@tuftsmedicalcenter.org
Ahmed T. Ahmed, MBBCh[5,6]
Ahmed.Ahmed1@mayo.edu
Wigdan Farah, MBBS[5,6]
Farah.Wigdan@mayo.edu
Jehad Almasri, M.D[5,6]
Almasri.Jehad@mayo.edu
Fares Alahdab, M.D[5,6]
Alahdab.Fares@mayo.edu
Khalid Benkhadra, M.D[5,6]
Benkhadra.Khalid@mayo.edu
Mohamed A. Mouchli, MD[7]
Mouchli.Mohamad@mayo.edu
Siddharth Singh, MD[8]
sis040@ucsd.edu
Essa A. Mohamed[8]
Mohamed.Essa@mayo.edu
Abd Moain Abu Dabrh, M.B., B.Ch[6]
AbuDabrh.AbdMoain@mayo.edu
Prokop J Larry, MLS[9]
Prokop.Larry@mayo.edu
Zhen Wang, Ph.D[5,6]
Wang.Zhen@mayo.edu
Mohammad Hassan Murad, MD, MPH [5,6,10]
Murad.Mohammad@mayo.edu

Khaled Mohammed, MBBCh, MPH[5,6,10]
Mohammed.khaled@mayo.edu

Affiliations:

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA

[2]Liver Diseases and Hepatitis Program, Alaska Native Tribal Health Consortium, AK, USA

[3]Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY, USA

[4]Division of Clinical Decision Making, Tufts Medical Center, Boston, Massachusetts, USA

[5]Evidence-Based Practice Research Program, Mayo Clinic, Rochester MN, USA

[6]Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA

[7]Division of Hospital Internal Medicine, Mayo clinic, Rochester, Minnesota, USA

[8]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

[9]Library Public Services, Mayo Clinic, Rochester, MN, USA

[10]Division of Preventive, Occupational and Aerospace Medicine, Mayo Clinic, Rochester, MN, USA

Keywords: cirrhosis, hepatocellular carcinoma, interferon, nucleos(t)ide analogues

Corresponding author: Anna S. Lok, MD, University of Michigan Health System, 1500 E Medical Center Drive, 3912 Taubman Center, SPC 5362, Ann Arbor, MI 48109. Email: aslok@umich.edu. Tel: 734-936-7511. Fax: 734-936-7392.

List of Abbreviations: Hepatitis B virus (HBV), American Association for the Study of Liver Diseases (AASLD), Randomized Controlled trials (RCTs), Interferon (IFN), Pegylated interferon (Peg IFN), Hepatocellular Carcinoma (HCC), Hepatitis B e antigen (HBeAg), Hepatitis B surface (HBsAg), Alanine Aminotransferase (ALT), Upper limit of normal (ULN), National Health and Nutrition Examination Surveys (NHANES).

Financial Support: This study was supported by a contract from the American Association for the Study of Liver Diseases to M Murad (Mayo Clinic).

Disclosures

Anna SF Lok has received research grants from Bristol-Myers Squibb and Gilead, and has served on advisory board of Gilead, GlaxoSmithKline and Merck.

Robert S Brown has received research grants from Gilead and has served as a consultant for Gilead.

B McMahon, J Wong, A Ahmed, W Farah, J Almasri, F Alahdab, K Benkhadra, M Mouchli, S Singh, E Mohamed, A Dabra, R Larry, Z Wang, M Murad, K Mohammed do not have any disclosures.

Abstract

Chronic hepatitis B virus (HBV) infection remains a significant global health problem. Evidence-based guidelines are needed to help providers determine when treatment should be initiated, which medication is most appropriate, and when treatment can safely be stopped. The American Association for the Study of Liver Diseases (AASLD) HBV guideline methodology and writing committees developed a protocol a priori for this systematic review. We searched multiple databases for randomized controlled trials (RCTs) and controlled observational studies that enrolled adults ≥18 years old diagnosed with chronic HBV infection who received antiviral therapy. Data extraction was done by pairs of independent reviewers. We included 73 studies; of which 59 (15 RCTs and 44 observational studies) reported clinical outcomes. Moderate quality evidence supported the effectiveness of antiviral therapy in patients with immune active chronic HBV infection in reducing the risk of cirrhosis, decompensated liver disease, and hepatocellular carcinoma. In immune-tolerant patients, moderate quality evidence supports improved intermediate outcomes with antiviral therapy. Only very low quality evidence informed the questions about discontinuing vs. continuing antiviral therapy in hepatitis B e antigen (HBeAg) positive patients who seroconverted from HBeAg to HBe antibody and about the safety of entecavir vs. tenofovir. Non-comparative and indirect evidence was available for questions about stopping vs. continuing antiviral therapy in HBeAg negative patients; monotherapy vs. adding a second agent in patients with persistent viremia during treatment; and the effectiveness of antivirals in compensated cirrhosis with low level viremia. ***Conclusion***: 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.

Introduction:

Chronic hepatitis B virus (HBV) infection remains a significant global health problem. Despite the availability of HBV vaccines for three decades, the global prevalence of chronic HBV infection has only declined slightly, from 4.2% in 1990 to 3.7% in 2005 (1). Worldwide, however, the absolute number of persons chronically infected has increased from 223 million in 1990 to 240 million in 2005. In the United States (US), based on 1999-2006 data from the National Health and Nutrition Examination Surveys (NHANES), the prevalence of chronic HBV infection was estimated to be 0.27% (2). However, NHANES under-sampled high prevalence groups, so when accounting for immigration from endemic countries, as many as 2.2 million US residents (instead of 730,000) may have chronic HBV infection (3).

The natural course of chronic HBV infection consists of four characteristic phases: immune tolerant, hepatitis B e antigen (HBeAg)-positive immune active, inactive, and HBeAg-negative immune active phases (4). The immune tolerant phase is characterized by the presence of HBeAg, normal alanine aminotransferase (ALT) levels and high levels of HBV DNA usually well over 20,000 IU/ml. The immune active phases, also called HBeAg-positive or HBeAg-negative chronic hepatitis, are characterized by intermittently or persistently elevated ALT with active hepatic inflammation and HBV DNA generally above 2,000 IU/ml. The inactive phase is characterized by absence of HBeAg and presence of hepatitis B e antibody (anti-HBe), normal ALT in the absence of other concomitant liver diseases, and undetectable or low levels of HBV DNA generally below 2,000 IU/ml. Although not all patients go through each phase and immune responses to HBV during each phase have not been fully characterized, this classification schema provides a useful framework when developing a management approach for chronic HBV infection.

Currently, seven medications are approved for treatment of chronic HBV infection: two formulations of interferon (IFN) - standard and pegylated (Peg IFN), and five nucleos(t)ide analogues: lamivudine, telbivudine, entecavir, adefovir and tenofovir. These medications suppress HBV replication and ameliorate hepatic inflammation but do not eradicate HBV. While IFN is given for a finite duration, nucleos(t)ide analogues are administered for many years and often for life. Long durations of treatment are associated with risks of adverse reactions, drug resistance, non-adherence, and increased cost. Therefore, there is a need to have evidence-based guidelines to help providers determine when treatment should be initiated, which medication is most appropriate, and when treatment can safely be stopped.

Methods:

The American Association for the Study of Liver Diseases (AASLD) HBV guideline methodology and writing committees developed a protocol a priori for this systematic review. The reporting of this review follows the standards set in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (5). The committee identified and developed a protocol for 7 key Population Intervention Comparison Outcome (PICO) questions (Supplemental Table 1). The outcomes of interest were clinical outcomes (cirrhosis, liver decompensation, hepatocellular carcinoma [HCC] and all-cause mortality); however, when such outcome data were unavailable, surrogate (intermediate) outcomes were sought, specifically durability of HBeAg seroconversion, loss of hepatitis B surface (HBsAg), long-term suppression of HBV DNA, and normalization of ALT.

Eligibility Criteria:

We included randomized controlled trials (RCTs) and controlled observational studies that enrolled adults ≥18 years old diagnosed with chronic HBV infection who received antiviral therapy as treatment. We excluded studies that included patients with acute HBV infection, patients who were pregnant, patients co-infected with hepatitis C or D or human immunodeficiency virus, patients receiving corticosteroids, chemotherapy or immunosuppressive therapy, transplant recipients and hemodialysis patients, as well as studies without control or comparison groups. Supplemental Table 1 summarizes the inclusion and exclusion criteria for each key question.

Search strategy:

An experienced Mayo Clinic librarian conducted a comprehensive search of 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 16th, 2014. Controlled vocabulary supplemented with keywords was used to search for comparative studies of antivirals for chronic hepatitis B. No language restrictions were used. Members from the AASLD HBV guideline methodology and writing committees helped identify additional studies. Supplemental Table 2 specifies the detailed search strategy.

Study selections:

Two reviewers independently screened titles and abstracts for potential eligibility using an online reference management system (DistillerSR, Evidence Partners, Inc.). Full text of the included abstracts were retrieved and screened in duplicate. Disagreements were resolved by seeking consensus or arbitration by a third reviewer. Inter-reviewer agreement (Kappa) was calculated during each screening level to assess agreement between reviewers. For PICO questions where

no studies meeting the predefined criteria were found, the AASLD HBV guideline methodology committee performed manual searches for uncontrolled observational studies. Data from these studies were summarized narratively and were in general consistent with low quality evidence.

Data Extraction:

Data extraction was done using a standardized, piloted form. We extracted data on study characteristics, patient characteristics, interventions details and outcomes of interest.

Methodological quality and risk of bias assessment:

We used the Cochrane Risk of Bias assessment tool and modified Newcastle-Ottawa Scale (NOS) 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 (GRADE) approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity) and publication bias (6).

Statistical analysis:

For dichotomized outcomes, we calculated risk ratios and 95% confidence intervals (95%CI) using binomial distribution. We then pooled the log transformed risk ratios using the DerSimonian and Laird random-effects models and estimated heterogeneity using the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, we calculated the I^2 statistic, where I^2 >50% suggests high degree of heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). To explore heterogeneity, we conducted subgroup analysis for studies enrolling patients with more advanced

liver disease; we performed stratified analysis for the following groups: compensated cirrhosis, decompensated cirrhosis, acute on chronic liver failure, and severe acute exacerbations of chronic hepatitis B. We explored the impact of publication bias by using the Egger regression asymmetry test and by constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low (7).

Results:

A total of 73 studies were included. Figure 1 describes the details of the selection process. Average weighted Kappa for study selection was 0.78. Controlled studies that reported the outcomes of interest were only available for questions 1, 2, 3 and 5. Uncontrolled studies that are relevant to questions 4, 6 and 7 are summarized in Supplemental File 3. Supplemental table 4 provides the GRADE summary of the evidence.

Question 1: Effectiveness of antiviral therapy in patients with immune active chronic HBV infection

We included 59 studies (15 RCTs and 44 observational studies) that evaluated antiviral therapy and reported clinical outcomes. Forty-two studies compared antiviral therapy vs. control and 18 studies compared one antiviral agent vs. another.

1.1 Effectiveness of antiviral therapy compared to control in patients with chronic hepatitis B infection:

Among 42 studies comparing antiviral therapy vs. control in 62,731 patients, 16 studies (8-23) compared IFN vs. no treatment; 16 studies (24-39) compared lamivudine vs. no treatment; 7 studies (28, 40-45) compared entecavir vs. no treatment;1 study each compared telbivudine (44)

and tenofovir (46) vs. placebo and 3 studies (47-49) compared a variety of oral antiviral vs. no treatment. Eleven studies enrolled only patients with compensated cirrhosis, 5 studies enrolled only patients with acute on chronic liver failure, 2 studies enrolled only patients with decompensated liver disease, 3 studies enrolled only patients with severe acute exacerbations of chronic hepatitis B and 21 studies enrolled patients with stable chronic hepatitis B. Study characteristics are illustrated in Table 1. Risk of bias assessment for RCTs was low to moderate as 2 of the included RCTs reported the randomization method, 2 reported utilization of allocation concealment and 6 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. Risk of bias is described in Tables 2-3.

In 7 RCTs (8, 23-25, 29, 33, 46) involving 3,463 subjects with mean follow up of 28 months, antiviral therapy vs. control (Figure 2) significantly decreased the overall risk of decompensated liver disease (1 RCT, RR 0.4 (95% CI, 0.3 - 0.7)) and cirrhosis (1 RCT, RR 0.4 (95% CI,0.2 - 0.8)). No significant differences were found in all-cause mortality (4 RCTs, RR 0.5 (95% CI, 0.2 - 1.3), I^2=72.9%) or HCC incidence (3 RCT, RR 0.6 (95% CI, 0.3 - 1.1), I^2=0%). The quality of the evidence was low to moderate. One RCT (29) examined adverse events including death and decompensation as outcomes but no events were observed in either the intervention or control group.

In 35 observational studies involving 59,201 patients with mean follow up of 60 months, meta-analysis showed that antiviral therapy vs. control decreased the risk of HCC (23 studies, RR 0.5 (95% CI, 0.4 - 0.7), I^2=87.4%), all-cause mortality (23 studies, RR 0.6 (95% CI, 0.5 - 0.8), I^2=92.3%) and cirrhosis (4 studies, RR 0.6 (95% CI,0.4 - 0.8), I^2=0%) but did not significantly reduce the risk of decompensated liver disease (6 studies, RR 0.7 (95% CI, 0.3 - 1.9), I^2= 96.5%)

when compared to untreated controls (Figures 3, 4 and 5). The quality of this evidence overall was low; however, these studies included large numbers of patients with long duration of follow-up, yielding precise and narrow 95% CI.

1.1.1 Effectiveness of antiviral therapy compared to control in the sub-group with stable chronic hepatitis B

Of the 21 studies that enrolled patients with stable chronic hepatitis B, 0 to 91% of the 54,719 patients included had compensated cirrhosis. Reduction in risk of decompensated cirrhosis was shown in only 1 RCT and reduction in HCC in 11 observational studies. No studies demonstrated reduction in all-cause mortality.

1.2 Effectiveness of antiviral therapy compared to control in patients with chronic HBV infection and compensated cirrhosis:

In one RCT (25) enrolling 222 cirrhotic patients with follow up of 53 months, lamivudine vs. control reduced all-cause mortality (RR 0.1 (95% CI, 0.1-0.3), moderate quality evidence).

In 10 observational studies (Figure 3) 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), I^2=36.3%), decompensated liver disease (2 studies, RR 0.5 (95% CI,0.2-0.9), I^2=67.2%) and all-cause mortality (3 studies, RR 0.5 (95% CI,0.4-0.6), I^2=0%).

In 5 observational studies (25, 26, 35, 38, 41) (Figure 4) with mean follow up of 84 months, IFN-alpha compared to no treatment significantly decreased the risk of HCC (5 studies, RR 0.6 (95% CI, 0.4-0.9), I^2=0%) but not of all-cause mortality (1 study, RR 0.7 (95% CI, 0.5-2.4), I^2=56.9%) or decompensated liver disease (1 study, RR 0.7 (95% CI, 0.3-1.5).

In 4 observational studies (26, 35, 38, 41) (Figure 5) with mean follow up of 45 months, lamivudine vs. no treatment significantly reduced the risk of HCC (4 studies, RR 0.6 (95% CI, 0.4-0.96), I^2=49.9%), all-cause mortality (1 study, RR 0.4 (95% CI, 0.3-0.6) and decompensated liver disease (1 study, RR 0.3 (95% CI, 0.3-0.5). In 1 cohort study (40) of 1,980 patients with cirrhosis followed for a mean of 52 months, entecavir vs. 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)).

1.3 Effectiveness of antiviral therapy compared to control in patients with chronic HBV infection and decompensated cirrhosis:

In 2 observational studies with follow up of 29 months (27, 32), lamivudine vs. control reduced all-cause mortality (2 studies, RR 0.5 (95% CI, 0.3-0.8) I^2=0%).

1.4 Effectiveness of antiviral therapy compared to control in patients with chronic HBV infection experiencing acute on chronic liver failure:

In 1 RCT (46) involving 26 patients followed for a year, tenofovir reduced all-cause mortality (RR 0.5 (95% CI, 0.3-0.99), moderate quality evidence). In 4 observational studies (28, 37, 42, 44) with mean follow up of 26 months, antiviral therapy vs. no therapy reduced all-cause mortality (RR 0.7 (95% CI, 0.6-0.8), I^2=5.4%). Similarly, reduced mortality was also found in studies evaluating individual therapies including lamivudine (RR 0.8 (95% CI, 0.7-0.9), I^2=50.2%) (28, 37, 44), entecavir (RR 0.7 (95% CI, 0.6-0.8), I^2=0%) (28, 42, 44) and telbivudine (RR 0.4 (95% CI, 0.2-0.9) (44).

1.5 Effectiveness of antiviral therapy compared to control in patients with chronic HBV infection with severe acute exacerbations:

In 3 observational studies (30, 43, 45) with more than 12 month mean follow up, meta-analysis of antiviral therapy vs. control showed no statistically significant reduction in all-cause mortality (RR 0.9 (95% CI, 0.5-1.5), I^2=54.5%) which was consistent with studies evaluating the effect of individual agents: lamivudine (RR 0.5 (95% CI, 0.2-1.7) (30) and entecavir (RR 0.9 (95% CI, 0.5-1.9), I^2=71.3%) (43, 45).

1.6 Head to head studies comparing individual antiviral agents:

We included 8 RCTs (50-57) enrolling 2,318 patients and 10 observational studies (28, 58-66) enrolling 6,737 patients that compared one antiviral agent with another. We considered most of these RCTs (52, 55-57) to have high risk of bias due to unclear randomization methods, allocation concealment, blinding and loss to follow up. The observational studies were also limited by the unclear description of the characteristics for cohort selection, ascertainment of the outcomes and inadequate follow up. Tables 1-2 describe the details of the included studies and risk of bias.

Among 5 studies enrolling 3,300 patients with chronic HBV infection and compensated cirrhosis (mean follow up 22 months), 1 RCT (55) compared adefovir vs. lamivudine, and 4 observational studies compared entecavir vs. lamivudine (58); entecavir vs. telbivudine (65); lamivudine vs. tenofovir (66); and telbivudine vs. lamivudine, respectively (61). Only 1 study (58) showed a significant difference in outcome with reduction in all-cause mortality in patients who received entecavir vs. lamivudine (1 study, RR 0.4 (95% CI, 0.3-0.6), very low quality of evidence).

Four studies enrolled 607 patients with chronic HBV infection and decompensated cirrhosis (mean follow up 28 months). Three RCTs compared entecavir vs. adefovir (57), adefovir vs. lamivudine (56), and telbivudine vs. lamivudine, respectively (50); and one cohort study (59)

compared entecavir vs. lamivudine. Reduction in risk of HCC was observed in the RCT (57) comparing entecavir vs. adefovir (RR 0.4 (95% CI, 0.2-0.8), and reduction in all-cause mortality was observed in the cohort study comparing entecavir vs. lamivudine (RR 0.4 (95% CI, 0.3-0.7) in patients who received entecavir.

Three cohort studies (28, 62, 63) 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 (60, 64) that compared entecavir vs. lamivudine in 320 patients with severe acute exacerbation of chronic hepatitis B (mean follow up 32 months) showed no significant effect on mortality.

Question 2. Effectiveness of antiviral therapy in patients with immune tolerant chronic HBV infection

Two studies (67) (68) evaluated antiviral therapy in HBeAg-positive patients with normal ALT levels. Detailed study characteristics and risk of bias are described in Tables 1-2.

One RCT (67) 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 vs. 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 (RR 0.3 (95%CI, 0.03- 2.2)), HBeAg seroconversion (RR 0.1 (95%CI, 0.01-2.8)) or HBsAg clearance (RR 1.0 (95%CI, 0.3-3.9)). The quality of evidence was low due to indirectness and imprecision.

In a cohort study (68) of 68 HBeAg positive postpartum women, Peg IFN and adefovir vs. untreated control significantly improved rates of HBeAg seroconversion (RR 41.8 (95% CI, 2.6 - 666.9)) and HBeAg loss (RR 20.3 (95% CI, 1.2 - 337.7)). The quality of evidence was very low, down rated due to observational nature of the study, risk of bias and imprecision.

Question 3: Discontinuing compared to continuing antiviral therapy in HBeAg positive patients who seroconverted from HBeAg to anti-HBe

Two observational studies (69, 70) compared patients with chronic hepatitis B who stopped therapy (61 patients) after HBeAg seroconversion to those who continued (128 patients) to receive antiviral therapy. For both studies, the median (range) duration of therapy leading to HBeAg seroconversion was 21 (1-120) months, median follow up after stopping therapy was 40 (range 2-120) months and median duration of consolidation treatment after HBeAg seroconversion was 12 (range 1-55) months. Characteristics and risk of bias for both studies are illustrated in Tables 1 and 3.

Compared to continued antiviral therapy, very low quality evidence suggests increased risk of relapse of viremia in patients who stopped antiviral therapy RR 94.4 (95% CI, 13.3-670.7), I^2=0%) with no effect on ALT flares. The rate of HBeAg seroreversion was 8% after a median of 6 months in 1 study (69) and a cumulative incidence of 9% at 5 years in another study (70). No clinical outcomes were reported. The quality of evidence was very low due to increased risk of bias, indirectness and imprecision. Additional non comparative and indirect evidence is summarized in Supplemental File 3.

Question 4. Stopping compared to continuing antiviral therapy in HBeAg negative adults with immune active chronic HBV infection

We were unable to find comparative studies for this question. Supplemental File 3 summarizes uncontrolled studies and indirect evidence that may address this question. Data from these studies indicate a high rate of viral relapse when treatment was stopped, but rates of clinical relapse were lower.

Question 5. Safety of entecavir compared to tenofovir

Eleven studies (1 RCT (71) and 10 observational studies (66, 72-74) (75-80)) compared entecavir vs. tenofovir in 1,300 patients with mean follow up of 18.6 months. Characteristics of the included studies and risk of bias are described in Table 1-2.

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. Table 4 describes the detailed outcomes reported for each study.

Question 6. 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 (Supplemental File 3) showed little to no benefit in adding a second antiviral agent compared to continuing monotherapy with entecavir or tenofovir.

Question 7. Antiviral therapy in patients with chronic HBV infection and compensated cirrhosis and low level viremia (HBV DNA <2000 IU/ml)

We were unable to identify comparative studies on outcomes of these patients with or without antiviral therapy. Supplemental File 3 summarizes uncontrolled studies and indirect evidence

that address this question. In patients with compensated cirrhosis and low level viremia, one study specifically examined the benefit of antiviral therapy and found a decrease in incidence of HCC but the results could be confounded by differences in the characteristics of treated versus untreated patients (81).

Publication bias:

We were unable to evaluate publication bias due to high heterogeneity and small number of studies for each outcome.

Discussion:

The members of the AASLD methodology and writing committees for the HBV Practice Guideline developed seven key clinical questions that challenge clinicians and patients in daily practice. The methodologists performed an extensive literature search, selected studies that included a comparison group and data on clinical outcomes, and then rated the quality of the evidence. Sufficient comparative evidence was found for four of the key questions, but evidence was sparse or absent for the remaining three questions: when to stop therapy in persons with immune active chronic HBV infection who are HBeAg-negative, the benefit of adding either entecavir or tenofovir in persons who fail to suppress HBV DNA to undetectable levels with either of these drugs alone, and whether antiviral therapy should be used in patients with compensated cirrhosis and HBV DNA levels below 2,000 IU/ml. For these three questions, the committee identified indirect and non-comparative evidence (Supplemental File 3).

Antiviral therapy in patients with immune active chronic HBV infection had 59 published studies available for review and evaluation. Moderate to low quality evidence supported the benefit of therapy in reducing adverse outcomes of chronic HBV infection including progression to

cirrhosis, liver decompensation and all-cause mortality. Because the observational studies had more patients (59,201 vs. 3,463) and longer follow-up (60 vs. 28 months), data on mortality and HCC from 35 observational studies were sufficiently precise, whereas data from 7 RCTs were imprecise. These larger sample sizes and longer follow-up in the observational studies account for the significant benefit of antiviral treatment on HCC and mortality found in the observational studies but not in the RCTs.

Given the indolent nature of chronic HBV infection, it is not surprising that evidence supporting the benefit of antiviral treatment on clinical outcomes was found only when the analysis was limited to patients with more advanced disease: compensated cirrhosis, decompensated cirrhosis or acute on chronic liver failure. Indeed, most RCTs of antiviral therapy in chronic HBV infection enrolled only or mostly patients with no cirrhosis, and very few trials that enrolled predominantly patients with no cirrhosis provided data on clinical outcomes. Provision of evidence to support that antiviral therapy improves clinical outcomes in patients with chronic HBV infection and no cirrhosis would require thousands of patients followed for many years, and withholding treatment in the control group until the completion of the study. Such a study would be unethical and likely infeasible. Thus, evidence supporting the benefit of antiviral therapy in patients without cirrhosis has to rely on intermediate outcomes such as HBV DNA suppression, ALT normalization, HBeAg seroconversion, HBsAg loss, and cirrhosis prevention or regression. These intermediate outcomes have been shown to correlate with improvement in clinical outcomes and represent a series of steps towards the ultimate goal of improving clinical outcome. For example, HBV DNA suppression precedes HBeAg seroconversion which precedes HBsAg loss; and HBsAg loss has been shown to be associated with decreased risk of HCC, particularly if it occurs before the development of cirrhosis.

Recent studies showed that high levels of HBV viremia are associated with an increased risk of cirrhosis, HCC and liver-related mortality (82-84). Patients in the immune tolerant phase have the highest level of viremia. In the two studies exclusively enrolling patients in the immune tolerant phase, clinical outcomes were not reported, but rates of intermediate outcomes were lower than those in patients in the HBeAg-positive immune active phase.

In the two observational studies comparing the risk of viral relapse and HBeAg seroreversion in HBeAg-positive patients who achieved HBeAg seroconversion during nucleos(t)ide analogue therapy and who stopped vs. continued therapy, very low quality evidence suggests an increased risk of relapse of viremia with stopping. Other observational studies (see Supplemental File 3) showed durable HBeAg seroconversion varying from 20-90% depending on the duration of consolidation therapy after achieving HBeAg seroconversion, the most consistent predictor of durable response. Studies directly comparing stopping vs. continuing therapy in HBeAg-negative patients on nucleos(t)ide analogue therapy were not found; however, observational studies in the literature on the virologic, serologic and biochemical outcomes of patients who stopped therapy showed that viral relapse is universal but that sustained clinical remission and even HBsAg loss is possible (see Supplemental File 3). Because hepatitis flares and hepatic decompensation may occur after stopping treatment, close monitoring after discontinuation of treatment is important, especially for those with cirrhosis at the start of therapy who have the highest risk for decompensation.

Entecavir and tenofovir have been used as first-line nucleos(t)ide analogues because of their potent antiviral activity and low risk of antiviral drug resistance. Tenofovir can cause impairment in renal function, renal tubular dysfunction including Fanconi anemia, and decreased bone mineral density. Meta-analysis of studies comparing monotherapy with entecavir or tenofovir did

not show a significant difference in serum creatinine level, estimated glomerular filtration rate or in serum phosphate level; however, the duration of treatment was short in these studies.

While entecavir and tenofovir have potent antiviral activity, some patients have persistent viremia despite being adherent to medication. This is more common among HBeAg-positive patients with high baseline serum HBV DNA. Studies comparing continuing entecavir or tenofovir monotherapy vs. adding a second antiviral agent in patients with persistent viremia were not found. Observational studies of patients who continued entecavir or tenofovir monotherapy showed that most patients ultimately achieved undetectable HBV DNA.

Patients with compensated cirrhosis have a high risk of liver failure and HCC particularly those with high levels of HBV DNA. The benefit of antiviral therapy in patients with compensated cirrhosis and low levels of HBV DNA has not been established. One retrospective study comparing outcomes of patients with compensated cirrhosis and low levels of HBV DNA (<2,000 IU/ml) with or without antiviral therapy suggest a benefit of antiviral therapy in decreasing the incidence of HCC, but patients who received treatment differed substantially from those who did not receive treatment and in most patients HBV DNA was level was higher than 2,000 IU/ml at the time treatment was started (81).

Several questions that had been addressed in the previous AASLD HBV Guidelines were not included in this systematic review: who should be screened for HBV infection, who should be vaccinated against HBV, what clinical and laboratory criteria (levels of HBV DNA and ALT) should be used to initiate antiviral therapy, who should undergo surveillance for HCC, and how frequently patients with chronic HBV infection who are not receiving antiviral therapy should be monitored. Management of special population such as those with HIV, HCV or HDV

coinfection, and those requiring immunosuppressive therapy were also not addressed in the current review because data from controlled studies for these patient populations were sparse. Additional recommendations can be found in the previous AASLD HBV Guideline, the Centers for Disease Control and Prevention and the World Health Organization Guidelines (85-88).

Conclusion: 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. In addition to evidence-based data, management of patients with chronic HBV infection should take into consideration individual patient preference and available resources. Recommendations for management of adults with chronic HBV infection based on this systematic review are provided in the updated AASLD guidelines (89).

References:

1. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212-2219.
2. Wasley A, Kruszon-Moran D, Kuhnert W, Simard EP, Finelli L, McQuillan G, Bell B. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. The Journal of infectious diseases 2010;202:192-201.
3. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. Hepatology 2012;56:422-433.
4. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507-539.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009;6:e1000097.
6. Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. JAMA 2014;312:171-179.
7. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
8. Anderson MG, Harrison TJ, Alexander G, Zuckerman AJ, Murray-Lyon IM. Randomised controlled trial of lymphoblastoid interferon for chronic active hepatitis B. Gut 1987;28:619-622.
9. IIHCSG. Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. International Interferon-alpha Hepatocellular Carcinoma Study Group. Lancet 1998;351:1535-1539.
10. Lin S-M, Yu M-L, Lee C-M, Chien R-N, Sheen IS, Chu C-M, Liaw Y-F. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. Journal of Hepatology 2007;46:45-52.
11. Truong BX, Seo Y, Kato M, Hamano K, Ninomiya T, Katayama M, et al. Long-term follow-up of Japanese patients with chronic hepatitis B treated with interferon-alpha. International Journal of Molecular Medicine 2005;16:279-284.
12. Tangkijvanich P, Thong-ngam D, Mahachai V, Kladchareon N, Suwangool P, Kullavanijaya P. Long-term effect of interferon therapy on incidence of cirrhosis and hepatocellular carcinoma in Thai patients with chronic hepatitis B. Southeast Asian Journal of Tropical Medicine & Public Health 2001;32:452-458.
13. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. Journal of Hepatology 2001;34:306-313.
14. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, Haussinger D. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. New England Journal of Medicine 1996;334:1422-1427.
15. Lin SM, Tai DI, Chien RN, Sheen IS, Chu CM, Liaw YF. Comparison of long-term effects of lymphoblastoid interferon alpha and recombinant interferon alpha-2a therapy in patients with chronic hepatitis B. Journal of Viral Hepatitis 2004;11:349-357.
16. Benvegnu L, Chemello L, Noventa F, Fattovich G, Pontisso P, Alberti A. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. Cancer 1998;83:901-909.

17. Tong MJ, Blatt LM, Tyson KB, Kao VWC. Death from liver disease and development of hepatocellular carcinoma in patients with chronic hepatitis B virus infection: A prospective study. Gastroenterology and Hepatology 2006;2 (1):41-47.
18. Di Marco V, Lo Iacono O, Camma C, Vaccaro A, Giunta M, Martorana G, et al. The long-term course of chronic hepatitis B. Hepatology 1999;30:257-264.
19. Brunetto MR, Oliveri F, Coco B, Leandro G, Colombatto P, Gorin JM, Bonino F. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long term cohort study. Journal of Hepatology 2002;36:263-270.
20. Mahmood S, Niiyama G, Kamei A, Izumi A, Nakata K, Ikeda H, et al. Influence of viral load and genotype in the progression of Hepatitis B-associated liver cirrhosis to hepatocellular carcinoma. Liver International 2005;25:220-225.
21. Ikeda K, Saitoh S, Suzuki Y, Kobayashi M, Tsubota A, Fukuda M, et al. Interferon decreases hepatocellular carcinogenesis in patients with cirrhosis caused by the hepatitis B virus: a pilot study. Cancer 1998;82:827-835.
22. Fattovich G, Giustina G, Realdi G, Corrocher R, Schalm SW. Long-term outcome of hepatitis B e antigen–positive patients with compensated cirrhosis treated with interferon alfa. Hepatology 1997;26:1338-1342.
23. Krogsgaard K, Thomas HC, Farrell G, Cooksley WGE, Moroni M, Perez V, et al. The long-term effect of treatment with interferon-alpha2a in chronic hepatitis B. Journal of Viral Hepatitis 1998;5 (6):389-397.
24. Chan HLY, Wang H, Niu J, Chim AML, Sung JJY. Two-year lamivudine treatment for hepatitis B e antigen-negative chronic hepatitis B: A double-blind, placebo-controlled trial. Antiviral Therapy 2007;12 (3):345-353.
25. Eun JR LH, Lee SH, Kim TN, Jang BIK, Choi JW, Park YS, Kim KO, Lee KH, Moon HJ, Lee SH. The effect of lamivudine and adefovir dipivoxil on preventing hepatocellular carcinoma in HBV-related liver cirrhosis. Hepatology 2007;46:664A-665A.
26. Tong MJ, Hsien C, Song JJ, Kao JH, Sun HE, Hsu L, et al. Factors associated with progression to hepatocellular carcinoma and to death from liver complications in patients with HBsAg-positive cirrhosis. Digestive Diseases & Sciences 2009;54:1337-1346.
27. Das K DK, Datta S, Pal S, Hembram JR, Dhali GK, Santra A, Chowdhury A. Course of disease and survival after onset of decompensation in hepatitis B virus-related cirrhosis. Liver International 2010;30:1033-1042.
28. Cui Y-L, Yan F, Wang Y-B, Song X-Q, Liu L, Lei X-Z, et al. Nucleoside analogue can improve the long-term prognosis of patients with hepatitis B virus infection-associated acute on chronic liver failure. Digestive Diseases & Sciences 2010;55:2373-2380.
29. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. New England Journal of Medicine 1999;341:1256-1263.
30. Chan HLY, Tsang SWC, Hui Y, Leung NWY, Chan FKL, Sung JJY. The role of lamivudine and predictors of mortality in severe flare-up of chronic hepatitis B with jaundice. Journal of Viral Hepatitis 2002;9:424-428.
31. Lok ASF, Lai C-L, Leung N, Yao G-B, Cui Z-Y, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714-1722.
32. Manolakopoulos S, Karatapanis S, Elefsiniotis J, Mathou N, Vlachogiannakos J, Iliadou E, et al. Clinical course of lamivudine monotherapy in patients with decompensated cirrhosis due

to HBeAg negative chronic HBV infection. American Journal of Gastroenterology 2004;99:57-63.
33. Liaw Y-F, Sung JJY, Chow WC, Farrell G, Lee C-Z, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. New England Journal of Medicine 2004;351:1521-1531.
34. Matsumoto A, Tanaka E, Rokuhara A, Omata M, Iino S, Tanikawa K, et al. Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2795 patients. Hepatology Research 2005;32 (3):173-184.
35. Ma H, Guo F, Wei L, Sun Y, Wang H. The prospective study of the clinical features and outcome of HBeAg-negative and HBeAg-positive cirrhosis in patients with chronic type B hepatitis. [Chinese]. National Medical Journal of China 2007;87 (26):1832-1835.
36. Yuen M-F, Seto W-K, Chow DH-F, Tsui K, Wong DK-H, Ngai VW-S, et al. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. Antiviral Therapy 2007;12:1295-1303.
37. Sun L-J, Yu J-W, Zhao Y-H, Kang P, Li S-C. Influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure. Journal of Gastroenterology & Hepatology 2010;25:583-590.
38. Kim CH, Um SH, Seo YS, Jung JY, Kim JD, Yim HJ, et al. Prognosis of hepatitis B-related liver cirrhosis in the era of oral nucleos(t)ide analog antiviral agents. Journal of Gastroenterology & Hepatology 2012;27:1589-1595.
39. Eun JR, Lee HJ, Kim TN, Lee KS. Risk assessment for the development of hepatocellular carcinoma: according to on-treatment viral response during long-term lamivudine therapy in hepatitis B virus-related liver disease. Journal of Hepatology 2010;53:118-125.
40. Wong GL-H, Chan HL-Y, Mak CW-H, Lee SK-Y, Ip ZM-Y, Lam AT-H, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology 2013;58:1537-1547.
41. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98-107.
42. Lin B, Pan CQ, Xie D, Xie J, Xie S, Zhang X, et al. Entecavir improves the outcome of acute-on-chronic liver failure due to the acute exacerbation of chronic hepatitis B. Hepatology International 2013;7 (2):460-467.
43. Xiao G-M, He K-Y, Jia W-D, Lei C-L, Yang Z. [Case-controlled study of entecavir treatment for chronic severe hepatitis B]. Chinese Journal of Experimental & Clinical Virology 2009;23:56-58.
44. Xu Q-h, Chen L-b, Xu Z, Shu X, Chen N, Cao H, et al. [The short-term efficacy of antiviral treatment in patients with acute-on-chronic hepatitis B liver failure]. Chinese Journal of Experimental & Clinical Virology 2009;23:467-469.
45. Chen J, Han JH, Liu C, Yu RH, Li FZ, Li QF, Gong GZ. Short-term entecavir therapy of chronic severe hepatitis B. Hepatobiliary & Pancreatic Diseases International 2009;8:261-266.
46. Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure.[Erratum appears in Hepatology. 2011 Sep 2;54(3):1114]. Hepatology 2011;53:774-780.

47. Wu CY, Lin JT, Ho HJ, Su CW, Lee TY, Wang SY, et al. Association of nucleos(T)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B - A nationwide cohort study. Gastroenterology 2014;147 (1):143-151.e145.
48. Gordon SC, Lamerato LE, Rupp LB, Li J, Holmberg SD, Moorman AC, et al. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2014;12:885-893.
49. Kumada T, Toyoda H, Tada T, Kiriyama S, Tanikawa M, Hisanaga Y, et al. Effect of nucleos(t)ide analogue therapy on hepatocarcinogenesis in chronic hepatitis B patients: a propensity score analysis. Journal of Hepatology 2013;58:427-433.
50. Chan HLY, Chen YC, Gane EJ, Sarin SK, Suh DJ, Piratvisuth T, et al. Randomized clinical trial: efficacy and safety of telbivudine and lamivudine in treatment-naive patients with HBV-related decompensated cirrhosis. Journal of Viral Hepatitis 2012;19:732-743.
51. Chang T-T, Gish RG, de Man R, Gadano A, Sollano J, Chao Y-C, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. New England Journal of Medicine 2006;354:1001-1010.
52. Lai C-L, Shouval D, Lok AS, Chang T-T, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B.[Erratum appears in N Engl J Med. 2006 Apr 27;354(17):1863]. New England Journal of Medicine 2006;354:1011-1020.
53. Lau GKK, Piratvisuth T, Kang XL, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. New England Journal of Medicine 2005;352 (26):2682-2695.
54. Marcellin P, Lau GKK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon Alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. New England Journal of Medicine 2004;351 (12):1206-1217.
55. Wang H, Ji YY, Yao GB, Ma XY, Xie Q, Pang HY, et al. Two years efficiency of lamivudine and adefovir dipivoxil combined therapy in chronic hepatitis B patients. European Review for Medical & Pharmacological Sciences 2013;17:636-643.
56. Yang Q, Gong Z-j, Hu D-f. [A clinical study of adefovir dipivoxil treatment for chronic hepatitis patients with cirrhosis in their decompensation period]. Chung Hua Kan Tsang Ping Tsa Chih 2009;17:515-519.
57. Liaw Y-F, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N, et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. Hepatology 2011;54:91-100.
58. Lim Y-S, Han S, Heo N-Y, Shim JH, Lee HC, Suh DJ. Mortality, liver transplantation, and hepatocellular carcinoma among patients with chronic hepatitis B treated with entecavir vs lamivudine. Gastroenterology 2014;147:152-161.
59. Hsu Y-C, Mo L-R, Chang C-Y, Perng D-S, Tseng C-H, Lo G-H, et al. Entecavir versus lamivudine in the treatment of chronic hepatitis B patients with hepatic decompensation. Antiviral Therapy 2012;17:605-612.
60. Wong VW-S, Wong GL-H, Yiu KK-L, Chim AM-L, Chu SH-T, Chan H-Y, et al. Entecavir treatment in patients with severe acute exacerbation of chronic hepatitis B. Journal of Hepatology 2011;54:236-242.
61. Liang J, Han T, Xiao S-X. [Telbivudine treatment on cirrhosis resulting from chronic hepatitis B]. Chung Hua Kan Tsang Ping Tsa Chih 2009;17:24-27.

62. Chen CH, Lin CL, Hu TH, Hung CH, Tseng PL, Wang JH, et al. Entecavir vs. lamivudine in chronic hepatitis B patients with severe acute exacerbation and hepatic decompensation. Journal of Hepatology 2014;60 (6):1127-1134.
63. Zhang Y, Hu XY, Zhong S, Yang F, Zhou TY, Chen G, et al. Entecavir vs lamivudine therapy for naive patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. World Journal of Gastroenterology 2014;20 (16):4745-4752.
64. Tsai WL, Chiang PH, Chan HH, Lin HS, Lai KH, Cheng JS, et al. Early entecavir treatment for chronic hepatitis B with severe acute exacerbation. Antimicrobial Agents and Chemotherapy 2014;58 (4):1918-1921.
65. Tsai MC, Yu HC, Hung CH, Lee CM, Chiu KW, Lin MT, et al. Comparing the efficacy and clinical outcome of telbivudine and entecavir naive patients with hepatitis B virus-related compensated cirrhosis. Journal of Gastroenterology and Hepatology (Australia) 2014;29 (3):568-575.
66. Koklu S, Tuna Y, Gulsen MT, Demir M, Koksal AS, Kockar MC, et al. Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clinical Gastroenterology & Hepatology 2013;11:88-94.
67. Chan HL, Chan CK, Hui AJ, Chan S, Poordad F, Chang TT, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 2014;146:1240-1248.
68. Lu J, Zhang S, Liu Y, Du X, Ren S, Zhang H, et al. Effect of Peg-interferon alpha-2a Combined with Adefovir in HBV Postpartum Women with Normal Levels of ALT and High Levels of HBV DNA. Liver Int 2015;35:1692-1699.
69. Chaung KT, Ha NB, Trinh HN, Garcia RT, Nguyen HA, Nguyen KK, et al. High frequency of recurrent viremia after hepatitis B e antigen seroconversion and consolidation therapy. Journal of Clinical Gastroenterology 2012;46:865-870.
70. Fung J, Lai CL, Tanaka Y, Mizokami M, Yuen J, Wong DKH, Yuen MF. The duration of lamivudine therapy for chronic hepatitis B: cessation vs. continuation of treatment after HBeAg seroconversion. American Journal of Gastroenterology 2009;104:1940-1946; quiz 1947.
71. Liaw Y-F, Sheen IS, Lee C-M, Akarca US, Papatheodoridis GV, Suet-Hing Wong F, et al. Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology 2011;53:62-72.
72. Dogan UB, Kara B, Gumurdulu Y, Soylu A, Akin MS. Comparison of the efficacy of tenofovir and entecavir for the treatment of nucleos(t)ide-naive patients with chronic hepatitis B. Turkish Journal of Gastroenterology 2012;23:247-252.
73. Batirel A, Guclu E, Arslan F, Kocak F, Karabay O, Ozer S, et al. Comparable efficacy of tenofovir versus entecavir and predictors of response in treatment-naive patients with chronic hepatitis B: a multicenter real-life study. Int J Infect Dis 2014;28:153-159.
74. Cholongitas E, Papatheodoridis GV, Goulis J, Vlachogiannakos J, Karatapanis S, Ketikoglou J, et al. The impact of newer nucleos(t)ide analogues on patients with hepatitis B decompensated cirrhosis. Annals of gastroenterology : quarterly publication of the Hellenic Society of Gastroenterology 2015;28:109-117.
75. Huang M, Jie Y, Shi H, Li X, Wu Y, Lin G, Chong Y. Comparison of the efficacy of tenofovir disoproxil fumarate and entecavir for initial treatment of patient with chronic hepatitis B in China. International journal of clinical and experimental medicine 2015;8:666-673.

76. Hung CH, Hu TH, Lu SN, Lee CM, Chen CH, Kee KM, et al. Tenofovir versus entecavir in the treatment of chronic hepatitis B with severe acute exacerbation. Antimicrobial Agents and Chemotherapy 2015;59:3168-3173.
77. Mallet V, Schwarzinger M, Vallet-Pichard A, Fontaine H, Corouge M, Sogni P, Pol S. Effect of Nucleoside and Nucleotide Analogues on Renal Function in Patients With Chronic Hepatitis B Virus Monoinfection. Clinical Gastroenterology and Hepatology 2014;13:1181-1188.e1181.
78. Mauss S, Berger F, Filmann N, Hueppe D, Henke J, Hegener P, et al. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. Journal of Hepatology 2011;55:1235-1240.
79. Tien C, Xu JJ, Chan LS, Chang M, Lim C, Lee S, et al. Long-term treatment with tenofovir in Asian-American chronic hepatitis B patients is associated with abnormal renal phosphate handling. Digestive diseases and sciences 2015;60:566-572.
80. Gish RG, Clark MD, Kane SD, Shaw RE, Mangahas MF, Baqai S. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2012;10:941-946; quiz e968.
81. Sinn DH, Lee J, Goo J, Kim K, Gwak GY, Paik YH, et al. Hepatocellular carcinoma risk in chronic hepatitis B virus-infected compensated cirrhosis patients with low viral load. Hepatology 2015;62:694-701.
82. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
83. Iloeje UH, Yang HI, Jen CL, Su J, Wang LY, You SL, Chen CJ. Risk and predictors of mortality associated with chronic hepatitis B infection. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2007;5:921-931.
84. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-686.
85. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661-662.
86. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control 2008;57:1-20.
87. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports / Centers for Disease Control 2006;55:1-33; quiz CE31-34.
88. WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en/ March 2015 ed: WHO Library Cataloguing-in-Publication Data, 2015: 166.
89. Terrault N, Bzowej N, Chang K-M, Hwang J, Jonas M, Murad H. AASLD Guidelines for Treatment of Chronic Hepatitis B. http://www.aasld.org/publications/practice-guidelines-0. HEPATOLOGY 2015.

Table 1: Characteristics of the included studies

Author name, year	Country	Patients (N)	Interventions	Age (years)	HBeAg Positive (N)	Baseline ALT (U/L)	Baseline HBV DNA (log10 IU/mL)*	Follow up duration (months)	Baseline cirrhosis (%)	Study design
Question 1: Effectiveness of antiviral therapy in patients with immune active chronic HBV infection (Antiviral vs control):										
Anderson, 1987(8)	England	14	IFN-alpha	36	14	77% elevated ALT	NR	12	20	RCT
		16	Control	35	16	77% elevated ALT	NR	12	20	
IIHCSG, 1998(9)	Italy and Argentina	49	IFN-alpha	54	NR	NR	NR	69.6	100	Case Control
		97	Control	54	NR	NR	NR	82.2	100	
Lin, 2007(10)	Taiwan	233	IFN-alpha	32±7	233	175± 112	40% >7.7	81.6±38.4	8.1	Cohort
		233	Control	31±8	233	187±109	40% >7.7	73.2±36	10.7	
Truong, 2005(11)	Japanese	27	IFN- alpha	33.2±10.4	17	238.6±250.1	NR	84±30	3	Case Control
		35	Control	36.6±10.9	20	142.3±152.1	NR	74.4±34.8	14.3	
Tangkijvanich, 2001(12)	Thailand	67	IFN-alpha	36.9±10.5	67	180.7±137.9	NR	59.4±30.9	17.9	Case Control
		72	Control	39.9±13.7	72	93.3±114.4	NR	60.1±35.3	22.2	
Papatheodoridis, 2001(13)	Greece	209	IFN-alpha	46.8±11.3	0	112 (13-1905)	5.4	72±32.4	27.3	Cohort
		195	Control	48.8±13.7	0	68 (20-1335)	5.4	73.2±46.8	34.9	
Niederau, 1996(14)	Germany	103	IFN-alpha	NR	103	NR	NR	50.0 ± 19.8	27	Cohort
		53	Control	NR	53	NR	NR	38.5±18.2	16	
Lin, 2004(15)	Taiwan	109	IFN-alpha	31±9	NR	132±86	NR	84.5	90	Cohort
		34	Control	32±6	NR	256±232	NR	92	85	
Benvegnu, 1998(16)	Italy	13	IFN-alpha	57	NR	NR	NR	72	100	Cohort
		24	Control	60	NR	NR	NR	72	100	
Tong, 2006(17)	USA	22	IFN-alpha	48	49%	NR	NR	84	35	Cohort
		378	Control	48	NR	NR	NR	84	35	
Di Marco, 1999(18)	Italy	109	IFN-alpha	33	NR	NR	NR	93.6	29	Cohort
		193	Control	35	NR	NR	NR	93.6	29	
Brunetto, 2002(19)	Italy	103	IFN-alpha	40	0	NR	NR	72	38	Cohort
		61	Control	40	0	NR	NR	72	38	
Mahmood, 2005(20)	Japan	23	IFN-alpha	49	NR	NR	NR	84	100	Case Control
		68	Control	49	NR	NR	NR	84	100	
Ikeda, 1998(21)	Japan	94	IFN-alpha	41	NR	NR	NR	81.6	100	Case Control

		219	Control	44	NR	NR	NR	84	100	
Fattovich, 1997(22)	Italy	40	IFN-alpha	47±1.8	40	5.3 (0.61xULN)	NR	74.4	100	Cohort
		50	Control	45 ± 2.2	50	5.3 (0.61xULN)	NR	74.4	100	
Krogsgaard, 1998(23)	Europe	210	IFN –alpha	36	210	100% elevated ALT	NR	15.6	19	RCT
		98	Control	36	98		NR	15.6	19	
Chan 2007 (24)	China	89	Lamivudine	39±11	6	2.1±1.7 (xULN)	5 ±0.0.9	120	31	RCT
		47	Placebo	39±11	4	2.6±2.3 (xULN)	4.9 ±0.8	120	21	
Eun, 2007(25)	Korea	111	Lamivudine	NR	NR	NR	NR	52.8	100	RCT
		111	Placebo	NR	NR	NR	NR	52.8	100	
Tong, 2009(26)	USA	27	Lamivudine	40	NR	NR	NR	63.6	100	Cohort
		101	Control	46	NR	NR	NR	63.6	100	
Das, 2010(27)	India	151	Lamivudine and adefovir	42	45%	NR	NR	48	100	Case Control
		102	Control	46	NR	NR	NR	45.6	100	
Cui, 2010(28)	China	33	Entecavir	38.4±10.8	10	364 (47–2861)	5.2±0.8	0.2-41.5	NR	Cohort
		34	Lamivudine	39.4±10.6	13	226.5 (22–2314)	5.1±0.6	0.2-41.5	NR	
		37	Control	41.±11.5	11	287 (17–2535)	5±0.9	0.2-41.5	NR	
Dienstag, 1999(29)	USA	66	Lamivudine	40 (18–73)	66	125 (46–401)	6.7 (4.6-7.9)	12	6	RCT
		71	Placebo	38 (20–67)	71	135 (33–592)	6.5 (4.6-7.6)	12	14	
Chan, 2002(30)	Hong Kong	28	Lamivudine	42.7±13.5	16	1416.6±577.7	NR	12	NR	Cohort
		18	Control	47.2±14	2	1659.5±1928.4	NR	12	NR	
Lok, 2003(31)	Multi-national	998	Lamivudine	32.0 (15–73)	998	1.6 (0.2–23.4) (/ULN)	6.7 (4.7–8.1)	48	10	Cohort
		200	Placebo	34.5 (15-67)	200	2.3(0.4-4.14) (/ULN)	6.6 (4.7–7.8)	12	13	
Manolakopoulos, 2004(32)	UK	30	Lamivudine	63.1±1.7	30	77 (26-280)	4.9 (3.2-7)	18 (3-36)	100	Case Control
		30	Control	62.8±1.4	30	80 (30-199)	NR	22 (2-55)	100	
Liaw, 2004(33)	Multi-national	436	Lamivudine	43 (17-74)	252	70 (14-959)	6.4 (<5.1-10.3)	32 (0-42)	31	RCT
		215	Placebo	44 (22-71)	124	68 (7-821)	6.6 (<5.1-8.9)	32 (0-42)	39	
Matsumoto, 2005(34)	Japan	657	Lamivudine	40.9±11.0	355	183.4± 211.1	NR	58.8 ±52.8	14.9	Case Control
		2138	Control	37.3±12.4	1272	163.5±234.3	NR	74.4±66	15.5	

Ma, 2007(35)	China	51	Lamivudine	NR	12	NR	NR	35	100	Cohort
		166	Control	NR	39	NR	NR	35	100	
Yuen, 2007(36)	Hong Kong	142	Lamivudine	33.9 (20.2-54.4)	142	125 (47–514)	8 (3.5-11)	89.9 (26.5-128.3)	0	Cohort
		124	Control	33.4 (20.8-59)	124	125 (47–514)	6.1 (0.8-8.9)	107.8 (30.9-127.3)	0	
Sun, 2009(37)	China	130	Lamivudine	44.3±3.5	90	474.1±83.4	> 4.3	3	10	Cohort
		130	Control	45.2±3.6	95	492.3±82.6	> 4.3	3	10	
Kim, 2012(38)	Korea	240	Lamivudine	49.6±10.9	145	159 ±265.4	6.2±0.6	46.4 (1–124)	100	Cohort
		481	Control	46.4±10.3	280	90.2 ±136.3	NR	51.4 (2–94)	100	
Eun, 2010(39)	Korea	872	Lamivudine	40.1±12.2	694	161±183.8	7.1±0.4	56.4±28.8	47.4	Cohort
		699	Control	35.5±12.9	637	141.3±199.1	6.7±0.3	68.4±50.4	37.2	
Wong, 2013(40)	Hong Kong	1466	Entecavir	51±12	443	145±319	5	36 ±13	100	Cohort
		424	Control	41±13	155	84 ±113	5	114±31	100	
Hosaka, 2013(41)	Japan	472	Entecavir	42±12.4	219	70 (42-163)	6 (4.6-7.3)	38.4 (25.2 –51.6)	25	Cohort
		1143	Control	39±13.1	398	33 (20-68)	5.1 (3.3-6.8)	114 (52.8-193.2)	17	
Lin, 2013(42)	China	53	Entecavir	38 (32–49)	16	360 (181–704)	5.8±0.8	12	32.1	Cohort
		55	Control	40 (34–47)	20	467 (107 –1192)	5.3±0.7	12	27.3	
Xiao, 2009(43)	China	39	Entecavir	NR	NR	NR	NR	NR	NR	Cohort
		39	Control	NR	NR	NR	NR	NR	NR	
Xu, 2009(44)	China	133	Telbivudine, entecavir or lamivudine	40.6±11.4	NR	534±712.8	4.3	NR	NR	Cohort
		215	Control	40.6±10.5	NR	526.1±688.5	3.8	NR	NR	
Chen, 2009(45)	China	55	Entecavir	43.6±10.9	14	357±405.2	5±0.65	3	NR	Cohort
		74	Control	40.3±11. 7	25	451.9±464.6	4.4±0.1.1	3	NR	
Garg, 2011(46)	India	14	Tenofovir	47.5 (16-62)	13	226 (188-1185)	5.2	3	NR	RCT
		13	Placebo	45 (16-67)	12	206 (186-2000)	5.5	3	NR	
Wu, 2014 (47)	Taiwan	21595	Variety of oral antivirals	43.5±13.4	26	179	5.3±0.3	40 (16.8-66)	13.2	Cohort
		21595	Control	43.6±13.6	12	185	5.3±1.3	78. (42.5-84)	14	
Gordon, 2014(48)	USA	820	IFN and variety of oral antiviral	NR	820	NR	NR	62.4 (36-108)	32.9	Cohort
		1851	Control	NR	1851	NR	NR	62.4 (36-108)	14.6	
Kumada, 2013 (49)	Japan	148	Variety of oral antiviral	53 (26-81)	76	65 (7-1088)	6.3 (1.9-8.9)	153.6(37.2 – 235.2)	62	Cohort

		637	Control	48 (4-85)	151	26 (5-3410)	3.1 (1.6-9.2)	164.4 (37.2-240)	91	
Question 1. Head to head studies comparing individual antiviral agents:										
Cui, 2010(28)	China	33	Entecavir	38.4±10.8	10	364 (47–2861)	5.2±0.8	0.2-41.5	NR	Cohort
		34	Lamivudine	39.4±10.6	13	226.5 (22–2314)	5.1±0.6	0.2-41.5	NR	
		37	Control	41.03±11.5	11	287 (17–2535)	5± 0.9	0.2-41.5	NR	
Chan, 2012(50)	China	114	Telbivudine	49.6±10.9	61	75.1±54.4	6.9 ± 1.2	24	100	RCT
		114	Lamivudine	51.9±10	55	84 ± 87.8	6.9 ± 1.2	24	100	
Chang, 2006(51)	Multi-national	354	Entecavir	35±13	348	140.5±114.3	8.9±1.3	12	8	RCT
		355	Lamivudine	35±13	351	146.3±132.3	9±1.3	12	8	
Lai, 2006(52)	Multi-national	325	Entecavir	44±11	3	141±114.7	6.9±1.1	12	5	RCT
		313	Lamivudine	44±11	4	143±119.4	6.9± 1	12	10	
Lau, 2005(53)	Multi-national	271	Peg-IFN plus Placebo	32.5±9.6	271	114.6±114.3	9.2±1.4	18	18	RCT
		271	Peg-IFN plus Lamivudine	31.7±10.3	271	114.9±94.1	9.4 ±1.2	18	15	
		272	Lamivudine	31.6±9.7	272	102.3±78.4	9.4±1.3	18	17	
Marcellin, 2004(54)	Multi-national	177	Peg-IFN plus Placebo	40±11.7	0	94.4±85.9	6.4±1.1	18	31	RCT
		179	Peg-IFN plus Lamivudine	41±10.8	0	90.8±76.2	6.5±1.1	18	22	
		181	Lamivudine	40±11.1	0	105.7±128.2	6.5±1.1	18	29	
Wang, 2013(55)	China	102	Adefovir	44±9.5	NR	72.76 ± 61.8	6.2 ± 1.2	24	100	RCT
		104	Lamivudine	44.9±10.03	NR	72.6±46.4	6.1 ± 1.1	24	100	
Yang, 2009(56)	China	32	Adefovir	31-62	NR	NR	NR	NR	100	RCT
		30	Lamivudine	25-69	NR	NR	NR	NR	100	
Liaw, 2011(57)	Taiwan	100	Entecavir	51±1.2	54	99.2± 11.1	6.8±0.01	24	100	RCT
		91	Adefovir	53±1.1	50	100± 8.6	7.5±0.01	24	100	
Lim, 2014(58)	Korea	2000	Entecavir	47±11	1168	101 (53-190)	7.1±1.6	37.2 (26.4-51.6)	53.6	Cohort
		3374	Lamivudine	43±11	2421	128 (68-244)	7.5±1.2	104.4 (78-138)	48	
Hsu, 2012(59)	Taiwan	53	Entecavir	48 (40-56)	18	467 (78-879)	6.1	12	45.3	Cohort
		73	Lamivudine	46 (37-58)	17	391 (68-1530)	6.3	12	48	
Wong, 2011(60)	Hong Kong	36	Entecavir	51±13	13	1151±724	6.6±1.4	18. ±12	14	Cohort
		117	Lamivudine	44±14	55	1499±841	6.8±0.9	79± 6	21	
Liang, 2009(61)	China	40	Telbivudine	51.8±10.7	20	NR	5.8±0.6	12	100	Cohort

		40	Lamivudine	52.4±8.5	18	NR	5.7± 0.6	12	100	
Chen, 2014(62)	Taiwan	215	Lamivudine	49.5±14.4	60	1239.4±941.7	5.8±1	20 (6.5-71.3)	42.8	Cohort
		107	Entecavir	48.6±14.1	35	1045.3±782.8	5.8±1.2	20 (6.5-71.3)	49.5	
Zhang, 2014(63)	China	65	Entecavir	42.8±13.1	21	352.5± 77.2	6.3 ± 0.7	12	NR	Cohort
		54	Lamivudine	45.6±11.4	23	345.2± 89.5	6.5± 0.9	12	NR	
Tsai, 2014(64)	Taiwan	53	Entecavir	49±13	15	1287± 788	8.2± 6.8	4	NR	Cohort
		114	Lamivudine	43±15	47	1629± 1011	7.5±6.9	4	NR	
Tsai, 2014(65)	Taiwan	88	Telbivudine	55.7±11.4	20	102.5± 137.5	5.1± 0.5	27.6	100	Cohort
		88	Entecavir	56.1±9.8	17	125.8± 179	5.3±0.4	53.1	100	
Koklu, 2013(66)	Turkey	72	Tenofovir	54.2±10.5	9	115.2±217.1	4.9± 1.2	12	100	Cohort
		76	Entecavir	54.2±11.2	17	86.2± 115.6	5± 1.2	12	100	
		74	Lamivudine	56.8±11.4	10	53.2±44.5	4 ± 1.3	12	100	
Question 2. Effectiveness of antiviral therapy in patients with immune-tolerant chronic HBV infection										
Chan, 2014(67)	Multi-national	64	Tenofovir and Placebo	33±9.5	63	26.9 ±14.05	8.4 ±0.4	48	NR	RCT
		62	Tenofovir and Emtricitabine	33 ±11.2	62	26.2 ±9.88	8.4 ± 0.4	48	NR	
Lu, 2015(68)	China	30	Peg-IFN and Adefovir	26.8 ± 3.1	30	<40	>5	6	NR	Cohort
		38	Control	26.8 ± 3.1	30			6	NR	
Question 3: Discontinuing vs continuing antiviral therapy in HBeAg positive patients who seroconverted from HBeAg to anti-HBe:										
Chaung, 2012 (69)	USA	49	Variety of oral antiviral alone or in combination	39±12	NR	87 (16-1281)	7±1.3	12	NR	Cohort
		39	Discontinued therapy	34±10	NR	139 (37-576)	7±1.2	12	NR	
Fung, 2009 (70)	Hong Kong	79	Lamivudine Continued therapy	32 (21 – 55)	NR	158 (21 – 2069)	7.9 (3 – 10.3)	45	NR	Cohort
		22	Discontinued therapy			176 (46 – 1670)	8.7 (6.4 – 10.2)	45	NR	
Question 5. Safety of entecavir compared to tenofovir:										
Koklu, 2013(66)	Turkey	54	Tenofovir	54.2±10.2	9	115.2±217.1	4.9±1.2	21.4±9.7	100	Cohort
		60	Entecavir	52.4±11.2	17	86.2±115.6	5±1.2	24.0±13.3	100	
Liaw, 2011 (71)	Multi-national	45	Tenofovir	52 (48-57)	14	48 (31-73)	5 (4.2-5.9)	12	NR	RCT
		45	Tenofovir and Emtricitabine	50 (42-58)	18	54 (34-98)	5.6 (3.8-6.6)	12	NR	
		22	Entecavir	54 (47-58)	7	52 (41-66)	5.2 (3.5-6.7)	12	NR	
Dogan, 2012 (72)	Turkey	65	Tenofovir	NR	29	114±181	7±6.9	12	NR	Cohort

		29	Entecavir	NR	10	84±69	7.2±7.6	12	NR	
Batirel, 2014(73)	Turkey	90	Tenofovir	43.3±12.9	29	116.7±92.6	7.6±4.6	30.2± 15.7	NR	Cohort
		105	Entecavir	42.0±11.2	36	120±96.6	7.6± 4.3	30.2± 15.7	NR	
Cholongitas, 2015(74)	Greece	31	Tenofovir	60±10	NR	57±40	3.8 (>0-5.6)	25 (6-66)	100	Cohort
		21	Entecavir	58±9	NR	75±34	4.6 (>0-7.4)	18 (7-68)	100	
Huang, 2015(75)	China	33	Tenofovir	35 (26-61)	NR	194.1±128.5	6.50 ± 0.69	13.4 (6.2-28.0)	NR	Cohort
		65	Entecavir	39 (20-67)	NR	157.6±216.8	6.15 ± 1.36	16 (6.0-27.0)	NR	
Hung, 2015(76)	Taiwan	41	Tenofovir	49.8±13.1	NR	1104 ±918	6.3±1.2	6	20	Cohort
		148	Entecavir	50.6±14.7	NR	1084 ±830	5.8±1.2	6	34	
Mallet, 2014(77)	France	70	Tenofovir	47 (37.8-56)	NR	52 (32–107)	4.4 (2.9–6.6)	22	NR	Cohort
		61	Entecavir	47 (37.8-56)	NR	52 (32–107)	4.4 (2.9–6.6)	22	NR	
Mauss, 2011(78)	Germany	37	Tenofovir	43 (19-75)	11	73 (21-528)	5.58 (2.41- >8.04)	12 (6-36)	NR	Cohort
		32	Entecavir	43 (20-73)	16	72 (18-2230)	6.38 (3.49- >8.04)	24 (6-48)	NR	
Tien, 2014(79)	USA	42	Tenofovir	49 ±12	11	NR	NR	26 ± 13	20	Cohort
		44	Entecavir	51 ±9	8	NR	NR	32 ± 24	10	
Gish, 2012(80)	USA	80	Tenofovir	54.5±13	NR	NR	6.99 (0-8.8)	20 (2 –45)	NR	Retrospective cohort study
		80	Entecavir	55.1 ±12	NR	NR	7.36 (0-8.7)	29 (1 – 55)	NR	

IFN=interferon, NR=not reported, RCT=randomized controlled trial, ULN=upper limit of normal

*Baseline HBV DNA in studies that used different units were converted using the formulas: 1 copy = 0.2 IU and 1 pg = 283,000 copies or 56,000 IU

Table 2: Risk of bias assessment in the included RCTs:

Author name, year	Sequence Generation	Allocation concealment	Blinding			Baseline imbalance	Attrition Bias or lost to follow up
			Participants	Providers	Outcome assessors		
Question 1: Effectiveness of antiviral therapy compared to control in patients with immune active chronic HBV infection (Antiviral vs control):							
Anderson , 1987 (8)	NR	NR	Yes	Yes	Yes	NR	NR
Krogsgaard, 1998 (23)	NR	NR	Yes	Yes	Yes	NR	NR
Chan, 2007(24)	Randomized /Randomization was centralized and stratified according to the geographical regions.	NR	Yes	Yes	Yes	No	More than 15%
Eun, 2007 (25)	Randomized	NR	NR	NR	NR	NR	NR
Dienstag, 1999(29)	Randomized	Yes	Yes	Yes	NR	No	10-15%,
Liaw, 2004(33)	Randomized	NR	Yes	NR	Yes	NR	NR
Garg, 2011 (46)	Randomized/ Randomization was done with a random number table.	Yes	Yes	Yes	NR	No	Less than 10%
Question 1. Head to head studies comparing individual antiviral agents:							
Chan, 2012 (50)	Randomized / Centralized, stratifying based on screening CPT score and ALT level.	Yes	Yes	Yes	Yes	No	Less than 10%
Chang, 2006(51)	Randomized	NR	Yes	Yes	Yes	NR	NR
Lai, 2006 (52)	Randomized	NR	Yes	NR	Yes	NR	NR
Lau, 2005 (53)	Randomized /Centralized and stratified according to geographic region and ALT levels.	NR	NR	NR	NR	NR	NR
Marcellin, 2004(54)	Randomized /Centralized and stratified according to geographic region and ALT levels.	NR	Yes	Yes	Yes	NR	NR
Wang, 2013 (55)	Randomized	NR	NR	NR	NR	No	NR
Yang, 2009 (56)	Randomized	NR	NR	NR	NR	NR	Less than 10%
Liaw, 2011(57)	Randomized / Randomization was not blocked or stratified	NR	No	No	No	No	Less than 10%
Question 2. Effectiveness of antiviral therapy in patients with immune-tolerant chronic HBV infection							
Chan, 2014(67)	Randomization	NR	Yes	Yes	NR	None	Less than 10%
Question 5. Safety of entecavir compared to tenofovir:							
Liaw, 2011 (71)	Randomization	NR	Yes	Yes	NR	None	Less than 10%

NR=not reported

Table 3: Risk of bias assessment for the included non-randomized studies:

Author name, year	Selection of Cohort / patients		Ascertainment of exposure	Assessment and clear ascertainment of outcome	Adequacy of follow up	Funding sources
	Exposed cohort	Non-exposed cohort/control				
Question 1: Effectiveness of antiviral therapy compared to control in patients with immune active chronic HBV infection (Antiviral vs control):						
IIHCSG, 1998 (9)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Lin, 2007 (10)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Truong, 2005 (11)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NA	NR
Tangkijvanich, 2001 (12)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Papatheodoridis, 2001 (13)	No description	No description of the derivation of the non-exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Niederau, 1996 (14)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Lin, 2004 (15)	Somewhat representative of the community or population	Drawn from a different community or population as the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Benvegnu, 1998 (16)	No description	No description	No description	No description	NR	NR
Tong, 2006 (17)	No description	No description	No description	No description	NR	NR
Di Marco, 1999 (18)	No description	No description	No description	No description	NR	NR
Brunetto, 2002 (19)	No description	No description	No description	No description	NR	NR
Mahmood, 2005 (20)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Ikeda, 1998 (21)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Fattovich, 1997(22)	Selected group of users	No description of the derivation of the non-exposed cohort	Secure records	Record linkage	NR	NR
Tong, 2009 (26)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Das, 2010 (27)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Cui, 2010 (28)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Chan, 2002(30)	Selected group of users	Drawn from a different community or population as the exposed cohort	Secure record	Record linkage	NR	NR
Lok, 2003 (31)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Follow-up rate < 90% and no description of the reasons for loss to follow-up	NR
Manolakopoulos, 2004 (32)	Selected group of users	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Matsumoto, 2005 (34)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NA	Reported
Ma, 2007 (35)	No description	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Yuen, 2007 (36)	Truly representative of the community or population	Drawn from a different community or population as the exposed cohort	Secure records	Record linkage	Follow-up rate < 90% and no description of the reasons for loss to	Reported

					follow-up	
Sun, 2010 (37)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Kim, 2012 (38)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Eun, 2010 (39)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Wong, 2013 (40)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Hosaka, 2013 (41)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Lin, 2013 (42)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Subjects lost to follow-up unlikely to introduce bias, small number lost to follow-up	Reported
Xiao, 2009 (43)	No description of the derivation of the cohort	Drawn from the same community as the exposed cohort	No description	No description	NR	NR
Xu, 2009 (44)	Truly representative of the community or population	No description of the derivation of the non-exposed cohort	No description	No description	NR	NR
Chen, 2009(45)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	No description	Record linkage	Complete follow-up, all subjects accounted for	Reported
Wu, 2014 (47)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Gordon, 2014(48)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	Reported
Kumada, 2013 (49)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	Reported
Question 1. Head to head studies comparing individual antiviral agents:						
Cui, 2010 (28)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Lim,2014 (58)	Selected group of users	Drawn from a different community or population as the exposed cohort	Secure records	Record linkage	Complete follow-up	Reported
Hsu, 2012(59)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	No description	NR	Reported
Wong, 2011 (60)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Independent blind assessment	Follow-up rate < 90% and no description of the reasons for loss to follow-up	Reported
Liang, 2009 (61)	No description	Drawn from the same community as the exposed cohort	Secure records	No description	Not reported	NR
Chen, 2014 (62)	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Secure records.	Record linkage	NR	Reported
Zhang, 2014 (63)	No description of the derivation of the cohort	No description of the derivation of the non-exposed cohort	Secure records	Record linkage	Follow-up rate < 90% and no description of the reasons for loss to follow-up	NR
Tsai, 2014 (64)	Selected group of users	Drawn from a different community or population as the exposed cohort	Secure records	Independent blind assessment	NR	NR
Tsai, 2014(65)	Truly representative of	Drawn from the same	Secure records	Record linkage	Follow-up rate <	Reported

	the community or population	community as the exposed cohort			90% and no description of the reasons for loss to follow-up	
Koklu, 2013 (66)	Truly representative of the community or population	Drawn from the same community as the exposed cohort	Secure records	Record linkage	Complete follow-up	NR
Question 2. Effectiveness of antiviral therapy in patients with immune-tolerant chronic HBV infection						
Lu 2015 (68)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Question 3: Discontinuing vs continuing antiviral therapy in HBeAg positive patients who seroconverted from HBeAg to anti-HBe						
Chaung, 2012 (69)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Fung, 2009 (70)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Question 5. Safety of entecavir compared to tenofovir:						
Koklu, 2013 (66)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Dogan, 2012 (72)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Batirel, 2014 (73)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Cholongitas, 2015 (74)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Huang, 2015 (75)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Hung, 2015 (76)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Mallet, 2014 (77)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Mauss, 2011 (78)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Tien, 2014 (79)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR
Gish, 2012 (80)	Selected group of users	Drawn from the same community as the exposed cohort	Secure records	Record linkage	NR	NR

NR=not reported

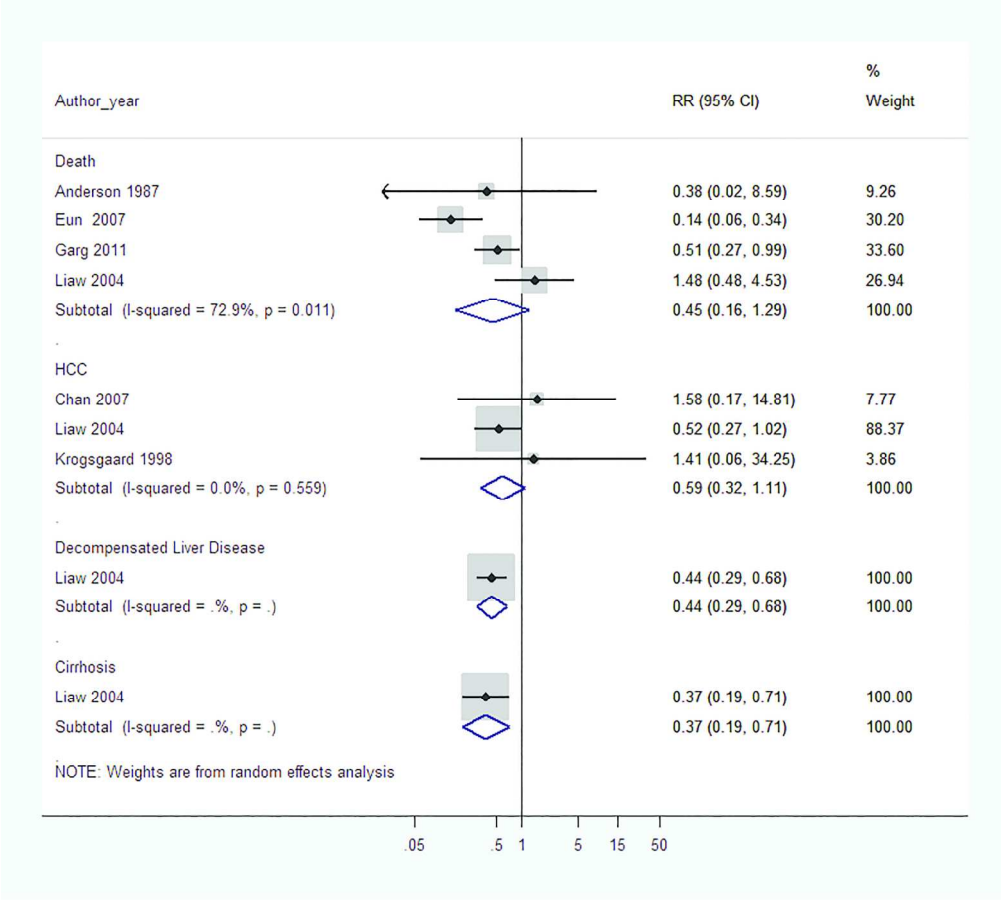
Table 4: Outcomes reported for Tenofovir vs. Entecavir in chronic HBV infection:

Author, year	Outcomes reported	Tenofovir	Entecavir	RR (95%CI)
		Events/total	Events/total	
Koklu, 2013(63)	Renal impairment	1/72	0/77	3.21 (0.13, 77.44)
	Hypophospothamia	1/72	0/77	3.21 (0.13, 77.44)
	Increase of creatinine kinase	0/72	1/77	0.36 (0.01 , 8.60)
Liaw, 2011(68)	Increase in Creatinine ≥ 0.5 mg/dL from baseline	4/45	1/22	1.96 (0.23, 16.47)
	Phosphorus of <2.0 mg/dL	1/45	0/22	1.50 (0.00, 35.40)
Batirel, 2014 (70)	Hypophospothamia	2/90	0/105	5.82 (0.28, 119.75)
Cholongitas, 2015(71)	eGFR <50 mL/min	3/31	2/21	1.02 (0.19, 5.57)
	Serum phosphate levels	NR	NR	NA
Hung, 2015(72)	Baseline in serum creatinine of 0.5 mg/dL	2/30	2/99	3.30 (0.49, 22.44)
	Reduction of estimated GFR	108 to 87 189 mL/min/1.73m^2	92 to 84 mL/min/1.73m^2	NA
Huang, 2015(73)	CK levels 2 times over the upper limit of normal	1/33	1/65	1.97 (0.13, 30.50)
Mallet, 2014(74)	Mean eGFR variation	0.6 (-0.8 to 1.94)	-0.1 (-1.5 to 1.3)	NA
Mauss, 2011(75)	Changes in eGFR (CKD-EPI formula)	-0.92 ml/ min	-1.00 ml/min,	NA
	Decrease of eGFR >20 ml/min	1/37	2/32	0.43 (0.04, 4.55)
Tien, 2014(76)	Phosphate threshold for renal tubular reabsorption < 2.8 mg/dL	18/42	10/44	1.89 (0.99, 3.60)
	GFR by Cockcroft Gault < 60 mL/min	1/42	2/44	0.52 (0.05, 5.56)
	GFR by MDRD < 60 mL/min	1/42	2/44	0.52 (0.05, 5.56)
	Serum phosphate (mg/dL) < 2.8 mg/dL	6/42	2/44	3.14 (0.67, 14.71)
	Serum creatinine (mg/dL) >1.5 mg/dL	0/42	0/44	NA
	Serum alkaline phosphatase (U/L) > 145 U/L	0/42	1/44	0.35 (0.01, 8.33)
Gish, 2012(77)	Confirmed SCr increase 0.5 mg/dL	3/80	11/80	0.27 (0.08, 0.94)
	New Cockcroft–Gault eGFR < 60 mL/min	15/80	6/80	2.50 (1.02, 6.12)
	Decrease in eGFR 20% (MDRD)	33/80	35/80	0.94 (0.66, 1.35)

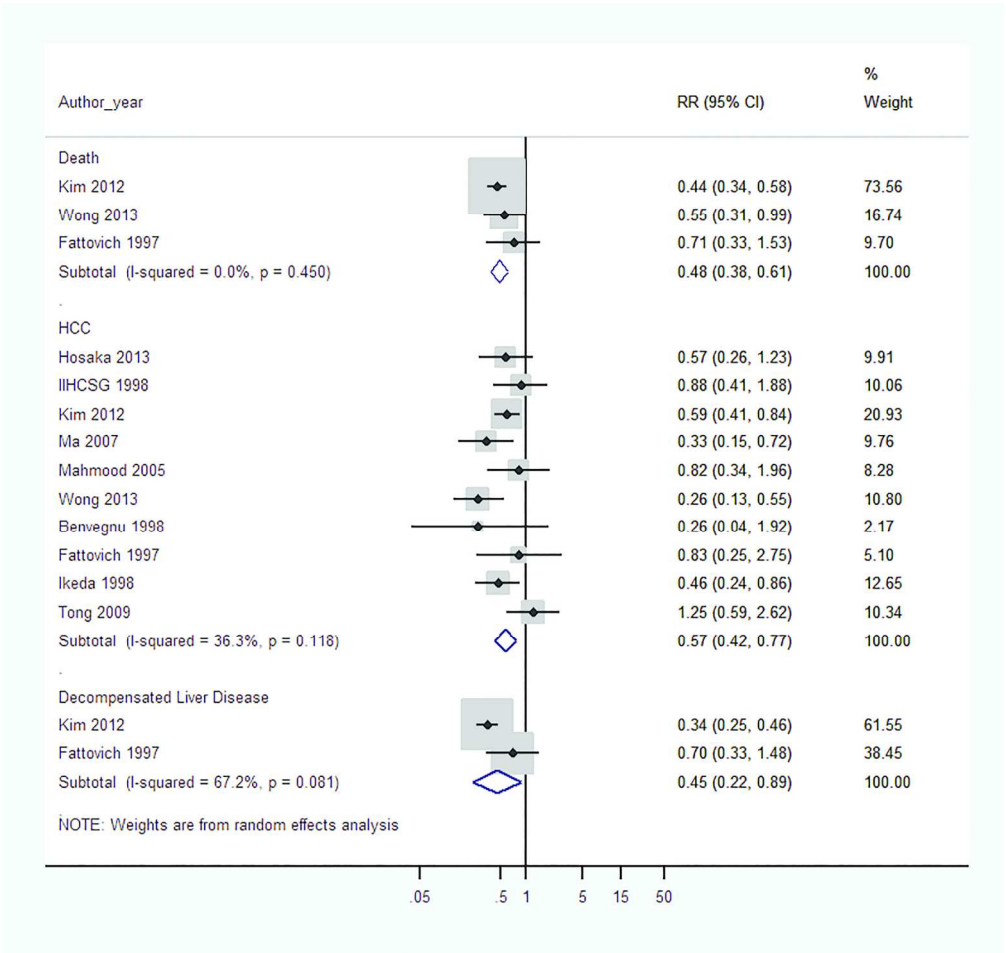
NR: not reported; NA: not available; SCr: serum creatinine; CK: creatine kinase; eGFR: estimated glomerular filtration rate

Unable to Convert Image

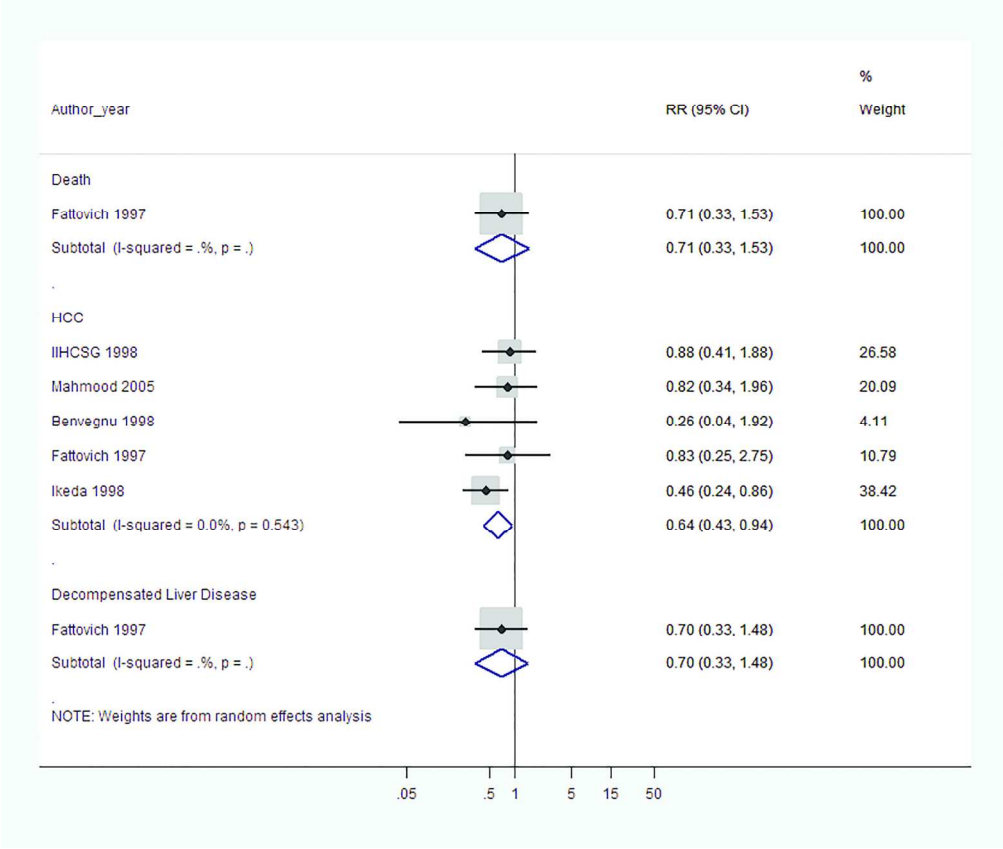
The dimensions of this image (in pixels) are too large to be converted. For this image to convert, the total number of pixels (height x width) must be less than 40,000,000 (40 megapixels).



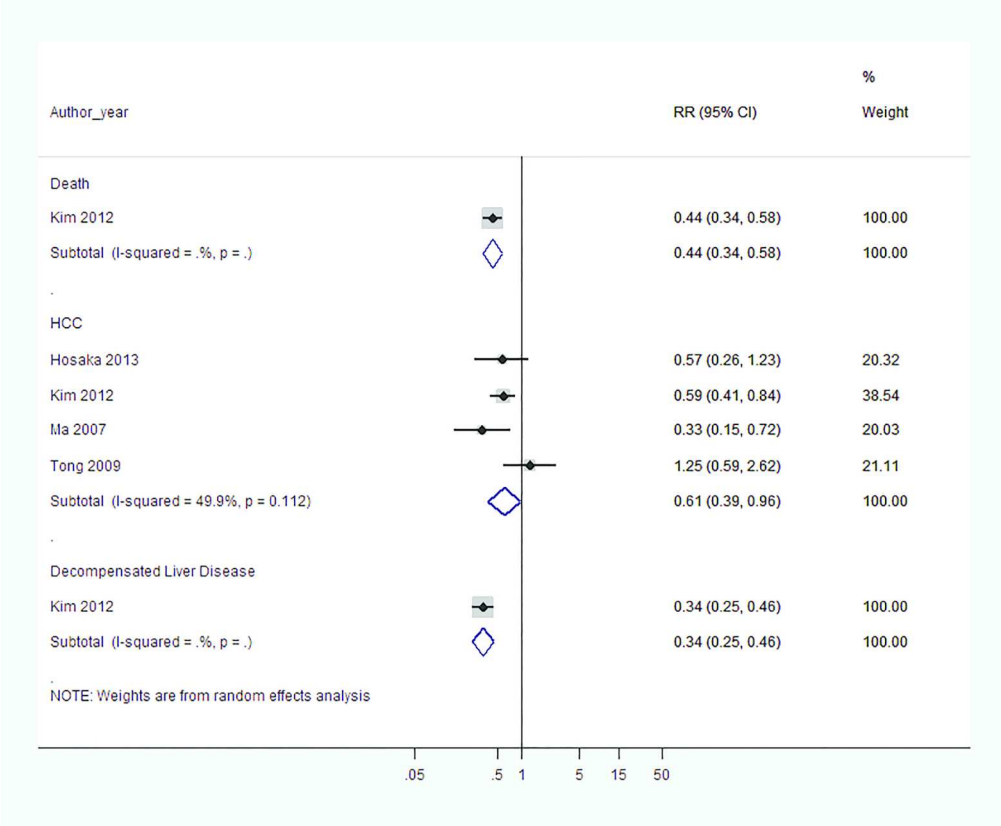
220x197mm (300 x 300 DPI)



220x208mm (300 x 300 DPI)



220x186mm (300 x 300 DPI)



220x181mm (300 x 300 DPI)

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 2: Detailed Search Strategy:

Ovid

Database(s): Embase 1988 to 2014 Week 37, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials August 2014, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2014
Search Strategy:

#	Searches	Results
1	exp Hepatitis B/dt	26410
2	("hepatitis B" or "serum hepatitis" or "hippie hepatitis" or "injection hepatitis" or "hepatitis type B").mp.	178548
3	1 or 2	178548
4	exp Antiviral Agents/	916254
5	exp antivirus agent/	612059
6	("1-Deoxynojirimycin" or absouline or "abt 333" or "abt 450" or Acetylcysteine or aciclovir or "acyclouridine derivative" or Acyclovir or "adenine xyloside" or "adenosine dialdehyde" or afovirsen or "al 721" or alamifovir or alisporivir or "aln rsv 01" or "alvircept sudotox" or amantadine or amenamevir or amidapsone or amitivir or "ammonium trichloro dioxyethylene o o tellurate" or amsacrine or "ana 975" or "anti viral agent" or AntiRetroviral* or "Anti-Retroviral*" or antiretrovirus or antiviral* or "anti-viral*" or Aphidicolin or arasangivamycin or arbidol or arildone or astodrimer or asunaprevir or avarol or avarone or avridine or "azd 7295" or balapiravir or bavituximab or "behenyl alcohol" or benzimidavir or besifovir or boceprevir or bonaphthone or "Brefeldin A" or brincidofovir or Bromodeoxyuridine or bropirimine or buciclovir or carbocyclic or carbodine or carrageenan or cidofovir or ciluprevir or clevudine or "cpg 10101" or crofelemer or cyclaradine or "cyclosporin A" or cytarabine or daclatasvir or damavaricin or danoprevir or dasabuvir or deitiphorin or deleobuvir or denotivir or deoxyaristeromycin or Deoxyglucose or deoxypenciclovir or deoxyribavirin or desciclovir or detiviciclovir or "didemnin A" or "didemnin B" or Dideoxyadenosine or Dideoxynucleoside* or disoxaril or "distamycin 5" or "distamycin A" or Ditiocarb or droxinavir or edoxudine or elbasvir or "enisamium iodide" or enviroxime or epetirimod or eudistomin or exbivirumab or faldaprevir or famciclovir or favipiravir or felvizumab or fiacitabine or fialuridine or filibuvir or Filipin or florenal or "flucytosine arabinoside" or fomivirsen or foravirumab or fosarilate or foscarnet or fosdevirine or fucoidin or "gamma venin" or ganciclovir or "gene expression modulator" or grazoprevir or "gs 9256" or "guanine 7 oxide" or hypericin or "hypoxanthine arabinoside" or idoxuridine or "idoxuridine derivative" or "idx 184" or imexon or imiquimod or "Inosine Pranobex" or iododeoxycytidine or ipilimumab or isatoribine or "isis 13312" or "isis 14803" or laninamivir or larifan or ledipasvir or letermovir or levovirin or lexithromycin or libivirumab or litomeglovir or lomibuvir or mericitabine or merimepodib or Methisazone or methisoprinol or methylcytidine or metisazone or miravirsen or	747988

	moroxydine or motavizumab or "mycophenolic acid" or "Myxovirus resistance protein" or "n bromoacetyldistamycin A" or narlaprevir or neceprevir or "neominophagen C" or nesbuvir or netivudine or netropsin or nivocasan or omaciclovir or ombitasvir or oseltamivir or palivizumab or penciclovir or "penciclovir triphosphate" or peramivir or "phosphonoacetic acid" or "Phosphonoacetic Acid" or pirazofurin or pirodavir or pleconaril or pocapavir or "pokeweed antivirus protein" or "Poly A-U" or "Poly I-C" or pritelivir or pseudohypericin or "pyran copolymer" or "Pyran Copolymer" or radavirsen or rafivirumab or "recombinant intercellular adhesion molecule 1" or regavirumab or resiquimod or ribavirin or "ribavirin derivative" or rifabutin or rimantadine or rintatolimod or riodoxol or rociclovir or rupintrivir or samatasvir or sangivamycin or "sangivamycin derivative" or "scopadulcic acid B" or setrobuvir or sevirumab or simeprevir or sofosbuvir or sorivudine or sovaprevir or streptovaricin or Streptovaricin or streptovirudin or suramin or suvizumab or synadenol or synguanol or taribavirin or tebrofen or tecovirimat or tegobuvir or telaprevir or telbivudine or "Tenuazonic Acid" or "thiarubrine A" or "thiophene A" or "thymine arabinoside" or tilorone or Tilorone or "tilorone derivative" or tiviciclovir or tomeglovir or torcitabine or trifluridine or tromantadine or tunicamycin or tuvirumab or umifenovir or "uracil arabinoside" or valaciclovir or valganciclovir or valomaciclovir or valopicitabine or valtorcitabine or vaniprevir or vapendavir or vedroprevir or vidarabine or Vidarabine or viracine or "viral inhibitor*" or virantmycin or virostatic* or viroxime or virucidal* or virucide* or "virus repressor*" or virustatic* or xanthogenate or "xenazoic acid" or zanamivir or Zanamivir or zinviroxime).mp.	
	4 or 5 or 6	1210019
	exp Interferons/	453948
	exp interferon/	453948
0	("cl 884" or cl884 or ifn or interferon* or interferone* or interferonogen* or interferron* or "interleukin 28A" or "interleukin 29" or "interleukin 6" or leif or peginterferon* or peginterferone* or peginterferonogen* or peginterferron*).mp.	629323
1	8 or 9 or 10	629423
2	exp Carcinoma, Hepatocellular/	142803
3	exp liver cell carcinoma/	142803
4	exp Fibrosis/	185872
5	exp liver cirrhosis/	157245
6	exp Morbidity/	612417
7	exp Mortality/	892082
8	exp Death/	531063
9	exp Survival/	616331
0	mo.fs.	448163
1	Virus Activation/	7949
2	exp virus reactivation/	7579
3	(((liver or hepatic) adj2 carcinoma*) or cirrhoses or cirrhosis or death or	4878731

	decompensat* or "e AG" or eAG or fatal* or fibroses or fibrosis or flare* or HCC or hepatocarcinoma* or "hepatocellular carcinoma*" or hepatoma* or morbidity or mortality or myxofibroses or myxofibrosis or reactivat* or "s AG" or sAG or surviv*).mp.	
4	or/12-23	5422174
5	3 and (7 or 11) and 24	19331
6	exp evidence based medicine/	722657
7	exp meta analysis/	134228
8	exp Meta-Analysis as Topic/	29609
9	exp "systematic review"/	79495
0	exp Guideline/ or exp Practice Guideline/	344743
1	exp controlled study/	4517923
2	exp Randomized Controlled Trial/	723728
3	exp triple blind procedure/	68
4	exp Double-Blind Method/	343004
5	exp Single-Blind Method/	51300
6	exp latin square design/	276
7	exp comparative study/	2460744
8	exp intervention studies/	29818
9	exp Cross-Sectional Studies/	307798
0	exp Cross-Over Studies/	101471
1	exp Cohort Studies/	1680879
2	exp longitudinal study/	1065173
3	exp retrospective study/	865208
4	exp prospective study/	701582
5	exp clinical trial/	1729495
6	clinical study/	53696
7	exp case-control studies/	784997
8	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (control* adj2 study) or (control* adj2 trial) or (randomized adj2 study) or (randomized adj2 trial) or (randomised adj2 study) or (randomised adj2 trial) or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analys*" or "cross- sectional survey*" or "cross-sectional design*" or crossover or "cross-over" or "cohort study" or "cohort survey" or "cohort analysis" or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "retrospective study" or "retrospective survey" or "retrospective analysis" or "prospective study" or "prospective survey" or "prospective analysis" or	13490340

	"concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case compeer study" or "case comparison study" or cohort* or ((study or trial or random* or control*) and compar*)).mp.	
9	or/26-48	14249133
0	25 and 49	10972
1	from 25 keep 13107-18830	5724
2	limit 51 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) [Limit not valid in Embase,CCTR,CDSR; records were retained]	1113
3	50 or 52	10981
4	limit 53 to (book or book series or editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	470
5	53 not 54	10511
6	from 25 keep 18831-19331	501
7	55 or 56	10673
8	limit 57 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19- 24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	9801
9	limit 58 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	5259
0	57 and (adult or adults or "middle age" or "middle aged").mp.	5349
1	59 or 60	5510
2	61 and chronic*.mp.	3604
3	62 not (exp animals/ not exp humans/)	3519
4	from 62 keep 3522-3604	83
5	63 or 64	3602
6	remove duplicates from 65	2441

Scopus

1 TITLE-ABS-KEY("hepatitis B" or "serum hepatitis" or "hippie hepatitis" or "injection hepatitis" or "hepatitis type B")

2 TITLE-ABS-KEY("1-Deoxynojirimycin" OR absouline OR "abt 333" OR "abt 450" OR Acetylcysteine OR aciclovir OR "acyclouridine derivative" OR Acyclovir OR "adenine xyloside" OR "adenosine dialdehyde" OR afovirsen OR "al 721" OR alamifovir OR alisporivir OR "aln rsv 01" OR "alvircept sudotox" OR amantadine OR amenamevir OR amidapsone OR amitivir OR "ammonium trichloro dioxyethylene o o tellurate" OR amsacrine OR "ana 975" OR "anti viral agent" OR AntiRetroviral* OR "Anti-Retroviral*" OR antiretrovirus OR antiviral* OR "anti-viral*" OR Aphidicolin OR arasangivamycin OR arbidol OR arildone OR astodrimer OR asunaprevir OR avarol OR avarone OR avridine OR "azd 7295" OR balapiravir OR bavituximab OR "behenyl alcohol" OR benzimidavir OR besifovir OR boceprevir OR bonaphthone OR "Brefeldin A" OR brincidofovir OR Bromodeoxyuridine OR bropirimine OR buciclovir OR carbocyclic OR carbodine OR carrageenan OR cidofovir OR ciluprevir OR clevudine OR "cpg 10101" OR crofelemer OR cyclaradine OR "cyclosporin A" OR cytarabine OR daclatasvir OR damavaricin OR danoprevir OR dasabuvir OR deitiphorin OR deleobuvir OR denotivir OR deoxyaristeromycin OR Deoxyglucose OR deoxypenciclovir OR deoxyribavirin OR desciclovir OR detiviciclovir OR "didemnin A" OR "didemnin B" OR Dideoxyadenosine OR Dideoxynucleoside* OR disoxaril OR "distamycin 5" OR "distamycin A" OR Ditiocarb OR droxinavir OR edoxudine OR elbasvir OR "enisamium iodide" OR enviroxime OR epetirimod OR eudistomin OR exbivirumab OR faldaprevir OR famciclovir OR favipiravir OR felvizumab OR fiacitabine OR fialuridine OR filibuvir OR Filipin OR florenal OR "flucytosine arabinoside" OR fomivirsen OR foravirumab OR fosarilate OR foscarnet OR fosdevirine OR fucoidin OR "gamma venin" OR ganciclovir OR "gene expression modulator" OR grazoprevir OR "gs 9256" OR "guanine 7 oxide" OR hypericin OR "hypoxanthine arabinoside" OR idoxuridine OR "idoxuridine derivative" OR "idx 184" OR imexon OR imiquimod OR "Inosine Pranobex" OR iododeoxycytidine OR ipilimumab OR isatoribine OR "isis 13312" OR "isis 14803" OR laninamivir OR larifan OR ledipasvir OR letermovir OR levovirin OR lexithromycin OR libivirumab OR litomeglovir OR lomibuvir OR mericitabine OR merimepodib OR Methisazone OR methisoprinol OR methylcytidine OR metisazone OR miravirsen OR moroxydine OR motavizumab OR "mycophenolic acid" OR "Myxovirus resistance protein" OR "n bromoacetyldistamycin A" OR narlaprevir OR neceprevir OR "neominophagen C" OR nesbuvir OR netivudine OR netropsin OR nivocasan OR omaciclovir OR ombitasvir OR oseltamivir OR palivizumab OR penciclovir OR "penciclovir triphosphate" OR peramivir OR "phosphonoacetic acid" OR "Phosphonoacetic Acid" OR pirazofurin OR pirodavir OR pleconaril OR pocapavir OR "pokeweed antivirus protein" OR "Poly A-U" OR "Poly I-C" OR pritelivir OR pseudohypericin OR "pyran copolymer" OR "Pyran Copolymer" OR radavirsen OR rafivirumab OR "recombinant intercellular adhesion molecule 1" OR regavirumab OR resiquimod OR ribavirin OR "ribavirin derivative" OR rifabutin OR rimantadine OR rintatolimod OR riodoxol OR rociclovir OR rupintrivir OR samatasvir OR sangivamycin OR "sangivamycin derivative" OR "scopadulcic acid B" OR setrobuvir OR

	sevirumab OR simeprevir OR sofosbuvir OR sorivudine OR sovaprevir OR streptovaricin OR Streptovaricin OR streptovirudin OR suramin OR suvizumab OR synadenol OR synguanol OR taribavirin OR tebrofen OR tecovirimat OR tegobuvir OR telaprevir OR telbivudine OR "Tenuazonic Acid" OR "thiarubrine A" OR "thiophene A" OR "thymine arabinoside" OR tilorone OR Tilorone OR "tilorone derivative" OR tiviciclovir OR tomeglovir OR torcitabine OR trifluridine OR tromantadine OR tunicamycin OR tuvirumab OR umifenovir OR "uracil arabinoside" OR valaciclovir OR valganciclovir OR valomaciclovir OR valopicitabine OR valtorcitabine OR vaniprevir OR vapendavir OR vedroprevir OR vidarabine OR Vidarabine OR viracine OR "viral inhibitor*" OR virantmycin OR virostatic* OR viroxime OR virucidal* OR virucide* OR "virus repressor*" OR virustatic* OR xanthogenate OR "xenazoic acid" OR zanamivir OR Zanamivir OR zinviroxime)
3	TITLE-ABS-KEY("cl 884" OR cl884 OR ifn OR interferon* OR interferone* OR interferonogen* OR interferron* OR "interleukin 28A" OR "interleukin 29" OR "interleukin 6" OR leif OR peginterferon* OR peginterferone* OR peginterferonogen* OR peginterferron*)
4	TITLE-ABS-KEY(((liver or hepatic) W/2 carcinoma*) OR cirrhoses OR cirrhosis OR death OR decompensat* OR "e AG" OR eAG OR fatal* OR fibroses OR fibrosis OR flare* OR HCC OR hepatocarcinoma* OR "hepatocellular carcinoma*" OR hepatoma* OR morbidity OR mortality OR myxofibroses OR myxofibrosis OR reactivat* OR "s AG" OR sAG OR surviv*)
5	TITLE-ABS-KEY(chronic*)
6	TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or guideline* or (control* W/2 study) or (control* W/2 trial) or (randomized W/2 study) or (randomized W/2 trial) or (randomised W/2 study) or (randomised W/2 trial) or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analys*" or "cross- sectional survey*" or "cross-sectional design*" or crossover or "cross-over" or "cohort study" or "cohort survey" or "cohort analysis" or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "retrospective study" or "retrospective survey" or "retrospective analysis" or "prospective study" or "prospective survey" or "prospective analysis" or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case compeer study" or "case comparison study" or cohort* or ((study or trial or random* or control*) and compar*))
7	TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged")
8	1 and (2 or 3) and 4 and 5 and 6 and 7
9	DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
10	8 and not 9
11	PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)

0 and not 11

Supplemental File 3:

Indirect and non-comparative evidence

PICO3: Can antiviral therapy, specifically nucleos(t)ide analogues be stopped in HBeAg-positive persons who achieved HBeAg seroconversion?

An extensive review by the Evidence Practice Center at Mayo Clinic found only 2 studies comparing HBeAg-positive persons receiving nucleos(t)ide analogue therapy for chronic hepatitis B who stopped treatment after achieving HBeAg seroconversion to those who did not. There are other studies in the published literature on this topic. These studies focused on describing viral relapse, hepatitis flares and HBeAg seroreversion but did not report on clinical outcomes. They also did not have a comparison group that continued treatment. Some studies did examine the durability of response in relation to the duration of consolidation therapy, i.e. duration of continued treatment after achieving HBeAg seroconversion.

One retrospective study in Korea included 178 patients who received lamivudine and achieved HBeAg seroconversion (1). Cumulative relapse rate 5 years after stopping treatment was 8.7% vs. 61.9% for patients who had <12 vs ≥12 months consolidation therapy ($p<0.001$). Independent predictors of relapse were age >40 years and duration of consolidation therapy <12 months.

Another retrospective study included 88 Asian patients who achieved HBeAg seroconversion on various nucleos(t)ide analogues, 49 continued treatment and all maintained undetectable HBV DNA. Of the 39 who stopped treatment, 35 had viral relapse, 15 had biochemical relapse (ALT >2 times upper limit of normal (x ULN)), and 3 had HBeAg seroreversion (2). Risk of viral relapse was not related to the duration of consolidation therapy.

A recent retrospective study from 3 Asian centers included 101 patients who stopped lamivudine treatment after achieving HBeAg seroconversion found that response was maintained in 25.6%, 39.0%, and 71.4% of patients who had consolidation therapy for <12, 12-18 and >18 months, respectively (3).

Despite these discrepant findings, duration of consolidation therapy is the most consistent predictor of durable response in patients who stopped nucleos(t)ide analogue therapy after achieving HBeAg seroconversion followed by age of patients (1, 3-8). Collectively, these data indicate that viral relapse is common in HBeAg-positive patients who stopped nucleos(t)ide analogue therapy after achieving HBeAg seroconversion. A longer duration of consolidation therapy (>12 months) decreases but does not eliminate the risk of relapse.

PICO 4: Can antiviral therapy, specifically nucleos(t)ide analogues be stopped in HBeAg-negative persons? What is the impact on cirrhosis, hepatic decompensation, HCC, relapse (viral and clinical) and HBsAg loss in patients who stopped versus those who continued therapy?

An extensive review by the Evidence Practice Center at Mayo Clinic failed to find any RCT or cohort studies examining the outcomes of cirrhosis, hepatic decompensation, HCC, relapse (viral and clinical), and HBsAg loss comparing HBeAg-negative persons receiving nucleos(t)ide analogue therapy for chronic hepatitis B who stopped treatment compared to those who did not. We reviewed the literature looking specifically for titles of articles describing case series of HBeAg-negative persons receiving nucleos(t)ide analogues who stopped treatment. We found 6 retrospective studies on this topic that provide some guidance on this clinically important question.

Of note, the Asian Pacific Association for the Study of the Liver (APASL) 2012 guidelines stated that treatment may be discontinued in HBeAg-negative patients who completed at least 2 years of nucleos(t)ide analogue treatment and have undetectable HBV DNA on at least 3 occasions that are at least 6 months apart (9). This recommendation was based on results of a study of 27 HBeAg-negative patients who stopped lamivudine after 2 years of treatment and had three consecutive undetectable HBV DNA ≥3 months apart in year 2 of treatment. In that study, the cumulative probability of viral relapse (defined as reappearance of HBV DNA by PCR) at 6, 12, and 18 months was 30%, 50%, and 50% respectively; and of clinical relapse (defined as HBV DNA >30,000 IU/ml and ALT >1.5x ULN) 12%, 18% and 30%, respectively (10). The APASL recommendations were mostly driven by financial considerations because coverage of HBV medications by the government in Asian countries, particularly for those with no cirrhosis, is often limited to 2-3 years.

A subsequent study in China of 61 HBeAg-negative patients who received lamivudine for a median of 27 (24-66) months and who had undetectable HBV DNA and normal ALT for 18 months found that cumulative rates of viral relapse (defined as HBV DNA >2,000 IU/ml on 2 consecutive samples at least 1 week part) at 1, 2, 3, 4 and 5 years were 43.6%, 49.7%, 52.1%, 56.1%, and 56.1%, respectively (11).

In the third study from Greece, 33 HBeAg-negative non-cirrhotic patients with undetectable HBV DNA and normal ALT after 4-5 years of adefovir treatment stopped therapy and were followed for a median of 69 (range 67-72) months (12). All had virologic relapse defined as increase in HBV DNA to >2000 IU/ml. In most patients, peak HBV DNA occurred during the first 2 months after treatment was stopped. 25 (76%) patients had biochemical relapse defined as ALT >1.2x ULN. During the follow-up period, 18 patients (55%) who had discontinued antiviral therapy achieved sustained virologic response (HBV DNA <2000 IU/ml and persistently normal ALT). Among these, 13 (72%) cleared HBsAg. Multivariate analysis found that higher pretreatment and end of treatment levels of ALT, no previous treatment with

interferon, and lower levels of HBsAg at the end of treatment were significantly associated with HBsAg clearance.

A fourth study conducted in Taiwan tested the validity of the APASL recommendations. In this study, 95 HBeAg-negative patients who met APASL criteria for stopping nucleos(t)ide analogue treatment and had at least 1 year post-treatment follow-up were studied (13). 39 (41.1%) of the patients had clinical or histological evidence of cirrhosis. Median duration of entecavir treatment prior to stopping therapy was 721 (range 395-1762) days. Within 1 year after stopping treatment, 43 (45.3%) patients experienced clinical relapse defined as ALT >2x ULN and HBV DNA >2000 IU/ml. Of the 39 patients with cirrhosis, 17 (43.6%) had clinical relapse and 1 (2.6%) had decompensation. Median duration to clinical relapse was 230 (range 79-368) days with74.4% clinical relapses occurring beyond 6 months after stopping treatment. Logistic regression analysis showed that baseline HBV DNA >200,000 IU/ml was the only predictor of clinical relapse.

The fifth study also conducted in Taiwan included 263 consecutive patients (94 with cirrhosis) who stopped lamivudine after recovering from a flare of hepatitis with hepatic decompensation (14). 147 patients (64 cirrhosis and 83 non-cirrhotic) were HBeAg-negative at the start of treatment. Mean duration of lamivudine was 12.1 ± 8.6 months. 139 patients resumed treatment. Within the first year of stopping treatment, 29.9% of patients had clinical relapse, 16.2% had hepatitis flares, and 8.2% had hepatic decompensation. Three patients with cirrhosis died of hepatic decompensation. Multivariate analysis showed that men were more likely to have hepatic decompensation.

The sixth study, conducted in Korea, presented at the AASLD Annual Meeting in 2014 and published in abstract form found that 54% of HBeAg-negative patients who met APASL criteria for stopping antiviral therapy relapsed within 1 year of stopping treatment (15).

Collectively, these studies showed that cessation of nucleos(t)ide therapy is possible in some HBeAg-negative patients who have completed 2-5 years of nucleos(t)ide analogue therapy and have persistently undetectable HBV DNA. Clinical factors associated with a successful outcome after stopping antiviral therapy have not been identified. Viral relapse is common but not all patients experience clinical relapse necessitating re-treatment. However, hepatic decompensation and death can occur and this risk appears to be higher in those with cirrhosis at the start of treatment.

PICO #6: **Adding a second antiviral agent compared to continuing monotherapy (entecavir or tenofovir) in patients with chronic HBV infection and persistent viremia?**

For add-on therapy in patients who failed to achieve viral suppression with either tenofovir or entecavir monotherapy, we did not identify any RCT comparing adding a second antiviral agent versus continuing tenofovir or entecavir monotherapy. We did identify 1 RCT comparing de novo combination of entecavir and tenofovir vs entecavir monotherapy. Clinical outcomes were not reported. De novo combination therapy did not result in higher rates of intermediate responses except in the subset of patients with high viremia (>10^8 IU/ml) where a higher proportion (79% vs 62%) of patients had HBV DNA suppression to <50 IU/ml at week 96 (16).

PICO 7: Hepatitis B and compensated cirrhosis with low level viremia (<2,000 IU/ml)

An extensive review by the Evidence Practice Center at Mayo Clinic failed to find any RCT or cohort studies examining the outcomes of liver related death, HCC and hepatic decompensation comparing persons who received antiviral therapy for HBV compensated cirrhosis and low level viremia (<2,000 IU/ml) compared to those who did not. We reviewed the literature looking specifically for titles of articles describing case series on persons with cirrhosis who had low level viremia and received antiviral therapy. No specific titles or abstracts were found. One retrospective study of 385 treatment-naïve patients with HBV-related compensated cirrhosis and HBV DNA <2,000 IU/ml found that 5-year cumulative HCC incidence rate was 2.2%, 8.0% and 14.0% for patients with baseline undetectable HBV DNA (<12 IU/ml), detectable HBV DNA <2,000 IU/ml and normal ALT, and detectable HBV DNA <2,000 IU/ml and elevated ALT, respectively (17). During follow up, 77 patients started antiviral therapy. In patients who did not receive antiviral therapy, the 5-year cumulative HCC incidence rates were 13.3%, 8.8% and 1.4% for patients who experienced HBV DNA increase, patients who maintained detectable HBV DNA <2,000 IU/ml, and patients who maintained undetectable HBV DNA, respectively. In patients who started antiviral therapy, the 5-year cumulative HCC incidence rate was 5.9% and longer duration of antiviral therapy and longer duration of complete virological response were associated with lower HCC risk. These data suggest that antiviral therapy may decrease the risk of HCC in patients with compensated cirrhosis and low level viremia but characteristics of patients who did and those who did not start antiviral therapy were different. In addition, in many patients who received treatment, HBV DNA levels were >2,000 IU/ml at the time treatment was started.

References:

1. Lee HW, Lee HJ, Hwang JS, Sohn JH, Jang JY, Han KJ, et al. Lamivudine maintenance beyond one year after HBeAg seroconversion is a major factor for sustained virologic response in HBeAg-positive chronic hepatitis B. Hepatology 2010;51:415-421.
2. Chaung KT, Ha NB, Trinh HN, Garcia RT, Nguyen HA, Nguyen KK, et al. High frequency of recurrent viremia after hepatitis B e antigen seroconversion and consolidation therapy. Journal of Clinical Gastroenterology 2012;46:865-870.
3. Dai CY, Tseng TC, Wong GL, Huang JF, Wong VW, Liu CJ, et al. Consolidation therapy for HBeAg-positive Asian chronic hepatitis B patients receiving lamivudine treatment: a multicentre study. The Journal of antimicrobial chemotherapy 2013;68:2332-2338.
4. Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology 2000;32:803-806.
5. Ryu SH, Chung YH, Choi MH, Kim JA, Shin JW, Jang MK, et al. Long-term additional lamivudine therapy enhances durability of lamivudine-induced HBeAg loss: a prospective study. Journal of Hepatology 2003;39:614-619.
6. Chien RN, Yeh CT, Tsai SL, Chu CM, Liaw YF. Determinants for sustained HBeAg response to lamivudine therapy. Hepatology 2003;38:1267-1273.
7. Wu IC, Shiffman ML, Tong MJ, Marcellin P, Mondou E, Frederick D, et al. Sustained hepatitis B e antigen seroconversion in patients with chronic hepatitis B after adefovir dipivoxil treatment: analysis of precore and basal core promoter mutants. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2008;47:1305-1311.
8. Song MJ, Song do S, Kim HY, Yoo SH, Bae SH, Choi JY, et al. Durability of viral response after off-treatment in HBeAg positive chronic hepatitis B. World journal of gastroenterology : WJG 2012;18:6277-6283.
9. Liaw Y-F, Kao J-H, Piratvisuth T, Chan H, Chien R-N, Liu C-J, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatology International 2012;6:531-561.
10. Fung SK, Wong F, Hussain M, Lok AS. Sustained response after a 2-year course of lamivudine treatment of hepatitis B e antigen-negative chronic hepatitis B. Journal of Viral Hepatitis 2004;11:432-438.
11. Liu F, Wang L, Li XY, Liu YD, Wang JB, Zhang ZH, Wang YZ. Poor durability of lamivudine effectiveness despite stringent cessation criteria: a prospective clinical study in hepatitis B e antigen-negative chronic hepatitis B patients. Journal of gastroenterology and hepatology 2011;26:456-460.
12. Hadziyannis SJ, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 2012;143:629-636 e621.
13. Jeng WJ, Sheen IS, Chen YC, Hsu CW, Chien RN, Chu CM, Liaw YF. Off-therapy durability of response to entecavir therapy in hepatitis B e antigen-negative chronic hepatitis B patients. Hepatology 2013;58:1888-1896.
14. Chang ML, Jeng WJ, Liaw YF. Clinical events after cessation of lamivudine therapy in patients recovered from hepatitis B flare with hepatic decompensation. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2015;13:979-986.
15. Jun Yong Park, Kyu sik Chung, Young Eun Chon, Hyon Suk Kim, Wonseok Kang, Seung Up Kim, et al. Prospective Observational Cohort Study For The Durability Of Oral Antiviral Treatment In Patients With Chronic Hepatitis B: Quit Study. Hepatology 2014;60:1088A-1128A.

16. Lok AS, Trinh H, Carosi G, Akarca US, Gadano A, Habersetzer F, et al. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naive patients with chronic hepatitis B. Gastroenterology 2012;143:619-628 e611.
17. Sinn DH, Lee J, Goo J, Kim K, Gwak GY, Paik YH, et al. Hepatocellular carcinoma risk in chronic hepatitis B virus-infected compensated cirrhosis patients with low viral load. Hepatology 2015;62:694-701.

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)	⊕◯◯◯[124] 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)	⊕◯◯◯[12] VERY LOW	RR 0.61 (0.46 to 0.81)
		HCC	(23 observational studies)	⊕◯◯◯[12] VERY LOW	RR 0.50 (0.0.35 to 0.73)
		Decompensated liver disease	(6 observational studies)	⊕◯◯◯[124] 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)	⊕◯◯◯[124] 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)	⊕◯◯◯[12] VERY LOW	RR 0.45 (0.22 to 0.89)
Compensated Cirrhosis	IFN vs. None	All-cause mortality	(1 observational study)	⊕◯◯◯[124] 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)	⊕◯◯◯[14] 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)	⊕◯◯◯[12] 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)	⊕⊕⊕◯[4] MODERATE	RR 0.51 (0.27 to 0.99)
		All-cause mortality	(4 observational studies)	⊕◯◯◯[1] 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)	⊕⊕⊕◯[4] MODERATE	RR 0.51 (0.27 to 0.99)
	Telbivudine vs. None	All-cause mortality	(1 observational study)	⊕◯◯◯[1] 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)	⊕◯◯◯[124] VERY LOW	RR 0.85 (0.48-1.5)
	Lamivudine vs. Control	All-cause mortality	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 0.51 (0.16-1.66)
	Entecavir vs. Control	All-cause mortality	(2 observational study)	⊕◯◯◯[124] 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)	⊕⊕◯◯[14] LOW	RR 1.02 (0.26 to 3.97)
		All-cause mortality (96)	(1 RCT)	⊕⊕◯◯[14] LOW	RR 0.94 (0.14 to 6.24)
	Entecavir vs. Adefovir	All-cause mortality (96)	(1 RCT)	⊕⊕◯◯[14] LOW	RR 0.72 (0.45 to 1.15)
		Liver transplant (96)	(1 RCT)	⊕⊕◯◯[14] LOW	RR 3.34 (0.96 to 11.58)
		HCC (221)	(1 RCT)	⊕⊕⊕◯[1] MODERATE	RR 0.42 (0.22 to 0.8)
Compensated Cirrhosis	Entecavir vs. Lamivudine	All-cause mortality (48)	(1 observational study)	⊕◯◯◯[1] VERY LOW	RR 0.42 (0.31-0.57)
		HCC (12-60)	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 1.01 (0.8 to 1.27)
Compensated Cirrhosis	Entecavir vs. Telbivudine	HCC (156)	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 0.73 (0.31-1.72)
		All-cause mortality (160)	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 0.2 (0.01 to 4.11)
	Lamivudine vs. Tenofovir	All-cause mortality (26)	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 0.86 (0.27 to 2.68)
		HCC (26)	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 0.34 (0.07 to 1.64)
		Liver transplant (26)	(1 observational study)	⊕◯◯◯[14] VERY LOW	RR 1.03 (0.07 to 16.12)
	Telbivudine vs. Lamivudine	HCC (104)	(1 RCT)	⊕⊕⊕◯[4] MODERATE	RR 0.94 (0.51 to 1.74)
		All-cause mortality (120)	(1 RCT)	⊕⊕⊕◯[4] MODERATE	RR 0.68 (0.37 to 1.25)
Acute on chronic liver failure	Entecavir vs. Lamivudine	All-cause mortality (48)	(5 observational studies)	⊕◯◯◯[14] 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.