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.	
7	4 or 5 or 6	1210019
8	exp Interferons/	453948
9	exp interferon/	453948
10	("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
11	8 or 9 or 10	629423
12	exp Carcinoma, Hepatocellular/	142803
13	exp liver cell carcinoma/	142803
14	exp Fibrosis/	185872
15	exp liver cirrhosis/	157245
16	exp Morbidity/	612417
17	exp Mortality/	892082
18	exp Death/	531063
19	exp Survival/	616331
20	mo.fs.	448163
21	Virus Activation/	7949
22	exp virus reactivation/	7579
23	(((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.	
24	or/12-23	5422174
25	3 and (7 or 11) and 24	19331
26	exp evidence based medicine/	722657
27	exp meta analysis/	134228
28	exp Meta-Analysis as Topic/	29609
29	exp "systematic review"/	79495
30	exp Guideline/ or exp Practice Guideline/	344743
31	exp controlled study/	4517923
32	exp Randomized Controlled Trial/	723728
33	exp triple blind procedure/	68
34	exp Double-Blind Method/	343004
35	exp Single-Blind Method/	51300
36	exp latin square design/	276
37	exp comparative study/	2460744
38	exp intervention studies/	29818
39	exp Cross-Sectional Studies/	307798
40	exp Cross-Over Studies/	101471
41	exp Cohort Studies/	1680879
42	exp longitudinal study/	1065173
43	exp retrospective study/	865208
44	exp prospective study/	701582
45	exp clinical trial/	1729495
46	clinical study/	53696
47	exp case-control studies/	784997
48	((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.	
49	or/26-48	14249133
50	25 and 49	10972
51	from 25 keep 13107-18830	5724
52	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
53	50 or 52	10981
54	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
55	53 not 54	10511
56	from 25 keep 18831-19331	501
57	55 or 56	10673
58	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
59	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
60	57 and (adult or adults or "middle age" or "middle aged").mp.	5349
61	59 or 60	5510
62	61 and chronic*.mp.	3604
63	62 not (exp animals/ not exp humans/)	3519
64	from 62 keep 3522-3604	83
65	63 or 64	3602
66	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*)

10 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.

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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

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