

Appendix Table 1. Effects of Drug Therapies for Chronic Hepatitis B on Nonclinical Intermediate Outcomes

Active Treatment vs. Control (Reference)	Treatment Duration/ Follow-up Off Therapy, wk/wk	Studies/ Participants Enrolled, n/n	Estimates (95% CI); Dose Response Heterogeneity; P Value/ I ² (%)	Level of Evidence/ Comments	Study Quality
A. Combined outcomes					
Combined outcomes (virologic, histologic, biochemical) at end of treatment					
Interferon- α 2b + prednisone vs. no treatment (38)	24/0	1/ 87	Absolute risk difference (RD) 0.29 (0.13 to 0.46)	Low. Negative HBV DNA and HBeAg	Allocation concealment: unclear; partially double-blinded; pathologist-blinded; intention-to-treat analyses: yes; attrition bias: yes; funding: government, pharmaceutical
Interferon- α 2b vs. no treatment (38)	24/0	1/84	RD, 0.30 (0.13 to 0.46) 35 MU/wk); RD, 0.10 (-0.04 to 0.24); 7 MU/wk)	Low. Negative HBV DNA and HBeAg after 35 but not 7 MU/wk	Allocation concealment: unclear; partially double-blinded; pathologist-blinded; intention-to-treat analyses: yes; attrition bias: yes; funding: government, pharmaceutical
Lamivudine vs. placebo (60)	96/0	1/136	RD, 0.46 (0.32 to 0.59)	Low. Negative HBV DNA, normal ALT	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: no; funding: pharmaceutical
Interferon- α 2b vs. no treatment (34, 54)	16-96/0	2/92	RD, 0.36 (0.20 to 0.51) 0.47/0%	Low. Negative HBV DNA and normal ALT	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (36), private (56)
Entecavir vs. lamivudine (47)	52-96/0	2/1418	RD, 0.03 (-0.01 to 0.08) 0.49/0%	Moderate. Negative HBV DNA and HBeAg	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (59)	52/0	1/75	RD, 0.13 (-0.05 to 0.31)	Low. Loss of HBV DNA + HBeAg seroconversion + HBeAg loss	Allocation concealment: unclear; open-label, intention-to-treat analyses: ongoing attrition bias: no; withdrawals reported funding: not reported
Lamivudine vs. telbivudine (58)	52/0	1/63	RD, -0.06 (-0.30 to 0.19)	Low. Loss of HBV DNA + HBeAg loss	Allocation concealment: unclear; double-blinded, intention-to-treat

						analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. lamivudine (78)	60/0	1/100	RD, 0.32 (0.14 to 0.50)	Low. Loss of HBV DNA +HBsAg seroconversion		Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/60	RD, -0.07 (-0.30 to 0.16)	Low. Loss of HBV DNA and HBeAg		Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/85	RD, -0.12 (-0.31 to 0.06)	Low. Loss of HBV DNA and HBeAg		Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Entecavir vs. lamivudine (44, 47)	52-96	2/1418	RD, 0.03 (-0.01 to 0.08) 0.49/0%	High. Negative HBV DNA and HBeAg		Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b, 5 MU/d vs. interferon- α 2b, 1 MU/d (38)	24/0	1/82	RD, 0.20 (0.01 to 0.38)	Low. HBV DNA and HBeAg loss		Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: government, pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (59)	52/0	1/75	RD, 0.13 (-0.05 to 0.31)	Low. Loss of HBV DNA + HBeAg seroconversion + HBeAg loss		Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Interferon- α 2b, 5 MU/d + prednisolone; interferon- α 2b, 1MU/d (38)	24/0	1/85	RD, 0.19 (0.01 to 0.38)	Low. Loss of HBV DNA + HBeAg loss		Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: government, pharmaceutical
Lamivudine vs. telbivudine (58)	52/0	1/63	RD, -0.06 (-0.30 to 0.19)	Low. Loss of HBV DNA + HBeAg loss		Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon α 2b + lamivudine vs. lamivudine	60/0	1/100	RD, 0.32 (0.14 to 0.50)	Low. Loss of HBV DNA + HBsAg		Allocation concealment: adequate; open-label, intention-to-treat analyses:

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Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/60	RD, -0.07 (-0.30 to 0.16)	Low. Loss of HBV DNA and HBeAg	seroconversion yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/85	RD, -0.12 (-0.31 to 0.06)	Low. No differences between telbivudine + lamivudine vs. telbivudine on loss of HBV DNA and HBeAg	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical

Combined outcomes (virologic, histologic, biochemical) end of follow-up

Interferon- α 2b+prednisone vs. no treatment (55)	24/24	1/76	RD, 0.00 (-0.05 to 0.05)	Low. Sparse data (0 events). HBV DNA, HBsAg, and HBeAg loss	Allocation concealment: unclear; blinding not stated intention-to-treat analyses: ongoing attrition bias: yes; funding: pharmaceutical and other
Interferon- α 2b vs. no treatment (33, 35, 54, 55)	16-96/24-144	4/282	RD, 0.22 (0.08 to 0.36) 0.042/63.4% Relative risk ratio (RR) 2.96 (1.40 to 6.25) 0.313/16%	Moderate. Negative HBV DNA + HBeAg	Allocation concealment: unclear (55), adequate (33, 35, 54); open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical and other (35, 55), not reported (33)
Lamivudine vs. placebo (60)	96/24	1/136	0.07 (-0.08 to 0.21) (RD)	Low. Loss of HBV DNA and HBeAg	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: no; funding: pharmaceutical
Interferon- α 2b vs. no treatment (56, 57)	16-96/24-48	2/116	RD, 0.03 (-0.03 to 0.10) 1/0%	Moderate. Negative HBV DNA, normal ALT, HBsAg and HBeAg loss	Allocation concealment: unclear; intention-to-treat analyses: ongoing attrition bias: not reported funding: not reported
Interferon- α 2b vs. no not reported treatment (57)	16/40	1/58	RD, 0.19 (-0.01 to 0.39)	Low. Negative HBV DNA and HBeAg seroconversion	Allocation concealment: unclear; intention-to-treat analyses: ongoing attrition bias: not reported funding: not reported

Interferon- α 2b vs. no treatment (56)	16/40	1/58	RD, 0.16 (-0.04 to 0.35)	Low. Negative HBV DNA, HBeAg loss	Allocation concealment: unclear; intention-to-treat analyses: ongoing attrition bias: not reported funding: not reported
Interferon- α 2b vs. no treatment (57)	16/40	1/58	RD, 0.27 (0.10 to 0.43)	Low. Negative HBV DNA, HBeAg loss and normal ALT	Allocation concealment: unclear; intention-to-treat analyses: ongoing attrition bias: not reported funding: not reported
Interferon- α 2b vs. no treatment (34, 54)	16-96/40-144	2/92	RD, 0.28 (0.14 to 0.42) 0.968/0%	Low. Sparse data (small number of events) Negative HBV DNA and normal ALT	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes funding: not reported (34), private (54)
Entecavir vs. lamivudine (44, 46)	52-63/76-87	2/995	Random differences in all comparisons	Moderate. Entecavir, 0.50 or 0.1mg vs. lamivudine did not increase rate of HBV DNA and HBeAg loss	Allocation concealment: unclear (44), adequate (46); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (44), unclear (46)
Interferon- α 2b + prednisone vs. interferon- α 2b (51,55)	24/48	1/56	RD, -0.17 (-0.42 to 0.07)	Low. HBV DNA loss, HBeAg loss and seroconversion	Allocation concealment: unclear; blinding not stated intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + prednisone vs. interferon- α 2b (51,55)	24/48	1/79	RD, 0.07(-0.10 to 0.24)	Low. HBV DNA loss, HBeAg loss and seroconversion	Allocation concealment: unclear; blinding not stated intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (61)	52/75	1/75	RD, 0.21 (0.06 to 0.35)	Low. Loss of HBVDNA+ HBeAg seroconversion + HBeAg loss	Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Pegylated interferon- α 2b + lamivudine vs. lamivudine (52)	60/24	1/ 100	RD, 0.20 (0.05 to 0.35)	Low. Loss of HBV DNA + HBeAg loss at two time points of follow-up	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. lamivudine (52)	60/40	1/100	RD, 0.12 (-0.01 to 0.25)	Low. Loss of HBV DNA + HBeAg loss at two time points of follow-up	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical

Pegylated interferon- α 2b + lamivudine vs. lamivudine (52)	60/57	1/100	RD, 0.20 (0.05 to 0.35)	Low. Loss of HBV DNA + HBeAg loss at two time points of follow-up	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Adefovir vs. placebo (65, 74)	48-52/0	2/995	RD, 0.11 (0.06 to 0.16)* 0.122/48.2%; no significant dose response	Moderate	Allocation concealment: unclear (65) adequate (74); double-blinded: yes; intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Adefovir + lamivudine vs. adefovir (72)	48/0	1/39	RD, -0.01 (-0.23 to 0.22)	Low. Sparse data (small N of events)	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Adefovir vs. adefovir then telbivudine (76)	52/0	1/91	RD, -0.06 (-0.23 to 0.11)	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: pharmaceutical
Adefovir + lamivudine vs. lamivudine (71, 72)	48-52/0	2/134	RD, 0.12 (0.03 to 0.21)* 0.699/0%	Moderate	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Adefovir (10 vs. 30 mg) (65)	48/0	1/344	RD, -0.01 (-0.11 to 0.08); no significant dose response	Low	Allocation concealment: unclear; double-blinded: yes; intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Adefovir (40 vs. 52 wk) (74)	40-52/0	1/360	RD, 0.08 (-0.01 to 0.16)	Low	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Entecavir (70)	24/0	1/76	NS differences for all comparisons. No dose response when 0.01; 0.1; or 0.5 g were compared	Low. Sparse data (small N of events)	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: no; attrition bias: yes; funding: several authors noted as receiving support from pharmaceutical.
Entecavir vs. lamivudine (44, 46, 70)	24-63/0	3/1112	RD, 0.03 (-0.03 to 0.08) 0.13/46.9%	Low	Allocation concealment: unclear (44), adequate (46, 70); double-blinded, intention-to-treat analyses: yes (44, 46),

					no (70); attrition bias: yes; funding: pharmaceutical (44), unclear (46), several authors noted as receiving support from pharmaceutical (70)
Interferon- α 2b + corticosteroid vs. interferon- α 2b (37, 39)	16-24/0	2/77	NS differences for all comparisons	Low	Allocation concealment: unclear (37), adequate (39); open-label (37), unclear although study placebo-controlled (39) intention-to-treat analyses: yes (37), no (39); attrition bias: yes (37), no (39); funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b (79)	24/0	1/144	RD, 0.00 (-0.12 to 0.12)	Low	Allocation concealment: adequate; blinded, \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b then lamivudine (99)	16/0	1/20	RD, 0.29 (-0.01 to 0.59)	Low	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Interferon- α 2b + lamivudine vs. lamivudine (59, 79, 80)	24-52/0	3/414	RD, -0.05 (-0.13 to 0.03) 0.499/0%	Moderate	Allocation concealment: adequate; double-blinded, (79, 80), open-label (59), intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (79), pharmaceutical/government/other (80), not reported (59)
Interferon- α 2b + lamivudine vs. placebo (80)	52/0	1/118	RD, 0.08 (-0.05 to 0.21)	Low	Allocation concealment: yes; double-blinded until wk 8 (IFN assigned), intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/ government/other
Interferon- α 2b vs. no treatment (40)	16/0	1/40	RD, 0.55 (0.29 to 0.81)*	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: not reported
Interferon- α 2b + placebo vs. lamivudine (79)	24-52/0	1/151	RD, -0.03 (-0.15 to 0.09)	Low	Allocation concealment: adequate; blinded \leq wk 8, intention-to-treat analyses: yes; attrition bias: yes;

Interferon- α 2b for 48 wk vs. interferon- α 2b for 24 wk (32)	24-48/0	1/65	RD, -0.14 (-0.36 to 0.07)	Low	funding: pharmaceutical Allocation concealment: unclear; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: not reported
Lamivudine vs. adefovir dipivoxil (72)	48/0	1/38	RD, -0.16 (-0.34 to 0.02)	Low. Sparse data (0 events in active group)	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Lamivudine vs. placebo (68, 80, 85, 122)	12-52/0	4/1349	RD, 0.13 (0.04 to 0.22)* 0.001/81%		Allocation concealment: unclear (68, 122), adequate (80); double-blinded, intention-to-treat analyses: yes (68, 80), no (125); attrition bias: yes (68, 80), no; (125) funding: pharmaceutical/government
Lamivudine vs. telbivudine (58)	52/0	1/63	RD, -0.08 (-0.32 to 0.16)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49)	48/0	1/543	RD, 0.05 (-0.02 to 0.12)	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/0	1/542	RD, -0.03 (-0.11 to 0.05)	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon-pharmaceutical α 2a + placebo vs. lamivudine (49)	48/0	1/543	RD, 0.08 (0.01 to 0.16)*	Moderate	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. lamivudine (50)	52-60/0	1/100	RD, 0.34 (0.16 to 0.52)*	Moderate	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical

Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/0	1/307	RD, 0.12 (0.01 to 0.22)*	Moderate	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/60	RD, -0.09 (-0.32 to 0.14)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/85	RD, -0.17 (-0.35 to 0.01)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine vs. adefovir dipivoxil (76)	24-52/0	1/135	NS differences for all comparisons	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: pharmaceutical

B. Virologic outcomes

HBeAg loss at the end of follow-up

Interferon- α 2b + corticosteroid vs. interferon- α 2b (39,123, 124)	16-40/24-26	3/122	NS differences for all comparisons.	Moderate	Allocation concealment: unclear (123, 124), adequate (39); open-label, intention-to-treat analyses: yes (126, 127), no (39); attrition bias: yes (126, 127), no (39); funding: not reported
Interferon- α 2b + lamivudine vs. interferon- α 2b (79, 85)	24/28-40	2/347	NS differences for all comparisons.	Moderate	Allocation concealment: adequate; double blind intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (59, 79, 80, 83, 85)	37-135/16-144	5/1167	One RCT in 5 reported significant improvement after combined therapy.	Moderate	Allocation concealment: adequate (59, 79, 80), unclear (83); double-blinded (79, 80), open-label (59, 83), intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (79), pharmaceutical/government/other (80), not reported (59, 83)

Interferon- α 2b + lamivudine vs. placebo (80, 85)	24-52/16-28	2/450	RD, 0.10 (-0.04 to 0.23) 0.077/68%	Moderate	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/ government/ other
Interferon- α 2b vs. lamivudine (79, 85)	24/28-40	2/625	NS differences for all comparisons.	Moderate	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/ government/ other
Interferon- α 2b vs. interferon- α 2b (dose, time) (32, 39)	24-48/24-72	2/103	NS differences for dose and duration of time comparisons.	Moderate	Allocation concealment: unclear (32), adequate (39); open-label, intention-to-treat analyses: no; attrition bias: no; withdrawals reported (32), no (39); funding: not reported
Interferon- α 2b vs. placebo or no treatment (32, 40, 85)	16-24/8-48	3/351	RD, 0.28 (0.07 to 0.50)* 0.025/73% RR 2.52 (1.55 to 4.1)* 0.359/2.4%	Moderate	Allocation concealment: adequate (32), unclear (40); intention-to-treat analyses: yes (33), no (40); attrition bias: yes; funding: not reported
Lamivudine vs. placebo (68, 80)	52/16 2/318		RD, 0.15 (0.05 to 0.24)* 0.519/0%	Moderate	Allocation concealment: unclear (68), adequate (80); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49)	48/24	1/543	RD, 0.07 (0.00 to 0.15)*	Moderate	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/24	1/542	RD, -0.05 (-0.13 to 0.03)	Moderate	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49)	48/24	1/543	RD, 0.13 (0.05 to 0.20)*		Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a vs. pegylated interferon- α 2a (125)	24/24	1/194	NS differences for dose and duration of time comparisons (RD)	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding:

Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90, 126)	52/26	2/614	RD, -0.01 (-0.09 to 0.06) 0.991/0%	Moderate	pharmaceutical Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b vs. interferon- α 2b (93)	24/24	1/230	RD, 0.10 (0.00 to 0.21)	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
HBeAg seroconversion at the end of treatment					
Adefovir + lamivudine vs. adefovir (72)	48/0	1/39	RD, -0.06 (-0.22 to 0.11)	Low. Sparse data (small number of events)	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Adefovir + lamivudine vs. lamivudine (71, 72)	48-52/0	2/134	Random differences in both RCTs	Low. Sparse data (small number of events)	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: not reported
Adefovir (dose, duration of treatment) (65, 74, 76)	48-52/0	3/795	Random differences in 2 of 3 RCTs (RD). No dose response.	Low. Sparse data (small number of events)	Allocation concealment: unclear (65), adequate (74, 76); double-blinded (65, 74), open-label (76), intention-to-treat analyses: yes (65, 74), no (76); attrition bias: yes; funding: pharmaceutical
Adefovir vs. placebo (65, 74)	48-52/0	2/700	RD, 0.05 (0.01 to 0.09)* No dose response 0.25/28%	High	Allocation concealment: adequate (74), unclear (65); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Entecavir (dose response association) (70)	24/0	1/177	NS differences for all comparisons (RD) No dose response association with HBeAg loss	Low	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: no; attrition bias: yes; funding: several authors noted as receiving support from pharmaceutical
Entecavir vs. lamivudine (44, 46, 70)	24-96/0	3/1185	Random differences in 2 of 3 RCTs.	Moderate	Allocation concealment: adequate (46, 70), unclear (44); double-blinded, intention-to-treat analyses: yes (44, 46),

Interferon- α 2b + lamivudine vs. interferon- α 2b (79)	24/0	1/144	RD, -0.02 (-0.11 to 0.07) (RD)	Low	no (70); attrition bias: yes; funding: unclear (46), pharmaceutical (44, 70) Allocation concealment: adequate; blinded \leq wk 8, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (31, 59, 79, 80)	52/0	4/565	Random differences in 3 of 4 RCTs.	High	Allocation concealment: adequate; open-label (31, 59), double-blinded (59, 80), intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (31, 59), pharmaceutical (79) pharmaceutical/government/other (80)
Interferon- α 2b + lamivudine vs. placebo (80)	52/0	1/119	RD, -0.01 (-0.13 to 0.10)	Low	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other
Interferon- α 2b + placebo vs. lamivudine (79)	52/0	1/151	RD, -0.05 (-0.12 to 0.02)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b (32)	24/0	1/65	RD, -0.10 (-0.33 to 0.12)	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: not reported attrition bias: no; withdrawals reported funding: not reported
Interferon- α 2b vs. placebo (40)	16/0	1/40	NS differences for dose comparisons.	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: not reported
Lamivudine vs. telbivudine (58)	52/0	1/63	RD, -0.11 (-0.34 to 0.12)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Lamivudine vs. adefovir (72)	48/0	1/38	RD, -0.11 (-0.27 to 0.06)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: not reported

Lamivudine (67)	48/0	1/285	RD, -0.03 (-0.11 to 0.05)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: no; funding: pharmaceutical
Lamivudine vs. placebo (53, 67, 68, 80, 85, 122)	12-80/0	6/1638	RD, 0.05 (0.00 to 0.10) 0.028/60% RR 1.69 (1.05 to 2.74)* 0.153/38%	High	Allocation concealment: adequate (53, 80), unclear (67, 68, 122); double-blinded, intention-to-treat analyses: yes (53, 67, 68, 80), no (67); attrition bias: yes (53, 68, 80), no (67, 125); funding: institution (53), pharmaceutical (67, 125), pharmaceutical/government (68, 80)
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49)	48/0	1/543	RD, 0.03 (-0.04 to 0.10)	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/0	1/542	RD, -0.03 (-0.10 to 0.04)	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes funding: pharmaceutical
Pegylated interferon-pharmaceutical α 2a + placebo vs. lamivudine (49)	48/0	1/543	RD, 0.06 (-0.01 to 0.13)	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes funding: pharmaceutical
Pegylated interferon α 2b + lamivudine vs. lamivudine (50)	60/0	1/100	RD, 0.32 (0.14 to 0.50)*	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/0	1/307	RD, 0.02 (-0.07 to 0.11)	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: pharmaceutical

Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/60	RD, -0.06 (-0.28 to 0.15)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/85	RD, -0.17 (-0.35 to 0.00)	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: pharmaceutical
Telbivudine vs. adefovir (76)	24-52/0	1/136	RR 6.03 (2.20 to 16.52)*	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
HBeAg seroconversion at time of follow-up					
Interferon- α 2b + corticosteroid vs. interferon- α 2b (123, 124)	24/24-26	2/85	RD, 0.10 (-0.11 to 0.31) 0.792/0%	Low	Allocation concealment: unclear (81), adequate (79); open-label, intention-to-treat analyses: no (81), yes (79); attrition bias: yes; funding: not reported (81), pharmaceutical (79)
Interferon- α 2b + lamivudine vs. interferon- α 2b (79, 81, 85)	24-48/4-56	3/482	Random difference in all comparisons. Active treatment at the longest 56 wk of follow-up in one RCT resulted in increase of 0.36 (95% CI 0.10 to 0.61)* in rate of the outcome.	Low. Limited evidence from one RCT suggest increase in HBeAg seroconversion at the longest 56 wk of follow-up	Allocation concealment: adequate; open-label (31), double blinded (79, 80), intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other (80), pharmaceutical (79)
Interferon- α 2b + lamivudine vs. lamivudine (31, 79, 80)	24-52/16-48	3/490	RD, 0.00 (-0.15 to 0.14) 0.002/84%	Moderate. (1 of 3 RCTs reported significant increase (0.182; 95% 0.050 to 0.315)	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other
Interferon- α 2b + lamivudine vs. placebo (80, 85)	24-52/16-28	2/450	RD, 0.05 (-0.12 to 0.22) 0.011/85%	Low. Secondary analysis of 4 RCTs reported significant increase (0.13; 95% 0.05 to 0.21)*	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b vs. lamivudine (79, 85)	24-52/12-40	2/776	Random difference in all comparisons.	Moderate	Allocation concealment: adequate; double blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b vs. placebo	16-96/28-64	2/346	RD, 0.120 (0.03 to 0.21)*	Moderate	Allocation concealment: unclear; open-

(40, 85)			0.353/0%			label (40), intention-to-treat analyses: yes (85), no (40); attrition bias: yes; funding: not reported (40) pharmaceutical (85)
Lamivudine vs. placebo (68, 80)	52/16	2/318	Random difference in all comparisons.	Low		Allocation concealment: unclear (68), adequate (80); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government
Peginterferon- α 2a + lamivudine vs. lamivudine (49)	48/24	1/814	RD, 0.08 (0.01 to 0.15)*	Low		Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/24	1/814	RD, -0.05 (-0.12 to 0.03)	Low		Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49)	48/24	1/814	RD, 0.13 (0.06 to 0.20)*	Moderate		Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a vs. pegylated interferon- α 2a (125)	24/24	1/194	Random difference in all dose comparisons. No dose response	Low		Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b+lamivudine vs. lamivudine (50)	52-60/40-96	1/100	Random difference in all time of follow-up comparisons.	Low		Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/26	1/307	Random difference in all comparisons.	Low		Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical

HBsAg loss at the end of treatment

Adefovir + lamivudine vs. adefovir (72)	48/0	1/39	RD, 0.05 (-0.08 to 0.18)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Adefovir + lamivudine vs. lamivudine (72)	48/0	1/39	RD, 0.05 (-0.08 to 0.18)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Adefovir dipivoxil (240 vs. 114 wk) (42)	240 vs. 114	1/250	RD, -0.048 (-0.088 to -0.008)*	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Entecavir vs. lamivudine (44, 47)	52-96/0	2/1117	Random difference in all comparisons.	Moderate	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + corticosteroid vs. interferon- α 2b (37, 38)	16-24/0	2/125	Random difference in all comparisons.	Moderate	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (37), government, pharmaceutical (38)
Interferon- α 2b + corticosteroid vs. no treatment (38, 48)	24/0	2/103	RD, 0.11 (0.02 to 0.20)* 0.917/0%	Moderate	Allocation concealment: unclear; partially double-blinded (38), open-label (48), intention-to-treat analyses: yes (38), no (48); attrition bias: yes; funding: government, pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (80, 82)	52-96/0	2/262	Random difference in all comparisons	Moderate	Allocation concealment: adequate; open-label (82), double-blinded (80), intention-to-treat analyses: unclear (82), yes (80); attrition bias: yes; funding: not reported (82), pharmaceutical/government/other (80)
Interferon- α 2b + lamivudine vs. placebo	52/0	1/119	RD, 0.06 (0.00 to 0.13)	Low	Allocation concealment: yes; double-blinded, intention-to-treat analyses:

(80)

Interferon- α 2b vs. interferon- α 2b (38)	24/0	1/82	RD, 0.10 (-0.01; 0.21) (RD) No dose response	Low	yes; attrition bias: yes; funding: pharmaceutical/government/ other Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: government, pharmaceutical
Interferon- α 2b vs. no treatment (38, 40, 54)	16-96/0	3/166	RD, 0.06 (-0.03 to 0.15) 0.209/36.2%	Moderate	Allocation concealment: unclear; open-label (40, 54), partially double-blinded (38), intention-to-treat analyses: no (40), yes (38, 54); attrition bias: yes; funding: not reported (40), private (54), government, pharmaceutical (38)
Lamivudine vs. placebo (80)	52/0	1/175	RD, 0.02 (-0.02 to 0.05)	Low. Sparse data (0 events in control group)	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other
Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/0	1/307	RD, 0.01 (-0.04 to 0.06)	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: pharmaceutical
HBsAg loss at follow-up					
Interferon- α 2b vs. no treatment (33, 35, 40, 54)	16-96/8-48	4/247	Random difference in all comparisons.	Low. Sparse data (0 events in control group)	Allocation concealment: unclear (35, 40, 54), adequate (33); double-blinded (35), open-label (40, 54), intention-to-treat analyses: yes (33, 35, 54), no (40); attrition bias: yes; funding: pharmaceutical (35), private (54), not reported (33, 40)
Interferon- α 2b + lamivudine vs. lamivudine (31, 80, 89)	24-52/16-48	3/495	Random difference in all comparisons.	Low. Sparse data (0 events in both groups)	Allocation concealment: unclear (89), adequate (31, 80); open-label (31, 89), double blinded (80), intention-to-treat analyses: yes; attrition bias: yes (none); funding: foundations (89) pharmaceutical/government/ other (80), none from pharmaceutical (31)

Interferon- α 2b + lamivudine vs. placebo (80)	52/16	1/119	RD, 0.05 (-0.01 to 0.11)	Low. Sparse data (0 events in control group)	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other
Interferon- α 2b vs. interferon- α 2b (32, 36)	24-48/48	2/103	Random difference in all comparisons. No dose response	Low. Sparse data (0 events in both groups)	Allocation concealment: unclear; open-label, intention-to-treat analyses: not reported (32), yes (36); attrition bias: yes; funding: not reported (32), foundation (36)
Interferon- α 2b + corticosteroid vs. interferon- α 2b (51, 123, 124)	24/24-26	3/141	Random difference in all comparisons.	Low. Sparse data (small number of events)	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (51), not reported (123, 124)
Lamivudine vs. placebo (60, 68, 80)	52-96/16-26	3/1068	Random difference in all comparisons.	Random difference in all comparisons.	Allocation concealment: adequate (80), unclear (60, 68); double-blinded, intention-to-treat analyses: yes; attrition bias: yes (68, 80), no (60); funding: pharmaceutical/government/ other
HBsAg seroconversion—end of treatment					
Adefovir vs. placebo (64)	96 wk/0	1/120	RD, 0.01 (-0.03 to 0.06)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Adefovir (longer treatment) (42, 64)	48-240 wk/ 0	2/390	Random differences in all comparisons.	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Entecavir vs. lamivudine (47)	96/0	1/408	RD, -0.02 (-0.06 to 0.01)	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical

HBsAg seroconversion at follow-up

Pegylated interferon- α 2b vs. interferon- α 2b (93)	24/24	1/230	Random difference in all comparisons.	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Interferon- α 2b vs. placebo (54)	96/48	1/42	RD, 0.10 (-0.05 to 0.24)	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: private
Interferon- α 2b vs. no treatment (40)	16/48-64	1/40	RD, 0.15 (-0.05 to 0.35)	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: no attrition bias: yes; funding: not reported
HBV DNA loss—end of treatment					
Adefovir + lamivudine vs. lamivudine (71, 72)	48-52/0	2/134	RD, 0.25 (0.10 to 0.39)* 0.219/34%	Low. Sparse data (0 events in control group)	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Adefovir vs. adefovir (42, 64, 65, 74, 76)	48-240/0	5/1520	RD, -0.08 (-0.16 to 0.01) 0.049/58% RR 0.84 (0.68 to 1.04) 0.034/62%	Moderate. One RCT reported greater HBV DNA loss after 30 vs. 10 mg (0.18; 95% CI 0.08 to 0.27)*	Allocation concealment: unclear (42, 64, 65), adequate (74, 76); double-blinded (42, 64, 65, 74), open-label (76), intention-to-treat analyses: yes (42, 64, 65, 74), no (75); attrition bias: not reported (42, 64); yes (65, 74, 76); funding: pharmaceutical
Adefovir + lamivudine vs. adefovir (72)	48/0	1/39	RD, 0.09 (-0.20 to 0.37)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Adefovir vs. placebo (63-65, 74)	48-96/0	4/1002	RD, 0.38 (0.23 to 0.53)* 0/93% RR 20.41 (6.79 to 61.32)* 0.267/24%	High	Allocation concealment: unclear (63-65), adequate (74); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Entecavir (Dose) (70)	24/0	1/177	Random difference in all comparisons.	Low	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: no attrition bias: yes; funding: several authors noted as receiving support from pharmaceutical

Entecavir vs. lamivudine (44, 45, 47, 70)	24-96/0	4/1636	RD, 0.23 (0.11 to 0.35)* 0/89% No dose response	Low	Allocation concealment: adequate (45, 70), unclear (44, 47); double-blinded, intention-to-treat analyses: no (45, 70), yes; (44, 47) attrition bias: yes; funding: pharmaceutical
Entecavir vs. lamivudine (44, 45, 47, 70)	24-96/0	4/1636	RR, 1.64 (1.22 to 2.22) 0/92% No dose response	Low	Allocation concealment: adequate (45, 70), unclear (44, 47); double-blinded, intention-to-treat analyses: no (45, 70), yes; (44, 47) attrition bias: yes; funding: pharmaceutical
Entecavir vs. lamivudine (44, 45, 47, 70)	24-96/0	4/1636	RD, >1 y of active treatment 0.30 (0.16 to 0.44)* RD, 6 mo of active treatment 0.09 (-0.04 to 0.21)	Moderate. Length of active treatment was associated with greater differences in absolute rates of HBV DNA loss with significant differences after >1 y of treatment	Allocation concealment: adequate (45, 70), unclear (44, 47); double-blinded, intention-to-treat analyses: no (45, 70), yes; (44, 47) attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + corticosteroid vs. interferon- α 2b (37, 39)	16-24/0	2/77	Random difference in all comparisons.	Low	Allocation concealment: unclear (37), adequate (39); open-label (37), unclear although study placebo-controlled (39) intention-to-treat analyses: yes (37), no (39); attrition bias: yes (37), no (39); funding: pharmaceutical
Interferon- α 2b + corticosteroid vs. no treatment (37)	16/0	1/34	RD, 0.25 (0.04 to 0.46)*	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b (79)	24/0	1/144	RD, 0.00 (-0.12 to 0.12)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b + lamivudine (99)	16/0	1/20	RD, 0.00 (-0.21 to 0.21)	Low. No differences between interferon- α 2b + lamivudine for 20 wk vs. interferon-	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported

				α 2b +4 wk placebo then 12 wk lamivudine on HBV DNA loss	
Interferon- α 2b + lamivudine vs. lamivudine (31, 59, 73, 79, 80, 82, 84)	24-96/0	7/786	RD, 0.03 (-0.11 to 0.17) 0/81%	High	Allocation concealment: adequate (31, 59, 79, 82), adequate (lottery cards) (73), unclear (84): yes (80); open-label (31, 59, 73, 82, 84), pathologist-blinded, (31, 59, 79, 80, 84), blinded \leq wk 8 (79), double-blinded (80), until wk 8 (IFN assigned) (80), intention-to-treat analyses: yes (31, 59, 73, 79, 80, 84), unclear (82); attrition bias: yes (31, 59, 73, 79, 80, 84), no withdrawals reported (82); funding: none from pharmaceutical (31), pharmaceutical (79), pharmaceutical/ government/other (80), not reported (59, 73, 82, 84)
Interferon- α 2b + lamivudine vs. placebo (80)	52/0	1/119	RD, in HBV DNA response <3 pg/mL 0.48 (0.33 to 0.63)* RD in sustained HBV DNA response: no two consecutive detectable HBV DNA 0.05 (-0.09 to 0.18)	Low	Allocation concealment: yes; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/ government/ other
Interferon- α 2b + placebo vs. lamivudine (79)	24/0	1/76	RD, -0.03 (-0.15 to 0.09)		Allocation concealment: adequate; blinded \leq wk 8 intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b vs. interferon- α 2b (32, 36, 39)	0/0	3/141	Random difference in all dose comparisons. No dose response	Moderate. Different length of treatment and doses of Interferon- α 2b were associated with random changes in HBV DNA loss	Allocation concealment: unclear (32, 36), adequate (39); open-label, intention-to-treat analyses: not reported (32, 39), yes (36); attrition bias: no (32, 39), yes (36); funding: not reported (32, 39), foundation (36)

Interferon- α 2b vs. no treatment (37)	16/0	1/34	RD, 0.45 (0.22 to 0.68)*	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Lamivudine vs. adefovir (72)	48/0	1/38	RD, -0.26 (-0.47 to -0.06)*	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Lamivudine (67, 126, 127)	24-104/0	3/581	RD, 0.21 (0.10 to 0.31)* 0.187/35% dose response association	Moderate. Larger doses of lamivudine resulted in greater HBV DNA loss, the length of treatment was not associated with greater dose response	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: no (67, 126), yes (127); funding: pharmaceutical
Lamivudine 60 vs. 48 wk (88)	60/0	1/429	RD, -0.08 (-0.08 to 0.2)	Low. Longer treatment did not increase HBV DNA loss	Allocation concealment: unclear; double-blind intention-to-treat analyses: no; attrition bias: no; funding: not reported
Lamivudine vs. placebo or usual care (60, 67, 68, 75, 80, 88, 126)	12-104/0	7/1305	RD, 0.48 (0.31 to 0.66)* 0/94% RR 3.79 (2.71 to 5.30)* 0.046/53%	High	Allocation concealment: yes (80), unclear (60, 67, 68, 75, 88, 126); open-label (75), double-blinded (60, 67, 68, 80, 88, 126) until wk 8 (IFN assigned) (80), pathologist-blinded (60, 68, 80), intention-to-treat analyses: yes (60, 67, 68, 75, 80, 126), no (88); attrition bias: yes (68, 80), no (60, 67, 88, 126), none reported (75); funding: pharmaceutical/government/ other (80), pharmaceutical/ government (68) pharmaceutical (58, 65, 126), not reported (75, 88)

Pegylated interferon- α 2a+ lamivudine vs. lamivudine (49)	48/0	1/543	RD, 0.29 (0.21 to 0.37)*	Moderate	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a+ lamivudine vs. pegylated interferon- α 2a (49)	48/0	1/542	RD, 0.44 (0.36 to 0.51)*	Moderate	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a+ placebo vs. lamivudine (49)	48/0	1/543	RD, -0.15 (-0.22 to -0.07)*	Moderate	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b+ lamivudine vs. lamivudine (78)	60/0	1/100	RD, 0.06 (-0.04 to 0.16)	Low	Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes
Lamivudine vs. telbivudine (58)	52/0	1/63	RD, -0.30 (-0.55 to -0.04)*	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/60	RD, 0.17 (-0.09 to 0.43)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/85	RD, -0.13 (-0.34 to 0.08)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine vs. adefovir (76)	24-52/0	1/136	RD, 0.28 (0.12 to 0.44)*	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: pharmaceutical

HBV DNA loss at time of follow-up

Adefovir vs. placebo (64)	96/18	1/120	RD, 0.59 (0.46 to 0.72)*	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported; funding: pharmaceutical
Entecavir vs. lamivudine (44)	52/24	1/709	RD, 0.01 (-0.02 to 0.05)	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + corticosteroid vs. interferon- α 2b (37-39, 51, 123, 124)	16-24/24-72	6/322	Random differences in all comparisons.	High	Allocation concealment: unclear (37, 38, 51, 123, 124), adequate (39); open-label (37, 123, 124), partially double-blinded (38, 51), blinding unclear (39); intention-to-treat analyses: yes (37, 38, 51, 123, 124), no (39); attrition bias: yes (37, 38, 51, 123, 124), no (39); funding: pharmaceutical (37, 51), not reported (39, 124); government, pharmaceutical (38)
Interferon- α 2b + corticosteroid vs. no treatment (37, 38)	16-96/24	2/121	Random differences in all Comparisons.	Moderate	Allocation concealment: unclear; open-label, (37), partially double-blinded (38), intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (37), government, pharmaceutical (38)
Interferon- α 2b + lamivudine vs. interferon- α 2b (79, 81)	24-48/4-56	2/278	RD, 0.15 (-0.06 to 0.35) 0.002/80.4%	Low	Allocation concealment: unclear (81), adequate (79); open-label (79), blinded \leq wk 8 (79); intention-to-treat analyses: no (81), yes (79); attrition bias: yes; funding: not reported (81), pharmaceutical (79)
Interferon- α 2b + lamivudine vs. lamivudine (59, 73, 79, 83)	24-176/12-40	4/365	RD, 0.04 (-0.07 to 0.14) 0.071/57%	Moderate	Allocation concealment: adequate (59, 73, 79), unclear (83); open-label (59, 73, 83), partially blinded, (79); intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (59, 73, 83), pharmaceutical (79)

Interferon- α 2b + placebo vs. lamivudine (79)	24-52/12-40	1/151	Random differences in all follow-up comparisons	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b vs. interferon- α 2b (32, 36, 38, 39)	24-48/4-72	4/297	Random differences in all dose, length of treatment, and follow-up comparisons	Moderate	Allocation concealment: unclear (32, 36, 38), adequate (39); open-label (32, 36), partially double-blinded (36), unclear (39) intention-to-treat analyses: not reported (32), yes (36, 38), no (39); attrition bias: yes (32, 36, 38), no (39); funding: not reported (32, 39), foundation (36), government, pharmaceutical (38)
Interferon- α 2b vs. no treatment (33, 37, 38)	16/8-24	3/168	RD, 0.44 (0.27 to 0.60)* 0.573/0%	Low	Allocation concealment: adequate (33), unclear (37, 38); open-label (37), partially double-blinded (38), intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (33), government, pharmaceutical (38), pharmaceutical (37)
Interferon- α 2b vs. no treatment (33, 37, 38)			RD, 0.28 (-0.04 to 0.60) 0/89%	The effects were attenuated at longer follow-up	Allocation concealment: adequate (33), unclear (37, 38); open-label (37), partially double-blinded (38), intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (33), government, pharmaceutical (38), pharmaceutical (37)
Lamivudine vs. placebo (60)	96/24	1/136	RD, 0.08 (0.01 to 0.15)*		Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: no funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49)	48/24	1/543	RD, 0.09 (0.04 to 0.13)*	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes;

Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/24	1/542	RD, -0.01 (-0.07 to 0.05)	Low	funding: pharmaceutical Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49)	48/24	1/543	RD, 0.09 (0.04 to 0.14)*	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. lamivudine (50)	52-60/24-57	1/100	RD, 0.00 (-0.04 to 0.04)	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical

C. Histologic outcomes

Histologic improvement at end of treatment

Adefovir vs. placebo (63-, 65)	48-96/0	3/819	RD, 0.26 (0.17 to 0.34)* 0.086/55%	High	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported (63); yes (65); funding: pharmaceutical
Adefovir vs. placebo (63, 65)	48-96/0	2/699	RD, 0.20 (0.14 to 0.26)* 0.395/0% No dose response	Moderate	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported (63); yes (65); funding: pharmaceutical
Lamivudine vs. placebo (60, 66-68)	48-96/0	4/580	RD, 0.25 (0.13 to 0.38)* 0.025/68% RR 2.09 (1.60 to 2.74)*	Moderate	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes (68), no (60, 66, 67); funding: pharmaceutical (60, 66, 67), pharmaceutical/government (66)
Adefovir vs. adefovir, 30 (42, 64, 65)	48-240/0	3/905	Random difference in all comparisons. No dose response	Moderate. Dose and duration of treatments with adefovir were	Allocation concealment: unclear; double-blinded: yes; intention-to-treat analyses: yes; attrition bias: yes (65),

Entecavir vs. lamivudine (44-46)	52-63/0	3/1633	RD, 0.14 (0.04 to 0.24)* 0.003/83% No dose response	not associated with improved histology Moderate	not reported (42, 64); funding: pharmaceutical Allocation concealment: unclear (44, 45), adequate (46); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (44, 45), unclear (46)
Entecavir vs. lamivudine (44, 46)	52-63/0	2/995	RD, 0.10 (-0.02 to 0.22) 0.008/86% No dose response	Moderate	Allocation concealment: unclear (44), adequate (46); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (44), unclear (46)
Interferon- α 2b + lamivudine vs. lamivudine (59, 80, 84)	24-52/0	3/327	RD, -0.04 (-0.17 to 0.09) 0.185/36%	Moderate	Allocation concealment: adequate (59, 80), unclear (84); open-label (59, 84), double blinded (80), intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (59, 84), pharmaceutical/government/ other (80)
Interferon- α 2b + lamivudine vs. lamivudine (31, 80)	52/0	2/389	RD, 0.00 (-0.38 to 0.38) 0/93%	Low	Allocation concealment: adequate; double-blinded (80), open-label (31), intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other (80), none from pharmaceutical (31)
Lamivudine for 144 vs. 96 wk (128)	96-144/0	1/250	RD, -0.16 (-0.24 to -0.08)*	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b (81)	48/0	1/48	RD, 0.54 (0.28 to 0.79)*	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: not reported
Interferon- α 2b + lamivudine vs. placebo (80)	52/0	1/119	Random difference in total and inflammatory scores	Low	Allocation concealment: yes; double-blinded until wk 8 (IFN assigned), pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/ other

Interferon- α 2b vs. no treatment (54)	96/0	1/72	RD, 0.24 (0.00 to 0.48)	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: private
Pegylated interferon α 2b + lamivudine vs. lamivudine (78)	52-60/0	1/100	Random difference in inflammatory and fibrosis scores	Low	Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes
Pegylated interferon α 2b + lamivudine vs. pegylated interferon α 2b (90)	52/0	1/307	RD, -0.04 (-0.12 to 0.05)	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Histologic improvement at follow-up					
Interferon- α 2b + lamivudine vs. interferon- α 2b (79)	24/28	1/144	RD, -0.08 (-0.23 to 0.07)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (79)	24/28	1/157	RD, -0.10 (-0.24 to 0.05)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + placebo vs. lamivudine (79)	24/28	1/151	RD, -0.02 (-0.17 to 0.14)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b vs. no treatment (40)	16/48	1/40	RD, 0.15 (-0.05 to 0.35)	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: not reported
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49, 69)	48/24	2/1366	Random difference in all comparisons	High	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a +	48/24	1/96	RD, 0.04 (-0.05 to 0.12)	Low	Allocation concealment: unclear;

lamivudine vs. pegylated interferon- α 2a (49)

partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical

Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/26	1/307	RD, 0.03 (-0.04 to 0.09)	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2 + placebo vs. lamivudine (69)	48/24	1/552	RD, -0.01 (-0.07 to 0.06)	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49, 69)	48/24	2/1366	Random difference in all comparisons	Moderate	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (69)	48/24	1/552	RD, 0.12 (0.02 to 0.22)*	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical

D. Biochemical outcomes

ALT normalization end of treatment

Adefovir + lamivudine vs. adefovir (72)	48/0	1/39	RD, 0.03 (-0.29 to 0.34)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Adefovir + lamivudine vs. lamivudine (71, 72)	48-52/0	2/134	RD, 0.32 (0.13 to 0.52)* 0.158/50%	Moderate	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported (72)
Adefovir (dose or duration) (42, 64, 65, 74, 76)	48-240/0	5/173	RD, -0.06 (-0.12 to -0.01)* for shorter treatment vs. longest) 0.709/0% No dose	Longer treatment with adefovir associated with increased rate of ALT normalization	Allocation concealment: unclear (42, 64, 65), adequate (74, 76); double-blinded (42, 64, 65, 74), open-label (76), intention-to-treat analyses: yes

			response		
Adefovir vs. placebo (63, 64, 65, 74)	48-96/0	4/1342	RD, 0.40 (0.30 to 0.49)* 0.007/72% No dose response 2.97 (2.38; 3.69)* (RR) 0.219/30%	High	(42, 64, 65, 74), no (76); attrition bias: not reported (42, 64); yes (65, 74, 76) funding: pharmaceutical
Entecavir (dose) (43, 70)	24-48/0	2/359	Random differences in all dose comparisons. No dose response	Moderate	Allocation concealment: unclear (63-65), adequate (74); double-blinded, intention-to-treat analyses: yes; attrition bias: yes (65, 74), not reported (63, 64); funding: pharmaceutical
Entecavir vs. lamivudine (43-47, 70)	24-96/0	6/2423	RD, 0.22 (0.11 to 0.32)* 0/87% RR 1.62 (1.28; 2.06)* 0/87%	High. The effect of entecavir on RD of ALT normalization was lower in RCTs with higher rates of the outcome after lamivudine administration	Allocation concealment: adequate (43, 46), unclear (44, 45, 47, 70); double-blinded, intention-to-treat analyses: yes (43-47), no (70); attrition bias: yes; funding: unclear (43, 46), pharmaceutical (44, 45, 44, 70)
Interferon- α 2b + lamivudine vs. interferon- α 2b (79)	24/0	1/144	RD, -0.01 (-0.14 to 0.11)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b + lamivudine (99)	16/0	1/20	RD, -0.05 (-0.42 to 0.32)	Low	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Interferon- α 2b + lamivudine vs. lamivudine (59, 73, 79, 80, 89)	24-96/0	5/626	RD, -0.02 (-0.16 to 0.12) 0.004/74%	Moderate	Allocation concealment: adequate; double-blinded (79, 80, 89), open-label (59, 73), intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (59, 73, 89), pharmaceutical (79), pharmaceutical/government/other (80)

Interferon- α 2b + lamivudine vs. placebo (80)	52/0	1/119	RD, 0.03 (-0.10 to 0.16)	Low	Allocation concealment: yes; double-blinded until wk 8 (IFN assigned), pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/ government/ other
Interferon- α 2b + placebo vs. lamivudine (79)	24/0	1/151	RD, -0.04 (-0.15 to 0.07)	Low	Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b (32, 36)	24-48/0	2/103	Random differences in all dose and time comparisons	Low	Allocation concealment: unclear; open-label, intention-to-treat analyses: not reported (32), yes (36); attrition bias: yes; funding: not reported (32), foundation (36)
Lamivudine vs. adefovir (72)	48/0	1/38	RD, -0.42 (-0.67 to -0.18)*	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: not reported
Lamivudine (67, 88, 130)	48-52/0	3/838	Random differences in all dose and time comparisons	Moderate	Allocation concealment: partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes
Lamivudine vs. no treatment or placebo (53) (60, 67, 68, 80, 88, 122)	12-96/0	7/1602	RD, 0.22 (0.13 to 0.31)* 0/78% RR 2.42 (1.94 to 3.01)* 0.44/0%		Allocation concealment: adequate (53, 80), unclear (60, 67, 68, 88, 122); double-blinded, intention-to-treat analyses: yes (53, 60, 67, 68, 80, 88), no (122); attrition bias: no (53, 60, 67), yes (68, 80, 88, 122); funding: institution (53), not reported (88), pharmaceutical/government/other (60), pharmaceutical/ government (68), pharmaceutical (67)
Lamivudine vs. telbivudine (58)	52/0	1/85	Random differences in two of three dose comparisons	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical

Pegylated interferon- α 2a + lamivudine vs. lamivudine (49, 69)	48/0	2/905	RD, -0.20 (-0.29 to -0.10)* 0.141/54%	High	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/0	1/542	RD, 0.08 (-0.01 to 0.16)	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49, 69)	48/0	2/905	RD, -0.29 (-0.42 to -0.17)* 0.045/75% RR 0.57 (0.46 to 0.70)* 0.13/56%	Moderate	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. lamivudine (78)	60/0	1/100	RD, 0.12 (-0.02 to 0.26)	Low	Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes
Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/0	1/307	RD, 0.14 (0.03 to 0.24)*	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/101	Random differences in all 3 dose comparisons	Low. Three tested doses of telbivudine + lamivudine vs. lamivudine alone did not increase rates of ALT normalization	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/101	Random differences in all 3 dose comparisons	Low. Three tested doses of telbivudine + lamivudine vs. telbivudine alone did not increase rates of ALT normalization	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine vs. telbivudine (58)	52/0	1/44	RD, 0.09 (-0.11 to 0.29) No dose response	Low. Telbivudine 600 mg vs. telbivudine	Allocation concealment: unclear; double-blinded, intention-to-treat

			association	400 mg did not improve rates of ALT normalization	analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine vs. adefovir (76)	24-52/0	1/135	Random differences in all dose and time comparisons	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: no; attrition bias: yes; funding: pharmaceutical
ALT normalization at follow-up					
Adefovir vs. placebo (64, 74)	12-96/18-40	2/600	RD, 0.26 (0.19 to 0.33)* 0.791/0%	Moderate	Allocation concealment: unclear (64), adequate (74); double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + corticosteroid vs. interferon- α 2b (38, 123, 124)	24/24-26	3/170	Random differences in all comparisons	Moderate	Allocation concealment: unclear; partially double-blinded (38), open-label (123, 124), intention-to-treat analyses: yes; attrition bias: yes; funding: government/pharmaceutical (38), not reported (123, 124)
Interferon- α 2b + corticosteroid vs. no treatment (38)	24/24	1/87	RD, 0.25 (0.06 to 0.43)*	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes; study withdrawals adequately described: yes; funding: government, pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b (79, 81)	24-48/4-56	2/192	Random differences in all time of follow-up comparisons, significant increase in RD at the onset 56 wk time of follow-up	Low	Allocation concealment: unclear (81), adequate (79); open-label (79), blinded \leq wk 8 (79) intention-to-treat analyses: no (81), yes (79); attrition bias: yes; funding: not reported (81), pharmaceutical (79)
Interferon- α 2b + lamivudine vs. lamivudine (31, 59, 73, 79, 83, 89)	24-176/24-96	6/751	RD, 0.03 (-0.03 to 0.08) 0.014/58.3%	Moderate. 2 of 6 RCTs reported an increase in rate	Allocation concealment: adequate (31, 59, 73, 79), unclear (83, 89); open-label (31, 59, 73, 83, 89), double blinded (79), intention-to-treat analyses: yes; attrition bias: yes; funding: foundations

Interferon- α 2b + placebo vs. lamivudine (79)	24/12-40	2/151	Random differences at different time of follow-up	Low	(89), pharmaceutical (79), not reported (31, 59, 73, 83) Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b vs. interferon- α 2b (32, 36, 38)	24-48/24-48	3/185	Random differences at different doses and time of follow-up	Moderate	Allocation concealment: unclear; partially double-blinded (38), open-label (32, 36), intention-to-treat analyses: yes (36, 38), not reported (32); attrition bias: yes; funding: government, pharmaceutical (38), not reported (32), foundation (36)
Interferon- α 2b vs. no treatment (33, 38)	16-24/8-24	2/131	RD, 0.31 (0.17 to 0.44)* 0.442/0%	Moderate	Allocation concealment: adequate (33), unclear (38); intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (33), government/pharmaceutical (38)
Lamivudine vs. placebo (60)	96/24	1/136	RD, 0.21 (0.04 to 0.38)*	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: no; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49, 69)	48/24	2/905	RD, 0.13 (0.06 to 0.19)* 0.569/0%	High	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/24	1/542	RD, -0.02 (-0.10 to 0.06)	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49, 69)	48/24	2/905	RD, 0.13 (0.07 to 0.20)* 0.904/0%	High	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical

Pegylated interferon α 2a vs. pegylated interferon- α 2a (125)	24/24	1/194	Random differences at all dose comparisons. No dose response	Low. No dose response association of pegylated interferon- α 2a on ALT normalization at time of follow-up	Allocation concealment: unclear; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/26	1/307	RD, 0.02 (-0.08 to 0.12)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: pharmaceutical
Peginterferon- α 2b vs. interferon- α 2b (93)	24/24	1/230	RD, -0.01 (-0.13 to 0.11)	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
E. Relapse and mutation					
Relapse end of treatment					
Adefovir vs. placebo (74, 86)	48-52/0	2/1055	RD, -0.08 (-0.37 to 0.21) 0.000/99%	Low	Allocation concealment: adequate; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Entecavir vs. lamivudine (45, 47)	52-96/0	2/1347	RD, -0.01 (-0.11 to 0.09) 0/96%	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (31, 73, 82, 87)	24-96/0	4/326	RD, -0.06 (-0.16 to 0.04) 0.063/59%	High	Allocation concealment: adequate (31, 73, 82), unclear (87); open-label, intention-to-treat analyses: yes (31, 73, 87), unclear (82); attrition bias: yes; funding: not reported
Lamivudine (88)	48-60/0	1/348	RD, 0.16 (0.08; to 0.24)*	Low	Allocation concealment: unclear; double-blind intention-to-treat analyses: no; attrition bias: no; funding: not reported
Lamivudine vs. telbivudine (58)	52/0	1/63	RD, 0.11 (-0.06 to 0.29)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes;

Pegylated interferon- α 2b + amivudine vs. lamivudine (78)	60/0	1/100	Random differences for virologic and biochemical outcomes	Low	funding: pharmaceutical Allocation concealment: adequate; open-label, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes
Telbivudine + lamivudine vs. lamivudine (58)	52/0	1/60	RD, -0.04 (-0.23 to 0.16)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Telbivudine + lamivudine vs. telbivudine (58)	52/0	1/85	RD, 0.08 (-0.04 to 0.19)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Relapse at follow-up					
Entecavir vs. lamivudine (44)	52/24	1/709	RD, -0.16 (-0.20 to -0.12)*	Low	Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + corticosteroid vs. interferon- α 2b (38, 51)	24/24	2/141	Random differences for all comparisons	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (51), government, pharmaceutical (38)
Interferon- α 2b + corticosteroid vs. no treatment (38)	24/24	1/87	RD, 0.02 (-0.04 to 0.08)	Low	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: government/pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (59, 83)	52-176/24-192	2/158	Random differences in all but at 96 and 144 wk of follow-up comparisons	Low. One RCT reported a significant decrease in relapse at wk 96 and 144 of follow-up	Allocation concealment: unclear (83), adequate (59); open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: not reported
Interferon- α 2b vs. interferon- α 2b (38)	24/24	1/82	RD, -0.02 (-0.09 to 0.04)	Low. No differences between 5 or 1 MU/d of interferon- α 2b on	Allocation concealment: unclear; partially double-blinded, intention-to-treat analyses: yes; attrition bias: yes;

Interferon- α 2b vs. no treatment (34, 35, 38, 54)	16-96/20-96	4/378	Random differences for all comparisons	relapse at follow-up High	funding: government, pharmaceutical Allocation concealment: unclear (34, 38, 54), adequate (35); open-label, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical (35). government/pharmaceutical (38), not reported (34, 54)
Pegylated interferon- α 2b + lamivudine vs. lamivudine (50)	52-60/24-72	1/100	Random differences for all time of follow-up comparisons (0.00; 0.00) (RD)	Low	Allocation concealment: adequate; open-label, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Mutation end of treatment					
Adefovir + lamivudine vs. lamivudine (71)	52/0	1/95	RD, -0.33 (-0.50 to -0.17)* RD, 0.04 (-0.03 to 0.11)	Low	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: not reported
Adefovir vs. adefovir (42)	114-240/0	1/250	RD, 0.18 (0.08 to 0.27)* RD, 0.12 (0.04 to 0.20)*	Low. Adefovir for 240 vs. 114 wk increased rates of adefovir resistant mutation	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Adefovir vs. placebo (63,86)	48/0	2/879	Random differences for all but 1 amino acid substitution rt221Y	Low. Adefovir dipivoxil vs. placebo increased rates of emerging amino acid substitutions in the HBV-RT domain and rates of rt221Y amino acid substitution but not rt134D; rt219A; rt91I; rt134N; rt54H; rt145M substitutions	Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (31) (59, 73, 80, 87, 89)	24-96/0	6/721	RD, -0.18 (-0.35 to -0.01)* 0/91% RR 0.42 (0.16 to 1.09)*	Moderate	Allocation concealment: unclear (87, 89), adequate (31, 59, 73, 80); open-label (31, 59, 73, 87, 89), double-

0.003/72.2%

blinded (80), intention-to-treat analyses: yes; attrition bias: yes; funding: not reported (59, 73, 87) pharmaceutical/government/other (80), foundations (89)

Interferon- α 2b + lamivudine vs. placebo (80)	52/0	1/118	RD, 0.00 (-0.03 to 0.03)	Low	Allocation concealment: yes; double-blinded until wk 8 (IFN assigned), pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical/government/other
Lamivudine for 60 wk vs. lamivudine for 48 wk (88)	48-60/0	1 /429	RD, 0.06 (0.01 to 0.11)* RD, 0.03 (0.00 to 0.06)*	Low	Allocation concealment: unclear; double-blind intention-to-treat analyses: no; attrition bias: no; funding: not reported
Lamivudine vs. placebo (41, 80)	52-130/0	2/826	RD, 0.43 (0.38 to 0.48)* 0.873/0%	High	Allocation concealment: unclear (41), adequate (80); double-blinded, intention-to-treat analyses: yes; attrition bias: no; funding: pharmaceutical (41), pharmaceutical/government/other (80)
Pegylated interferon- α 2a + lamivudine vs. lamivudine (49)	48/0	1/543	RD, -0.22 (-0.28 to -0.16)*	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + lamivudine vs. pegylated interferon- α 2a (49)	48/0	1/542	RD, 0.03 (0.01 to 0.06)*	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2a + placebo vs. lamivudine (49)	48/0	1/543	RD, -0.25 (-0.31 to -0.20)*	Low	Allocation concealment: unclear; partially double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes; funding: pharmaceutical
Pegylated interferon- α 2b +	60/0	1/100	RD, -0.18 (-0.35 to -	Low	Allocation concealment: adequate;

lamivudine vs. lamivudine (78)			0.01)*			open-label, pathologist-blinded, intention-to-treat analyses: yes (1 dose required); attrition bias: yes
Pegylated interferon- α 2b + lamivudine vs. pegylated interferon- α 2b (90)	52/0	1/307	RD, 0.09 (0.04 to 0.14)*	Low		Allocation concealment: unclear; double-blinded, pathologist-blinded, intention-to-treat analyses: yes (1 dose); attrition bias: yes; funding: pharmaceutical
Follow-up						
Adefovir for 96 vs. 48 wk (64)	96/18	1/140	Random differences in all mutations and duration of treatment	Low. No differences in mutations after adefovir for 96 vs. 48 wk		Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Adefovir vs. placebo (64)	96/18	1/140	Random differences in all mutations and duration of treatment	Low		Allocation concealment: unclear; double-blinded, intention-to-treat analyses: yes; attrition bias: not reported funding: pharmaceutical
Interferon- α 2b + lamivudine vs. interferon- α 2b (79)	24/28	1/144	RD, 0.00 (-0.03 to 0.03)	Low		Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + lamivudine vs. lamivudine (79)	24/28	1/157	RD, -0.23 (-0.32 to -0.14)*	Low		Allocation concealment: adequate; blinded \leq wk 8 pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical
Interferon- α 2b + placebo vs. lamivudine (79)	24/28	1/151	RD, -0.23 (-0.33 to -0.14)*	Low		Allocation concealment: adequate; blinded \leq wk 8, pathologist-blinded, intention-to-treat analyses: yes; attrition bias: yes; funding: pharmaceutical