Systematic Review of the Literature on Comparative Effectiveness of Antiviral Treatments for Chronic Hepatitis B Infection

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OBJECTIVES: To evaluate the comparative effectiveness of antiviral drugs in adults with chronic hepatitis B monoinfection for evidence-based decision-making.

METHODS: A systematic review of randomized controlled clinical trials (RCTs) published in English. Results after interferon and nucleos(t)ides analog therapies were synthesized with random-effects meta-analyses and number needed to treat (NNT).

RESULTS: Despite sustained improvements in selected biomarkers, no one drug regimen improved all intermediate outcomes. In 16 underpowered RCTs, drug treatments did not reduce mortality, liver cancer, or cirrhosis. Sustained HBV DNA clearance was achieved in one patient when two were treated with adefovir (NNT from 1 RCT=2 95%CI 1;2) or interferon alfa-2b (NNT from 2 RCTs=2 95%CI 2;4), 13 with lamivudine (NNT from 1 RCT=13 95%CI 7;1000), and 11 with peginterferon alfa-2a vs. lamivudine (NNT from 1 RCT=11 95%CI 7;25). Sustained HBeAg seroconversion was achieved in one patient when eight were treated with interferon alfa-2b (NNT from 2 RCTs=8 95%CI 5;33) or 10—with peginterferon alfa-2b vs. interferon alfa-2b (NNT from 1 RCT=10 95%CI 5;1000). Greater benefits and safety after entecavir vs. lamivudine or pegylated interferon alfa-2b vs. interferon alfa-2b require future investigation of clinical outcomes. Adverse events were common and more frequent after interferon. Treatment utilization for adverse effects is unknown.

CONCLUSIONS: Individual clinical decisions should rely on comparative effectiveness and absolute rates of intermediate outcomes and adverse events. Future research should clarify the relationship of intermediate and clinical outcomes and cost-effectiveness of drugs for evidence-based policy and clinical decisions.

KEY WORDS: antiviral agents/adverse effects; antiviral agents/therapeutic use; hepatitis B/therapy; treatment outcome; cost-benefit analysis; decision trees.
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INTRODUCTION

Chronic hepatitis B infection (CHB) afflicts over 1 million adults in the United States alone and presents a significant public health problem[1]. Treatment goals include prevention of cirrhosis, liver decompensation, and hepatocellular carcinoma[2,3] that cause an estimated 2,000 to 4,000 deaths annually; over $1 billion is spent per year on hepatitis B-related hospitalizations. Although we do not have good evidence that antiviral drugs can prevent overall mortality, liver-specific mortality, or development of hepatocellular carcinoma in patients with chronic hepatitis B[2,4], therapeutic nihilism is difficult to justify as this is a potentially dangerous disease[5]. Physicians and patients have to make decisions based on benefits of antiviral drugs on virologic, biochemical, and histologic markers including hepatitis B virus (HBV) deoxyribonucleic acid (DNA) clearance, HBeAg loss or seroconversion, decreases in alanine aminotransferase (ALT) levels, and improvement in liver histology[1,2,4,6]. The National Institutes of Health (NIH) consensus development conference synthesized evidence from available research suggesting feasible intermediate endpoints[3,7] and harms of interferon[8] and nucleos(t)ides analog therapies[9]. The aim of this report is to present a comprehensive analysis of the benefits and harms of antiviral drug therapies for HBeAg positive CHB mono infection in terms of available intermediate outcomes. In addition to the systematic review on the management of chronic HBV infec-

Corporate names, city, and state of manufacturers of brand-name materials *STATA software (The Statistics/Data Analysis StataCorp. Stata statistical software: Release 9.2. College Station, Texas, USA)*

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Table 1. Absolute Risk Difference in Tested Intermediate Outcomes After Antiviral Drugs for Chronic Hepatitis B in Adults

Comparison	HBsAg (RCTs/ patients)	HBeAg (RCTs/patients)	HBV DNA clearance (RCTs/patients)	Histology improved (RCTs/patients)	ALT normal (RCTs/ patients)	Relapse/Mutation (RCTs/patients)
Adefovir vs. placebo	SC: NS [1/120] L	Loss: 0.11 (0.06; 0.16) [2/995] M	0.38 (0.23; 0.53) [4/1002] H	Fibrosis: 0.20 (0.14; 0.26) [2/699] M	0.40 (0.30; 0.49) [5/1342]	NS [2/1055] L
		SC: 0.05 (0.01; 0.09) [2/700] H	*20.41 (6.79; 61.32) [4/1002]* 0.59 (0.46; 0.72)* [1/120] L	Necroinflammation scores: 0.26 (0.17; 0.34) [3/819] H	*2.97 (2.38; 3.69)* H 0.26 (0.19; 0.33) * [2/600] M	NS* [1/140] L
LAM vs. placebo	Loss: NS [1/175] L NS* [3/1068] L	Loss: 0.13 (0.04; 0.22) [4/1349] M 0.15 (0.05; 0.24)* [2/318] M SC: 0.05 (0.001; 0.10) [6/1638] H *1.70 (1.05; 2.74)* NS * [2/318] L	0.48 (0.31; 0.66) [7/1305]H *3.79 (2.71; 5.30)* H 0.08 (0.00; 0.15)* [1/136] L	Necroinflammation: *2.09 (1.60; 2.74)* M 0.25 (0.13; 0.38) [4/580] M	0.22 (0.13; 0.31) [7/1602]M *2.42 (1.94; 3.01)* M 0.21 (0.04; 0.38) * [1/136] L	YMDD mutation: 0.43 (0.38; 0.48) [2/826] H
Adefovir+LAM vs. LAM	Loss: NS [1/39] L	Loss: 0.12 (0.03; 0.21) [2/134] M SC: NS [2/134] L	0.25 (0.10; 0.39) [2/134] L		0.32 (0.13; 0.52) [2/13] M	YMDD:-0.33 (-0.50; -0.17) [1/95] L Wild type mutation: NS [1/95] L
Adefovir+LAM vs. adefovir	Loss: NS [1/39] L	Loss: NS [1/39] L SC: NS[1/39] L	NS:[1/39] L		NS [1/39] L	
Entecavir vs. LAM	Loss: NS [2/1117] M	Loss: NS [3/1112] L	0.23 (0.11; 0.35) [4/1636]	Necroinflammation: 0.14 (0.04; 0.24) [3/1633] M	0.22 (0.11; 0.32) [6/2423]	NS [0/1347] L
	SC: NS [1/408] L	SC: NS [3/1185] M	*1.64 (1.22; 2.22)* L/M NS*1/709] L	Fibrosis: NS [2/995] M	*1.62 (1.28; 2.06)* H	-0.16 (-0.20; -0.12)* [1/709] L
LAM vs. adefovir		Loss: NS [1/38] L SC:NS [1/38] L	-0.26 (-0.47; -0.06) [1/38] L		-0.42 (-0.67; -0.18) [1/38] L	
LAM vs. telbivudine		Loss: NS [1/63] L SC: NS [1/63] L	-0.30 (-0.55; -0.04) [1/63] L		NS [1/85] L	NS [1/63] L
Telbivudine vs. adefovir		Loss: NS [1/135] L SC: *6.03 (2.20; 16.52) [1/136]* L	0.28 (0.12; 0.44) [1/136] L		NS [1/135] L	
Telbivudine+LAM vs. LAM		Loss: NS[1/60] L SC: NS [1/60] L	NS [1/60] L		NS [1/101] L	NS [1/60] L
Telbivudine+LAM vs. telbivudine		Loss: NS [1/85] L SC: NS [1/85] L	NS [1/85] L		NS [1/101] L	NS [1/85] L
Interferon alfa-2b vs. placebo	Loss: NS [3/166] M NS* [4/247] L SC: NS* [2/82] L	Loss: 0.55 (0.29; 0.81) [1/40] L *2.52 (1.55; 4.10)* 0.28 (0.07; 0.50)* [3/351] M SC:NS [1/40] L 0.12 (0.03; 0.21) * [2/304] M	0.45 (0.22; 0.68) [1/34] L 0.44 (0.27; 0.60)* [3/168] L	Total scores: NS* [1/40] L HAI scores:0.24 (0.00; 0.48) [1/72] L	0.31 (0.17; 0.44) * [2/131] M	Relapse: NS* [5/378] H
Interferon alfa-2b+lamivudine vs. placebo	Loss: 0.06 (0.00; 0.13) [1/119] L NS* [1/119] L	Loss: NS [1/118] L NS* [2/450] M SC: NS [1/119] L NS* [2/450] L	0.48 (0.33; 0.63) [1/119] L NS* [1/119] L	HAI scores NS [1/119] L	NS [1/119] L	YMDD mutation NS [1/118] L
Interferon alfa-2b+corticosteroid vs. no treatment	Loss: 0.11 (0.02; 0.20) [2/103] M		0.25 (0.04; 0.46) [1/34] L NS* [2/121] M		0.25 (0.06; 0.43) * [1/87] L	Relapse NS* [1/87] L
Interferon alfa-2b vs. LAM		Loss: NS [1/151] L NS* [2/625] M SC: NS[1/151] L NS* [3/776] M	NS [1/76] L NS* [1/151] L	Knodell scores: NS* [1/151] L	NS [1/151] L NS* [2/151] L	YMDD mutation -0.23 (-0.33; -0.14)* [1/151] L
Interferon Alfa 2b+LAM vs. interferon alfa-2b		Loss: NS [1/144] L NS* [2/347] M SC: NS [1/144] L NS* [3/482] L	NS [1/144] L NS* [2/278] L	HAI scores 0.54 (0.28; 0.79) [1/48] L Knodell scores NS* [1/144] L	NS [1/144] L NS* [2/192] L	YMDD mutation NS* [1/144] L

(*continued on next page*)

Table 1. (continued)

Comparison	HBsAg (RCTs/ patients)	HBeAg (RCTs/patients)	HBV DNA clearance (RCTs/patients)	Histology improved (RCTs/patients)	ALT normal (RCTs/ patients)	Relapse/Mutation (RCTs/patients)
Interferon alfa-2b+LAM vs. LAM	Loss: NS [2/262] L NS* [3/495] L	Loss: NS [3/414] M NS* [5/1167] M SC: NS [4/565] H NS* [3/490] M	NS [7/786] H NS* [4/365] M	HAI scores NS [3/327] M necroinflammation NS [2/389] L Knodell scores NS* [1/157] L	NS [5/626] M NS* [6/751] M	Relapse: NS [4/326] H NS* [2/158] L YMDD mutation: -0.18 (-0.35; -0.01) [6/721] M *0.42 (0.16; 1.09) M* -0.23 (-0.32; -0.14) * [1/157] L
Interferon alfa-2b+corticosteroid vs. IFN alfa-2b	Loss: NS [2/125] M NS* [3/141] L	Loss: NS [2/77] L NS* [3/122] L SC: NS* [2/85] L	NS [2/77] L NS* [6/322] H		NS* [3/170] M	Relapse: NS* [2/141] L
Peginterferon alfa-2a vs. LAM		Loss: 0.08 (0.01; 0.16) M 0.13 (0.05; 0.20)* [1/543] M SC: NS [1/543] L 0.13 (0.06; 0.20) [1/814]* M	-0.15 (-0.22; -0.07) [1/543] M 0.09 (0.04; 0.14) [1/543]* L	Necroinflammation 0.12 (0.02; 0.22) [1/552]* L Fibrosis: NS* [1/552] L HAI: NS [2/1366]* M	-0.29 (-0.42; -0.17) [2/905] *0.57 (0.46; 0.70)* [2/905] M 0.13 (0.07; 0.20) * [2/905] H	YMDD mutation -0.25 (-0.31; -0.20) [1/543] L
Peginterferon alfa-2a+LAM vs. LAM		Loss: NS [1/543] L 0.07 (0.00; 0.15)* [1/543] M SC: NS [1/543] L 0.08 (0.01; 0.15) * [1/814] L	0.29 (0.21; 0.37) [1/543] M 0.09 (0.04; 0.13) [1/543]* L	Total scores: NS [2/1366]* H	-0.20 (-0.29; -0.10) [2/905] H 0.13 (0.06; 0.19) [2/905]* H	YMDD mutation -0.22 (-0.28; -0.16) [1/543] L
Peginterferon alfa-2a+LAM vs. peginterferon alfa-2a		Loss: NS [1/542] L NS [1/542]* M SC: NS [1/542] L NS [1/814]* L	0.44 (0.36; 0.51) [1/542] M NS[1/542]* L	Total scores: NS [1/96]* L	NS [1/542] L NS [1/542]* L	YMDD mutation: 0.03 (0.01; 0.06) [1/542] L
Peginterferon alfa-2b vs. interferon alfa-2b	SC: NS* [1/230]	Loss: 0.10 (0.00; 0.21) [1/230]* L			NS [1/230]* L	
Peginterferon alfa-2b+LAM vs. LAM	Negative HBVDNA+ HBsAg SC 0.32 (0.14; 0.50) [1/100]	Loss: 0.34 (0.16; 0.52) [1/100] M SC: 0.32 (0.14; 0.50) [1/100] L NS: [1/100]* L	NS [1/100] L NS [1/100]* L	HAI scores NS: [1/100] L	NS [1/100] L	NS: [1/100]* L YMDD mutation: NS [1/100] L
Peginterferon alfa-2b+LAM vs. peginterferon alfa-2b	Loss: NS [1/307]	Loss: 0.12 (0.01; 0.22) [1/307] M NS [2/614]* M SC: NS [1/307]L NS: [1/307]* L		fibrosis scores: NS [1/307]* L necroinflammation scores: NS [1/307] L	0.14 (0.03; 0.24) [1/307] L NS [1/307]* L	YMDD mutation: 0.09 (0.04; 0.14) [1/307] L

*SC=seroconversion; NS = not significant; italic = relative risk; * = outcomes off treatments; LAM = lamivudine*
Level of evidence: L = low; M = moderate; H = high

tion,[2,4] we have created a comprehensive evidence map with pooled risk differences, the number needed to treat to achieve favorable changes in biomarkers, number of events that are attributable to the drugs, and absolute rates of clinical events after available treatments. We included only the results from RCTs because such studies prove the causal effects of the treatments[10]. Comparative effectiveness of antiviral drugs should provide the basis for evidence-based decision making in clinical settings[11,12]. This review was commissioned as background material for the NIH Consensus Development Conference on Management of Chronic Hepatitis B in Adults[2].

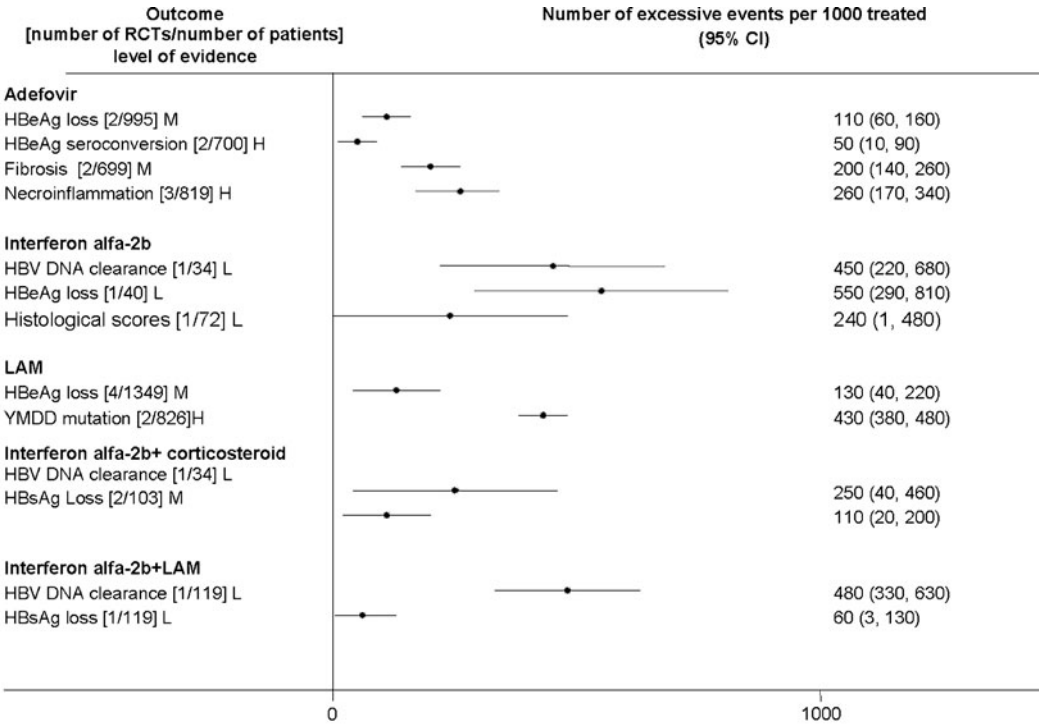
METHODS

In our analytical framework we examined pooled rates, relative risks, and absolute risk differences in intermediate outcomes

Table 2. Number Need to Treat to Have One Additional Event After Antiviral Treatments of Chronic Hepatitis B infection; Results from Randomized Controlled Clinical Trials

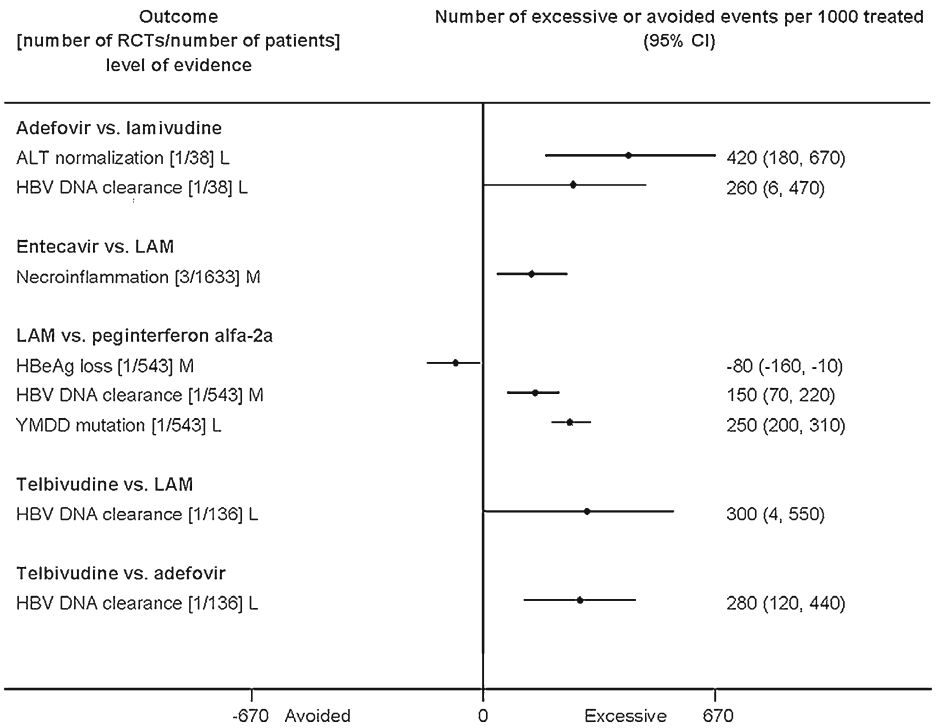
Drug	Outcome	Number needed to treat (95%CI)
End of treatment		
Monotherapy vs. placebo		
Adefovir	Reduced fibrosis [2/699] M	5(4;7)
	Reduced necroinflammatory scores [3/819] H	4(3;6)
	HBeAg loss [2/995] M 110	9(6;17)
	Seroconversion [2/700] H	20(11;100)
Lamivudine	HBeAg loss [4/1349] M	8(5;25)
	YMDD mutations [2/826]H	2(2;3)
Interferon alfa-2b	Histological scores [1/72] L	4(2;1000)
	HBV DNA clearance [1/34] L	2(1;5)
	HBeAg loss [1/40] L	2(1;3)
Combined therapy vs. placebo		
Interferon alfa-2b+lamivudine	HBsAg Loss [1/119] L	17(8;333)
	HBV DNA clearance [1/119] L	2(2;3)
Interferon alfa-2b+ corticosteroid	HBsAg Loss [2/103] M	9(5;50)
	HBV DNA clearance [1/34] L	4(2;25)
Monotherapy vs. active control		
LAM vs. peginterferon alfa-2a	HBV DNA clearance [1/543] M	7(5;14)
	YMDD mutation [1/543] L	4(3;5)
	HBeAg Loss [1/543] M	-13(-100;-6)
Entecavir vs. lamivudine	Reduced necroinflammation [3/1633] M	7(4;25)
Adefovir vs. lamivudine	HBV DNA clearance [1/38] L	4(2;167)
	ALT normalization [1/38] L	2(1;6)
Telbivudine vs. lamivudine	HBV DNA clearance [1/136] L	3(2;250)
	HBV DNA clearance [1/136] L	4(2;8)
Combined therapy vs. active control		
Adefovir + LAM vs. LAM	HBV DNA clearance [2/134] L	4(3;10)
	HBeAg Loss [2/134] M	8(5;33)
	ALT normalization [2/13] M	3(2;8)
	YMDD mutation [1/95] L	-3(-6;-2)
Interferon alfa-2b + LAM vs. interferon alfa-2b	Improved HAI scores [1/48] L	2(1;4)
Interferon alfa-2b+ LAM vs. LAM	YMDD mutation [6/721] M	-6(-100;-3)
Peginterferon alfa-2a+LAM vs. LAM	HBV DNA clearance [1/543] M	3(3;5)
	YMDD mutation [1/543] L	-5(-10;-3)
Peginterferon alfa-2a+LAM vs. peginterferon alfa-2a	HBV DNA clearance [1/542] M	2(2;3)
	YMDD mutation [1/542] L	33(17;100)
Peginterferon alfa-2b+LAM vs. LAM	HBV DNA clearance combined with HBsAg seroconversion [1/100]L	3(2;7)
	HBeAg Loss [1/100] M	3(2;6)
	HBeAg seroconversion [1/100] L	3(2;7)
Peginterferon alfa-2b+LAM vs. peginterferon alfa-2b	HBeAg Loss [1/307] M	8(5;100)
	ALT normalization [1/307] L	7(4;33)
	YMDD mutation [1/307] L	11(7;25)
Off treatment		
Monotherapy vs. placebo		
Adefovir	HBV DNA clearance [1/120] L	2(1;2)
	ALT normalization [2/600] M	4(3;5)
Lamivudine	HBV DNA clearance [1/136] L	13(7;1000)
	ALT normalization [1/136] L	5(3;25)
Interferon alfa-2b	HBV DNA clearance [3/168] L	2(2;4)
	HBeAg loss [3/351] M	4(2;14)
	HBeAg seroconversion [2/304] M	8(5;33)
	ALT normalization [2/131] M	3(2;6)
Combined therapy vs. placebo		
Interferon alfa-2b+ corticosteroid	ALT normalization [1/87] L	4(2;17)
Monotherapy vs. active control		
Interferon alfa-2b vs. LAM	YMDD mutation [1/151] L	-4(-7;-3)
Peginterferon alfa-2a vs. LAM	Reduced necroinflammation [1/552] L	8(5;50)
	HBV DNA clearance [1/543] L	11(7;25)
	HBeAg loss [1/543] M	8(5;17)
	ALT normalization [2/905] H	8(5;14)
Peginterferon alfa-2b vs. interferon alfa-2b	HBeAg Loss [1/230] L	10(5;1000)
Entecavir vs. LAM	Relapse [1/709] L	6(5;8)
Combined therapy vs. active control		
I nterferon alfa-2b+ LAM vs. LAM	Mutation [1/157] L	-4(-7;-3)
Peginterferon alfa-2a+LAM vs. LAM	HBV DNA clearance [1/543] L	11(8;25)
	HBeAg loss [1/543] M	14(7;1000)
	HBeAg seroconversion [1/814] L	13(7;100)
	ALT normalization [2/905]H	8(5;17)

abbreviation: LAM- lamivudine; negative number needed to treat demonstrate reduced rates of the events after active vs. control treatments



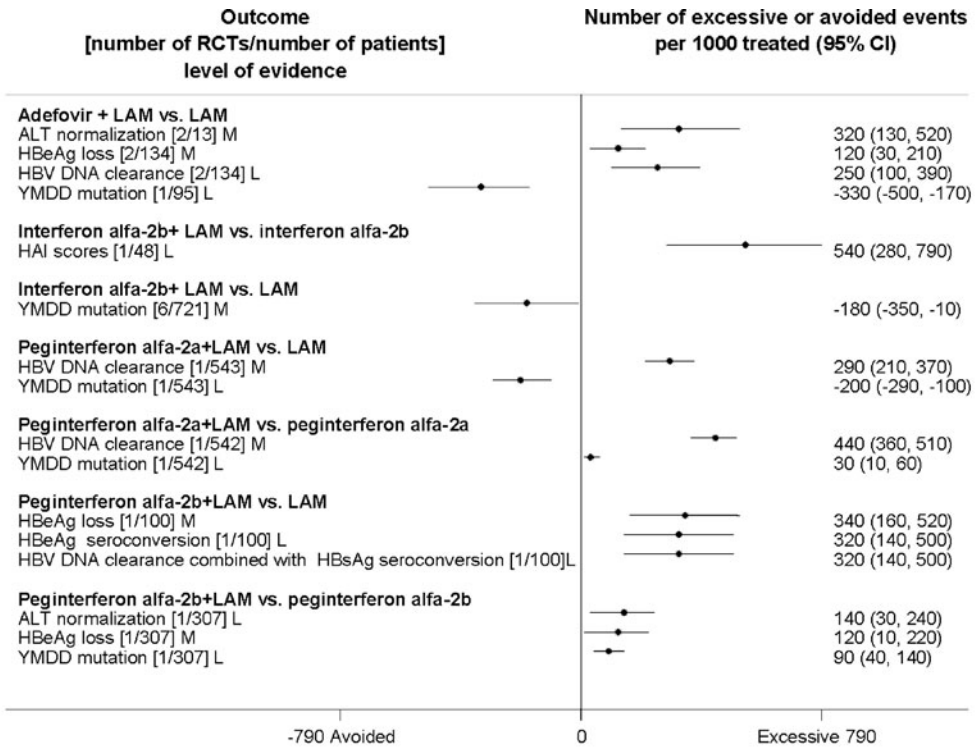
RCT- randomized controlled clinical trial; LAM- lamivudine; L- low level of evidence; M- moderate level of evidence; H- high level of evidence

Figure 1. Results from randomized controlled clinical trials that compared active treatments to placebo at the end of the treatment.



RCT- randomized controlled clinical trial; LAM- lamivudine; L- low level of evidence; M- moderate level of evidence; H- high level of evidence

Figure 2. Results from randomized controlled clinical trials that compared active mono-treatments at the end of the treatment.



RCT- randomized controlled clinical trial; LAM- lamivudine; L- low level of evidence; M- moderate level of evidence; H- high level of evidence

Figure 3. Results from randomized controlled clinical trials that compared combined therapy vs. monotherapy at the end of the treatment.

and clinical harms after antiviral drugs. We then calculated attributable events[13,14].

We searched MEDLINE® via PubMed®, the Cochrane Library[15], and Medwatch[16] to find randomized controlled clinical trials of adults with CHB published in English between 1989 and September 2008 that reported mortality, incidence of hepatocellular carcinoma, liver failure, prevalence and incidence of cirrhosis, HBeAg or HBsAg presence or seroconver-

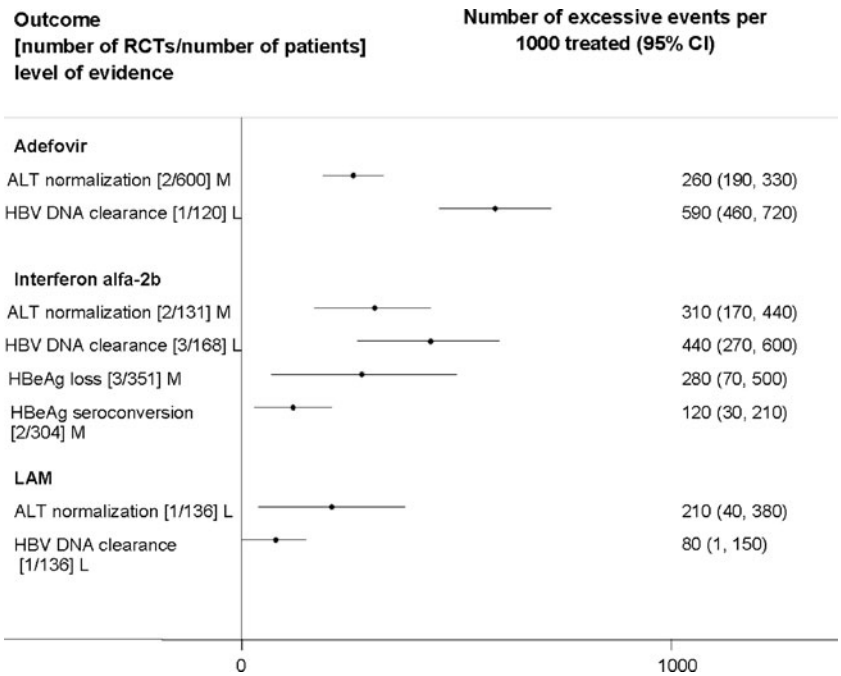
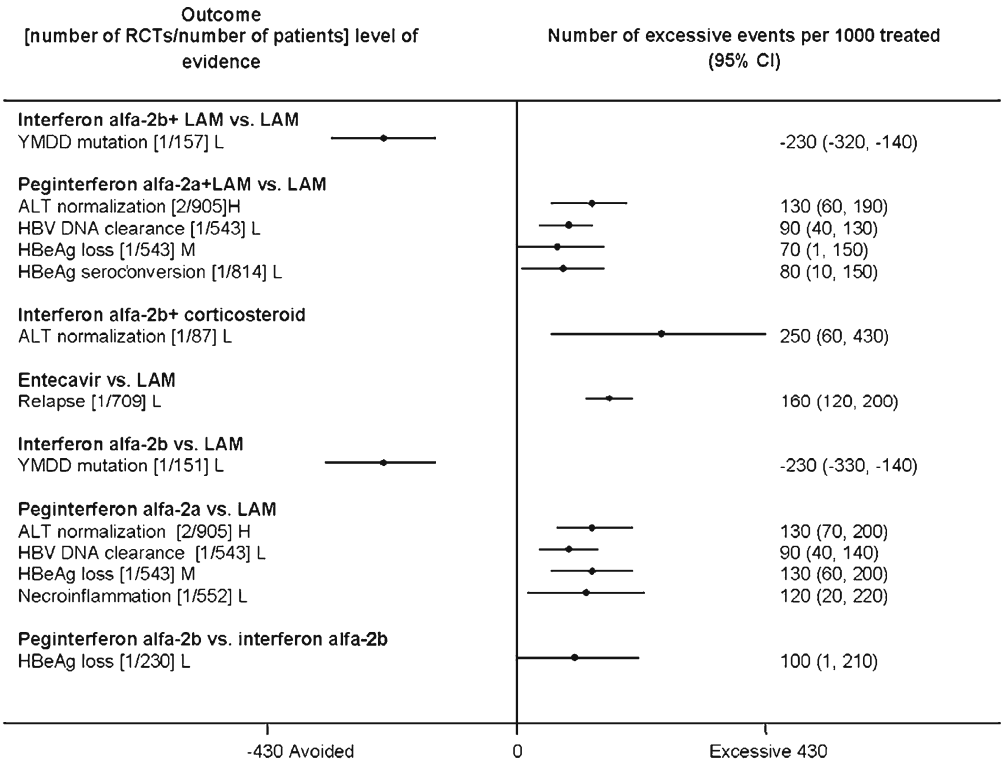


Figure 4. Sustained results from randomized controlled clinical trials that compared active treatments to placebo at follow up off the treatment.



RCT- randomized controlled clinical trial; LAM- lamivudine; L- low level of evidence; M- moderate level of evidence; H- high level of evidence

Figure 5. Sustained results from randomized controlled clinical trials that compared active treatments at follow up off the treatment.

sion, viral load of HBV deoxyribonucleotide acid (HBV DNA), ALT levels, histological necroinflammatory and fibrosis scores[17], and adverse events after antiviral drugs, including interferon alfa-2b, pegylated interferon alfa-2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. We used the following definitions for intermediate biomarkers:

- *Complete response (resolved hepatitis B)* included HBsAg loss or seroconversion in combination with undetectable HBV DNA and normal ALT.
- ALT normalization.
- *Virological outcomes* included HBsAg and HBeAg clearance or seroconversion, and HBV DNA clearance.
- *Histological outcomes* included improvement in necroinflammatory scores without worsening in fibrosis scores.
- *Resistance* was defined as worsening of histological scores or persistent HBV DNA load, or rates of genetic mutations.

We prioritized HBsAg loss or seroconversion (diagnostic marker of resolved hepatitis) and improvement in histological necroinflammatory scores without worsening in fibrosis scores (diagnostic markers of liver cirrhosis)[3,18]. We focused on sustained improvement in biomarkers at follow up off the treatments[3,19]. Our review focuses on HBeAg-positive patients since we previously reported effects of antiviral drugs on HBeAg-negative patients[4].

We analyzed study quality using the following criteria: subject selection, length and loss of follow-up, adjustment for confounding factors in observational studies and intention to treat principle in clinical trials, masking treatment status, randomization scheme and adequacy, allocation concealment, and justification of sample sizes in RCTs[10,20].

The protocol for the meta-analyses was created according to recommendations for meta-analysis of RCTs[21,22]. Meta-analysis was used to assess the consistency of the association between treatments and outcomes using the DerSimonian–Laird inverse-variance weighting method, and random effects models[23]. We chose the random effects models to incorporate differences across trials in patient populations, baseline rates of the outcomes, dosing of drugs, and other factors in the pooled analysis. For pooled relative risks and absolute risk differences we excluded trials with no events in both groups and added a correction coefficient of 0.5 in the trials with no events only in one group. Statistical heterogeneity was assessed by calculating the percent of the total variance due to between-study variability (I2 statistic) and Chi square tests[24,25]. Higher I2 values indicate greater between-study heterogeneity. All calculations were performed with STATA software 10.1 (The Statistics/Data Analysis StataCorp. Stata statistical software: Release 9.2. College Station, Texas). We tested the consistency of the results by comparing the direction and strength of the association. We assumed that publication bias was present and did not conduct formal statistical tests to measure it[26].

We assessed the level of evidence based on modified GRADE Working Group criteria[27,28]. We assigned low level of evidence to data from small RCTs, or from RCTs with serious flaws in

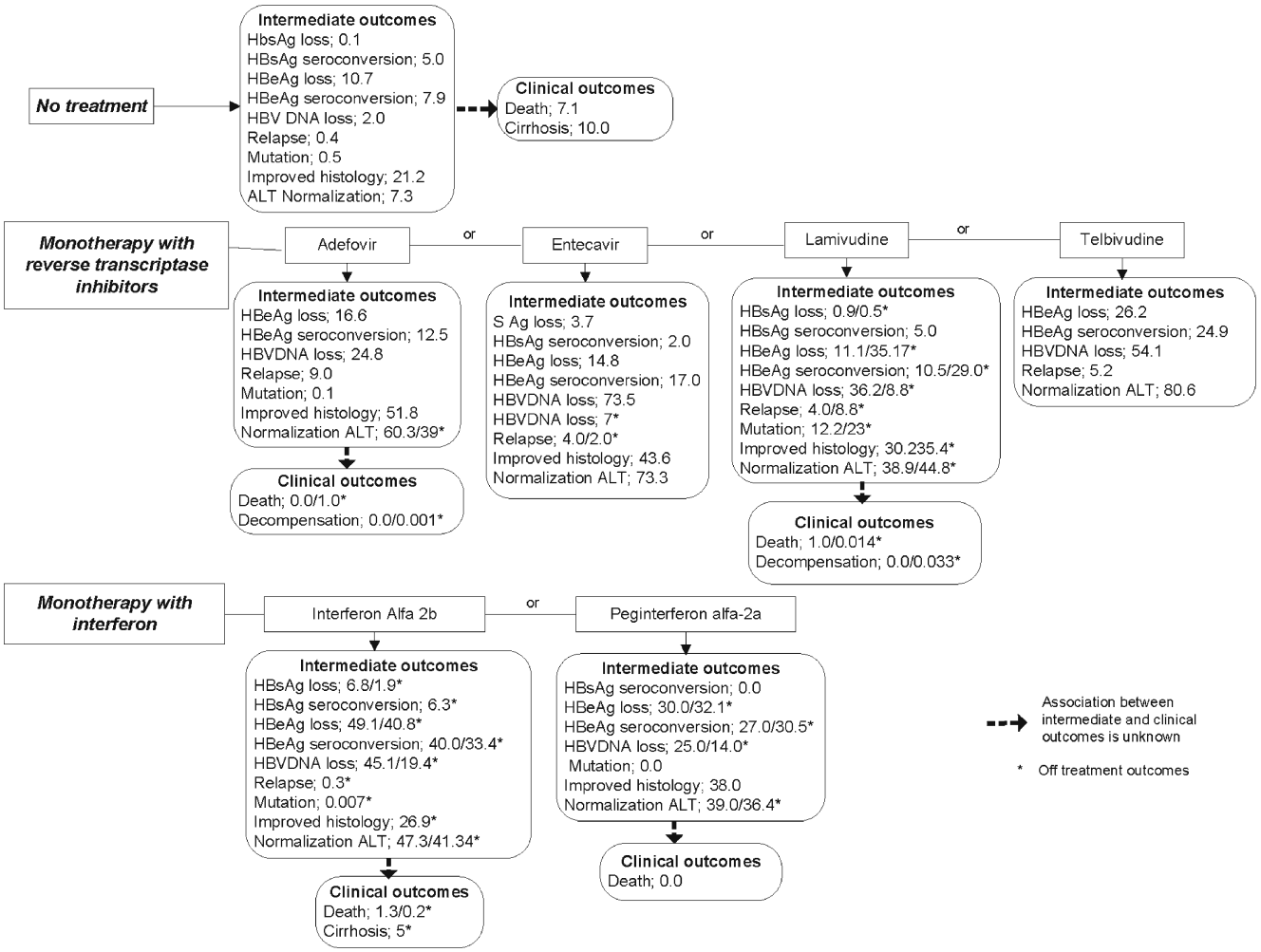


Figure 6. Rates (%) of clinical and intermediate outcomes in HBe antigen positive patients (pooled from randomized controlled clinical trials with random effects models).

design/analysis, and from post hoc subgroup analysis. We assigned moderate level of evidence when a single large multinational study or several small RCTs reported consistent effects of the same drugs. We assigned a high level of evidence to data from multiple high quality studies that reported consistent sustained effects at least 6 months post therapy[29].

We used pooled absolute risk difference to calculate the number needed to treat and the number of events attributable to treatment per 1000 patients[29,30]. We calculated means and 95% confidence intervals for number needed to treat as reciprocal to pooled absolute risk difference when absolute risk difference was significant [31]. We calculated means and 95% confidence intervals for treatment eventsper 1000 treated, multiplying pooled absolute risk difference by 1000. For clinical decision making we also calculated pooled rates of the outcomes and all reported in the trials adverse effects[32] with random effects models using MetaAnalyst software[33].

We based the estimated medication cost needed to achieve one specified event on recommendations for reported weekly doses and length of treatment found in the Red Book: Pharmacy's Fundamental Resource®[34-36].

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RESULTS

We identified 93 relevant articles representing RCTs of interferon alfa-2b[37-68], peginterferon alfa-2a[69-73], adefovir[74-85], peginterferon alfa-2b[86-97], entecavir[98-103], lamivudine[40,43,71,72,84,104-119], or telbivudine[85,104,120,121]. We also reviewed one recently published study of tenofovir[122]. The studies enrolled predominately HBeAg-positive individuals. We excluded eleven reports that described outcomes in HBeAg-negative patients[47,50,52,55,57,67,69,71,74-76,119]. We identified 16 RCTs (4431 patients) that analyzed the effects

of antiviral drugs on clinical outcomes and concluded that drug treatments did not improve clinical outcomes of chronic hepatitis B infection. Clinical outcomes were rarely reported, and the trials were underpowered to detect differences in mortality, liver cancer or cirrchosis[2,4]. The results of meta-analyses with pooled relative risk, absolute risk differences, and weights from random effects models are presented in Online Appendix 1. We summarized the results of the RCTs into an evidence map (Table 1). No one treatment improved all outcomes, and there was limited evidence on comparative effects.

Only interferon therapies resulted in HBsAg loss, which is one of the criteria of resolved hepatitis B. One RCT demonstrated a significant increase in HBsAg loss at the end of administration of interferon alfa-2b[60] and after interferon alfa-2b with corticosteroid. Pooled analysis of two RCTs that compared steroid pretreatment followed by interferon alfa-2b to no antiviral drugs found a significant increase in HBsAg loss at the end of treatment[46,60]. Combined therapy of interferon alfa-2b with lamivudine resulted in HBsAg loss and HBV DNA clearance in one RCT[43]. Peginterferon alfa-2b combined with lamivudine when compared to lamivudine alone increased HBV DNA clearance and HBsAg seroconversion[95]. All treatments failed to increase rates of post-treatment HBsAg loss at follow up off drug administration (range 8-48 weeks off treatment)[37,43,59,63,67,113,116].

Monotherapy with oral antiviral drugs resulted in HBV DNA clearance and HBeAg seroconversion compared to placebo. For instance, lamivudine at the end of monotherapy compared to placebo increased the rates of HBeAg loss[40,43,113,117] and HBeAg seroconversion,[40,43,113,117,118,123] but it also increased rate of YMDD mutations (mutation in amino acid sequence tyrosine, methionine, aspartate, aspartate)[43,109]. Adefovir improved fibrosis and necroinflammatory scores[74,75,77], and HBeAg loss[77,78] and seroconversion[77,78].

Evidence on the comparative effectiveness of antiviral drugs was limited. Some antiviral drugs demonstrated superior effects on intermediate markers when compared to each other but no one regime demonstrated superior benefits on all biomarkers. For instance, lamivudine compared to peginterferon alfa-2a improved HBV DNA clearance[72] but reduced HBeAg loss[72]. Entecavir compared to lamivudine improved necroinflammation in three studies[98,99,102] with no differences on fibrosis scores in two studies that examined this biomarker[99,102]. Entecavir compared to lamivudine also increased the rates of HBV DNA clearance[98-100,103], with no differences in HBsAg[99,103] and HBeAg loss[99,100,102], or HBsAg[103] and HBeAg[99,100,102] seroconversion. Low levels of evidence suggested greater effects of telbivudine on HBV DNA clearance when compared to lamivudine[104], or to adefovir[85] with no differences in other outcomes. Moderate evidence from two RCTs suggested better effects from combined therapy with adefovir plus lamivudine on HBeAg loss[82,84] and ALT normalization[82,84] when compared to lamivudine alone, but not adefovir alone. Limited evidence from one recently published RCT[122] suggested superior effects from tenofovir compared to adefovir on viral suppression, normalized ALT levels and loss of HBsAg at the end of 48 weeks of treatment.

Evidence about the comparative effectiveness of combined therapies is very limited. We found only one study that demonstrated peginterferon alfa-2a combined with lamivudine, compared to monotherapy with either lamivudine or peginterferon alfa-2a improved HBV DNA clearance[72].

Sustained Effects. Few of the drugs evaluated demonstrated sustained benefits superior to placebo. Interferon alfa-2b improved sustained HBV DNA and HBeAg clearance[40,59,63], seroconversion[40,59], and ALT normalization[60,63]. Adefovir improved sustained ALT normalization[75,78] and HBV DNA clearance[75].

Pegylated interferon alfa-2a demonstrated superior sustained effects when compared to lamivudine. Pegylated interferon alfa-2a vs. lamivudine improved sustained HBV DNA[72] and HBeAg clearance[72], seroconversion[72], and ALT normalization[71,72]. Pegylated interferon alfa-2a plus lamivudine improved sustained HBV DNA[72] and HBeAg seroconversion[72] and ALT normalization[71,72] compared to lamivudine, but not pegylated interferon alfa-2 monotherapy.

Number Needed to Treat. The number needed to treat to achieve one event of improved biomarker was fewer than ten for most of the treatments (Table 2). Examining how many patients should be treated to improve liver histology (diagnostic markers of liver cirrhosis), we found that effectiveness is comparable among antiviral drugs. For instance, monotherapy with interferon alfa-2b was needed in four patients to achieve reduction in liver histological scores in one of them[67]. We would need to treat two patients with combined therapy of interferon alfa-2b and lamivudine to achieve improvement in histological scores in one of them[44]. Adefovir administration in four[74,75,77] or entecavir in seven patients[98,99,102] would result in reduced necroinflammation in one patient. Peginterferon alfa-2a administered in eight patients would result in sustained depression of necroinflammation in one patient when compared to lamivudine[71]. Adefovir is the only drug that reduced fibrosis scores; administration to four patients would result in reduction of fibrosis scores in one patient[74,77].

Sustained HBV DNA clearance was associated with favorable clinical outcomes in observational studies[18,19,124]. According to our analysis, sustained HBV DNA clearance in one patient would be possible if two were treated with interferon alfa-2b or adefovir or 13 with lamivudine. Sustained HBeAg loss in one patient would be achieved if four were treated with interferon alfa-2b. We would need to treat eight patients with interferon alfa-2b to have one case of sustained HBeAg seroconversion. Sustained ALT normalization could be seen in one patient when three were treated with interferon alfa-2b or four with adefovir. Viral resistant YMDD mutations would be detected in one from two treated with lamivudine patients.

Medication Cost. Finite courses of interferon were more expensive than oral drugs. Among interferon formulations, the cost of pegylated interferon alfa-2b administration was lower when compared to interferon alfa-2b or pegylated interferon alfa-2a. We estimate an average cost per patient[34] of about $16,176 for 48 weeks of pegylated interferon alfa-2b administration, versus $60,390 for 24 weeks of interferon alfa-2b administration, or $97,065 for 48 weeks of pegylated

interferon alfa-2a administration. Treatments with oral antiviral drugs are less expensive, averaging around $17,302 for 96 weeks of adefovir administration, $1,565 for 52 weeks of lamivudine administration, $8,274 for 52 weeks of entecavir administration, and $7,644 for 52 weeks of telbivudine administration.

Sustained HBeAg loss in one patient can cost $161,760 if treated with peginterferon alfa-2b, or $215,681 if treated with interferon alfa-2b, and treatment with peginterferon alfa-2a alone or combined with lamivudine will cost to three to four times more. Sustained HBeAg seroconversion in one patient would cost more than $500,000 with interferon alfa-2b and more than $770,000 with peginterferon alfa-2a combined with lamivudine. Actual costs may be less due to possible price discounts, but relative differences would remain the same.

Attributable Events. The number of events that were attributable to treatment with antiviral drugs varied across treatments (Figs. 1, 2, 3, 4, 5). Compared to placebo, interferon alfa-2b alone or combined with lamivudine resulted in greater improvement in histological scores and HBV DNA clearance (Fig. 1). HBV DNA clearance was greater after adefovir treatment when compared to lamivudine and greater after telbivudine when compared to lamivudine or adefovir (Fig. 2). Improvement in histological scores was attributable only to interferon alfa-2b combined with lamivudine therapy when compared to interferon monotherapy (Fig. 3). One RCT demonstrated that 320 cases of resolved hepatitis B per 1000 treated would be attributable to combined administration of peginterferon alfa-2b with lamivudine vs. lamivudine alone. Sustained HBV DNA clearance in more than 400 per 1,000 treated was attributable to adefovir or interferon alfa-2b administration when compared to placebo (Fig. 4). Sustained intermediate outcomes could be attributed to the examined treatments when compared to active control in less than 300 per 1,000 treated patients (Fig. 5).

Absolute Rates of the Outcomes. Physicians and patients make individual decisions based on known average probabilities of clinically important benefits and harms[125]. Probabilities vary depending on individual patient characteristics that can influence the expected treatment effects[126,127]. We have synthesized the probabilities of clinical and intermediate outcomes in HBeAg positive patients that participated in RCTs (Fig. 6). We hesitated to use indirect statistical comparisons that have not been examined in head-to-head RCTs. For example, mortality has never been examined in placebo controlled RCTs of pegylated interferon alfa-2a; therefore, lower rates of death after active drug (0%) vs. placebo (7.1%) could not provide good evidence of better survival. However, the rates of patient outcomes after placebo could provide a reasonable estimation of baseline risk in adults with CHB.

Published studies examined the effects of antiviral drugs only on selected outcomes; none of the RCTs reported all outcomes. Analyzing the rates of all outcomes from different RCTs can give a more complete estimation of drug effects. Combined treatments did not result in better outcomes when compared to monotherapy. Relapse and treatment failure were more common after active treatments than after placebo[128,129].

The most common adverse events during antiviral therapy included flu-like symptoms after interferon, fatigue, headache, abdominal pain, nausea, diarrhea, or laboratory abnormalities, which were reported in over 50% of patients[2,4]. Absolute rates of adverse events (in >10% of the patients) after placebo and active treatments are presented in Online Appendix Table 2. Direct comparisons in published RCTs reported non significant differences in serious adverse events and withdrawal rates when compared to placebo[2]. Laboratory toxicity after adefovir restricted usage of the drug in patients with impaired renal function[2]. Entecavir was better tolerated than lamivudine. Dose modifications due to neutropenia and thrombocytopenia were necessary in 50% of patients after interferon treatment[4]. Withdrawal rates were 24% higher after interferon-alfa-2b than with no treatment[4]. Pegylated interferon-alfa-2a combined with lamivudine resulted in greater discontinuation versus placebo or lamivudine alone[4]. Patients had serious adverse events more often after combined therapy of lamivudine with interferon-alfa-2b or pegylated interferon-alfa-2a than after lamivudine alone[4]. Long-term adverse drug events include reduced bone mineral density after tenofovir and moderate serum creatine phosphokinase elevations after telbivudine[130].

DISCUSSION

For our original report, we created a comprehensive evidence map which compares absolute rates of the outcomes, number needed to treat, number attributable to treatment events, and cost of treatment. The map provides the most complete information about the comparative effectiveness of antiviral drugs and can be used for decision-making in clinical settings.

At the present time, decision-making in clinical settings is based on the published guidelines. Current guidelines recommend finite treatment with pegylated interferon alfa or nucleos (t)ides analogs based on rates of HBV DNA clearance and HBs Ag seroconversion[131,132]. The recommendations of the European Association for the Study of the Liver are based on the rates of HBeAg seroconversion and HBV DNA clearance from individual studies and do not differentiate benefits, harms, and cost among different interferon alfa or nucleos(t)ides analogs[131].

Our present analysis and the evidence map we created gives clinicians data on the comparative effectiveness of each therapy on intermediate outcomes. It includes the number needed to treat to achieve the selected outcome. The evidence map also identifies gaps in our knowledge about sustained effects from antiviral drugs on clinical outcomes, liver histology, resolved HBV infection, and consistent improvement in virologic and biochemical outcomes. The map suggests that future research should investigate a balance between long term benefits and harms from both mono and combined therapy. The next step in our analyses was to estimate the number needed to treat in order to inform clinicians about the effectiveness of antiviral drugs. For instance, sustained HBV DNA clearance in one patient can be achieved when two are treated with interferon alfa- 2b or adefovir, but they would need to treat 13 with lamivudine.

Clinicians can then compare harms. Viral resistant YMDD mutations would be detected in one of two patients treated

with lamivudine[43,109]. Adefovir is contraindicated in patients with impaired renal function[2]. Around 21% of patients treated with interferon alfa-2b would require reduction in dose due to adverse events[37]. Clinicians now have actionable information about anticipated benefits and harms from antiviral drugs and laboratory parameters to monitor during and after the treatments. Our analyses also provide patients with information about rates of improvement in intermediate markers (Fig. 6) and harms of each available treatment (Online Appendix 2). Patients should be informed that no good evidence exists about preventive effects of the drugs against liver cancer or cirrhosis, the rates of sustained HBV DNA loss are 14% after peginterferon alfa-2A and 19.4% after interferon alfa-2B but both drugs caused fever in 57-61% of the patients respectively.

The costs of oral antiviral drugs are lower than that of interferon, but a more complete cost estimation should include the price of treatment of adverse effects, e.g. cost of long term osteopenia after treatment with tenofovir, or elevations in serum creatine phosphokinase after telbivudine[130].

Our analysis uncovered a lack of good evidence from RCTs that antiviral drugs prevent cirrhosis, liver decompensation, cancer, or mortality. Few studies were specifically designed to assess these clinical outcomes; most were intended to assess the relatively short-term effects of therapies on intermediate virological, histological, or biochemical outcomes. Observational studies suggested a strong positive association between viral load and liver fibrosis with clinical outcomes[124]. Low or undetectable DNA, however, did not eliminate the risk of liver cancer or cirrhosis[124]. Furthermore, observational studies could not provide a valid estimation of drug-induced reductions in viral level in association to improved clinical outcomes[124]. Therefore, we hesitated to predict drug prevention of clinical outcomes based on observed effects on biomarkers. Previously published cost-effectiveness analyses relied on assumptions from available natural history data[133,134]. We avoided such assumptions and used the results from RCTs that could establish causality between drug administration on intermediate outcomes. Additional costs for patients with treatment failure, relapse, or adverse events are unknown.

Limitations

As noted above, almost all studies were designed to assess the relatively short-term comparative effectiveness of the drugs on intermediate laboratory markers, not clinical outcomes. We could not find high quality evidence that antiviral drugs prevent liver carcinoma or death. One large RCT of 651 patients with advanced liver disease reported that lamivudine compared to placebo reduced the rates of the combined end point of disease progression, which was defined as the first occurrence of any of the following: an increase of at least two points in the Child–Pugh score, spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, bleeding, gastric or esophageal varices, development of hepatocellular carcinoma, or death related to liver disease (34/436 in lamivudine vs. 38/215 in placebo group, hazard ratio 0.45, P=0.001)[109]. However, the effects on liver cancer was either borderline (p=0.047) or not significant (p=0.052) when the authors excluded five patients who developed hepatocellular carcinoma during the first year of the study[109]. We prioritized laboratory measures based on observational research[3,124] and expert consensus about validity of intermediate outcomes.

Treatment effects in population subgroups, including patients with drug resistance, patients with HBeAg negative CHB, age, gender, and other subgroups are reported elsewhere[2,4]. We could not find evidence about comorbidities and concomitant treatments with respect to comparative effectiveness, harms, and cost.

Key Messages and Conclusions

A moderate level of evidence suggests positive sustained effects of antiviral drugs on intermediate biomarkers of CHB infection, liver histology, and function. No one drug regimen improved all biomarkers. There was no high quality evidence of the effects on clinical outcomes. Cost and attributable events vary across outcomes and drugs. Low to moderate evidence suggested lower cost and better effects from pegylated interferon alfa-2b when compared to interferon alfa-2b and entecavir when compared to lamivudine, but sustained effects on liver histology and function are unknown. Adverse events after antiviral drug use are common in adults with CHB. Individual clinical decisions should be made based on number needed to treat, cost, and absolute rates of positive outcomes and adverse events with respect to patient autonomy. Future research should clarify the cost-effectiveness of antiviral drugs on clinical outcomes.

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