

Research Article

Virological Changes of Chronic Hepatitis B Patients with Minimally Elevated Levels of Alanine Aminotransferase: A Meta-Analysis and Systematic Review

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Background. Chronic hepatitis B (CHB) patients with normal or minimally increased levels of alanine aminotransferase (ALT) are still at the risk of hepatocellular carcinoma, cirrhotic events, and mortality. However, there is a debate over the initiation of antiviral treatment for these patients. This systematic review and mate-analysis aimed to explore this problem. *Methods*. MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science databases were systematically searched for retrieving relevant studies with risk ratios (RRs) or risk differences (RDs) for virological changes between antivirus-treated and no antivirus-treated CHB patients with ALT levels less than two-fold of the upper limit of normal. Retrieved data ranged from January 1990 to October 2020. *Results*. Of 6783 abstracts screened, 9 studies met the criteria for inclusion in the systematic review and had a low risk of bias. Among studies that were involved in the meta-analyses, it was found that the rates of HBsAg loss (RR = 12.22, 95% confidence interval (CI): 4.28-34.95, P < 0.001), HBsAg seroconversion (RR = 19.90, 95% CI: 2.75-144.09, P = 0.003), and undetectable HBV DNA (RR = 11.89, 95% CI: 2.44-57.89, P = 0.002) were both higher in the antiviral treatment group compared with placebo or no treatment group. Subgroup analysis suggested that patients who received interferon (IFN)-based therapy were more inclined to achieve HBsAg loss (P = 0.010), HBsAg seroconversion (P = 0.020), and HBeAg loss (P = 0.002). *Conclusion*. From a sizable population, it was revealed that CHB patients with normal or minimally increased levels of ALT could benefit from the antiviral therapy, especially those who received IFN-based treatment.

1. Introduction

Chronic hepatitis B (CHB) virus infection remains a worldwide health burden, afflicting approximately 257 million people [1]. Up to 40% of untreated CHB patients progress to cirrhosis, and these patients are at the risk of developing decompensated cirrhosis and hepatocellular carcinoma (HCC) [2, 3]. Studies have shown that a significant proportion (40%) of CHB patients have normal or minimally increased levels of alanine aminotransferase (ALT), while they may still be at the risk of HCC, cirrhotic events, and mortality in patients with CHB-related cirrhosis [4–7]. Hence, timely treatment can delay disease progression and improve the prognosis.

At present, it is still an area of ongoing controversy on whether CHB patients with mildly raised ALT levels (more than one-fold, while less than two-fold of the upper limit of normal (ULN)) should be treated. The American Association for the Study of Liver Diseases (AASLD, updated in 2018) [8] and the Asian-Pacific guideline (updated in 2015) [9] concluded that the threshold of the ALT level for initiating antiviral therapy is no less than two-fold of the ULN. Conversely, the European Association for the Study of the Liver (EASL, updated in 2017) recommended treatment for patients with a serum ALT concentration of more than the ULN and hepatitis B virus (HBV) DNA >2000 IU/L [1]. In the current Chinese guideline, patients with the ALT level more than the ULN and detectable HBV DNA should receive treatment [10]. Therefore, the agreement on the initiation of antiviral therapy was not reached worldwide. In a retrospective cohort study with involvement of 3624 untreated CHB patients that was conducted in South Korea, it was revealed that patients whose conditions did not meet therapeutic indications for EASL, AASLD, and other authoritative guidelines still had a cumulative 5-year HCC incidence of 2.1–3.2% [11]. At present, the notion that whether this group of CHB patients should be treated remains controversial and whether they can benefit from the antivirus therapy is still undiscovered.

Hepatitis B surface antigen (HBsAg) loss with or without HBsAg seroconversion is regarded as a functional cure and the ultimate endpoint for CHB therapy [1, 8, 9]. For patients who achieved partial cure, HBV DNA is undetectable in their serum [12]. The present study aimed to identify the proportion of HBsAg loss with or without the seroconversion to hepatitis B surface antibody (HBsAb) in CHB patients with only normal or minimally elevated ALT levels. The secondary objective was to identify the proportions of undetectable HBV DNA, hepatitis B e antigen (HBeAg) loss, and HBeAg seroconversion.

2. Results

2.1. Search Results. Totally, 6783 articles were retrieved through searching in the four databases mentioned below, of which 512 articles were eliminated because of duplicate publication. After screening of titles and abstracts, the full texts of 22 studies were downloaded to assess their eligibility. Finally, 7 articles [13–20] and 2 abstracts [21] which met the eligibility criteria are included in this meta-analysis (Figure 1). The details of the study selection are shown in Table 1. During the analysis, one of the abstracts was published and our collected data were renewed subsequently [18].

2.2. Study and Patients' Characteristics. In the primary analysis, there were a total of 898 patients in the 9 included studies. Most of the included studies were randomized controlled trials (RCTs), except for 2 studies [13, 15], which did not assign patients randomly. In addition to one study published in 2002 [20], the year of publication of the other studies was between 2014 and 2021. Of note, patients were treated exclusively with nucleotide analogs (tenofovir) in Hsu et al. [18], nucleoside analogs (entecavir) in Tseng et al. [17], nucleotide analogs plus nucleoside analogs (tenofovir and emtricitabine) in Chan et al. [16], and IFN combined with NAs in 5 studies. In 2 studies [19, 20], two or more different regimens were used in the experimental group, whereas only one study [20] reported the outcome of each regimen. In 3 studies [13, 14, 21], patients in the experimental group were given IFN at the beginning, and in 2 studies [13, 14], they additionally received NAs based on their conditions.

It was found that 2 studies [17, 18] enrolled both HBeAgpositive and HBeAg-negative patients, regardless of their HBeAg status, in which enrolled subjects were grouped in one research [17]. However, the remaining 7 studies involved either in HBeAg-negative or HBeAg-positive patients. As for 4 studies that enrolled HBeAg-positive patients, one study [20] reported HBV DNA level in pg/mL, and the others [14–16] reported in IU/mL and enrolled patients with high viral load (>20000 IU/mL). Furthermore, regarding 3 studies [13, 19, 21] that enrolled only HBeAgnegative individuals, the level of HBV DNA ≤20000 IU/ml (all reported in IU/mL unit) was covered in the inclusion criterion.

Most of the studies mainly enrolled male adult patients. Nevertheless, 2 HBV-infected children with immunetolerant characteristic and HBV postpartum women were enrolled, respectively. The majority of patients were Asian except for those in 3 studies [16, 19, 20]. Besides, 2 trials measured the outcomes at 192 weeks [16] and 144 weeks [18], and 7 studies performed measurement within 96 weeks.

2.3. Results of Meta-Analysis. Of the 9 studies, 6, 5, 4, 5, and 6 studies reported the outcomes of HBsAg loss, HBsAg seroconversion, HBeAg loss, HBeAg seroconversion, and undetectable HBV DNA, respectively. Stratified by the treatment strategy, treatment duration, or baseline parameters, subgroup analysis was performed to assess the association between antiviral therapy and each endpoint in the meta-analysis using a random-effects model.

2.4. HBsAgLoss. Compared with the control group, antiviral therapy was associated with a significantly higher incidence of HBsAg loss (RR = 12.22, 95% CI: 4.28–34.95, P < 0.001) (Figure 2(a)). Then, it was attempted to explore how the characteristics of viral replication could affect HBsAg loss, and patients were stratified by the status of HBeAg and HBV DNA. Both subjects with HBeAg-positive and HBV DNA >20000 IU/mL (RR = 15.11, 95% CI: 2.08–109.69, P = 0.007) and subjects with HBeAg-negative and HBV DNA ≤20000 IU/mL (RR = 9.93, 95% CI: 2.84–34.67, *P* < 0.001) exhibited a superior effect of HBsAg loss than that of the control one. The difference between the two subgroups (subjects with HBeAg-positive and HBV DNA>20000 IU/ mL subgroup and subjects with HBeAg-negative and HBV DNA ≤20000 IU/mL subgroup) was also not significant (P = 0.730) (Figure 2(b)). Besides, in studies with IFN treatment, antiviral therapy was associated with a significantly higher incidence of HBsAg loss (RR = 11.19, 95% CI: 3.89–32.22, P < 0.001). In addition, there was no event of HBsAg loss in the interferon-free studies, regardless of antiviral or viral event (Figure 2(c)). When the outcomes were calculated as RD, there was a remarkable difference in HBsAg loss between IFN-based subgroup and IFN-free subgroup (P = 0.010) (Supplementary Figure 1). These results indicated that IFN therapy had a higher incidence of HBsAg loss in CHB patients. Furthermore, stratified by treatment strategy, both combination therapy (RR = 9.83, 95% CI: 1.31-74.03, P = 0.030) and monotherapy



FIGURE 1: Flowchart showing selection of articles for meta-analysis.

(RR = 8.00, 95% CI: 1.11–57.49, P = 0.040) exhibited a superior effect of HBsAg loss than that of the control one. However, the difference between the subgroups (monotherapy subgroup and combination therapy subgroup) was not significant (P = 0.890) (Figure 2(d)). In conclusion, patients with antiviral treatment were inclined to have the clearance of HBsAg.

2.5. HBsAg Seroconversion. Compared with nonantiviral therapy, antiviral therapy was associated with a significantly higher incidence of HBsAg seroconversion (RR = 19.90, 95% CI: 2.75–144.09, P = 0.003) (Figure 3(a)). Among 5 studies that reported the events of HBsAg seroconversion, all events happened in the combination group. In studies with IFNbased treatment, antiviral therapy was associated with a significantly higher incidence of HBsAg seroconversion (RR = 15.75, 95% CI: 2.19–113.47, P = 0.006). In contrast, in studies that adopted IFN-free regimen, no event of HBsAg seroconversion occurred (Figure 3(b)). When the outcomes were calculated as RD, there was a significant difference between IFN-based subgroup and IFN-free subgroup (P = 0.020) (Supplementary Figure 2). Collectively, patients with antiviral therapy, especially those undergoing IFN treatment, were more inclined to have HBsAg seroconversion.

2.6. HBeAg Loss. Compared with nonantiviral treatment, antiviral therapy was associated with no significant difference in the rate of HBeAg loss (RR = 1.68, 95% CI: 0.14–19.67, P = 0.680; with a noticeable heterogeneity $I^2 = 75\%$) (Figure 4(a)). Therefore, sensitivity analysis was performed to find the source of heterogeneity. The results showed that with the removal of Lu's study (2014), the heterogeneity could reduce to a degree where it was not

significant (Supplementary Figure 3). In studies that involved IFN-based treatment, antiviral therapy was associated with a significantly higher incidence of HBeAg loss (RR = 23.86, 95% CI: 3.03 - 187.80, P = 0.003). In contrast, in studies that adopted IFN-free regimen, there were no significant difference between the two groups in HBeAg loss (RR = 0.47, 95% CI: 0.12-1.81, P = 0.280). Besides, the difference between the subgroups (IFN-based subgroup and IFN-free subgroup) was statistically significant (P = 0.002) (Figure 4(b)). Both combination therapy (RR = 8.66, 95% CI: 0.34-222.33, P = 0.190; with a noticeable heterogeneity $I^2 = 79\%$) and monotherapy (RR = 0.80, 95% CI: 0.17-3.86, P = 0.780; with a noticeable heterogeneity $I^2 = 60\%$) exhibited the same effect of HBsAg loss than that of the control one. In addition, the difference between the two subgroups (monotherapy subgroup and combination therapy subgroup) was not significant (P = 0.200) (Figure 4(c)). To further investigate the association between therapy duration and HBeAg loss, subgroup analysis was conducted in short-term (≤96 weeks) and long-term (>96 weeks). Although a significant difference was found between the two subgroups (P = 0.030), neither the long duration subgroup nor the other subgroup showed a significant difference between the antiviral therapy group and control group (Figure 4(d)). Collectively, only patients who underwent IFN-based antiviral therapy were more inclined to have HBeAg loss, and patients may not benefit from a long-term treatment.

2.7. *HBeAg Seroconversion*. Compared with nonantiviral treatment, antiviral therapy was associated with no significant difference in the rate of HBeAg seroconversion (RR = 1.66, 95% CI: 0.32–8.60, P = 0.540; with a noticeable heterogeneity $I^2 = 53\%$) (Figure 5(a)). In studies that adopted IFN-based treatment, antiviral therapy was associated with

SON	score		ſ	`			6	,	6	7		7		7		~	9		ע	elbivudine;
Study timenoints	weeks		ſ	70			52		192	96		72		96		96	48		144	ine; LdT, t
ALT analveis	method		div.	NK			NR	1	NK	NR		NR		NR		XX	NR		NK	, emtricitab
Samules	oampres			Serum			Serum	,	Serum	Serum		Serum		Serum	,	Serum	Serum		Serum	arate; FTC
Baseline	HBV DNA	Median: 98 (pg/mL, LLOD-2,264)	Median: 111 (pg/mL, LLOD-1,322)	Median: 94 (pg/mL, LLOD-786)	Median: 79 (pg/mL, LLOD-1,150)	Mean: 5.95±1.3 log ₁₀ conies/ml	Mean: 6.31 ± 1.42 log ₁₀ copies/ml	Mean: 8.42 (0.402) log ₁₀ IU/ mL	Mean: 8.40 (0.395) log ₁₀ IU/ mL	$>5 \times 10^6$ IU/ml	Mean: 2.65 (1.23) log ₁₀ IU/ mL	Mean: 2.79 (1.03) log ₁₀ IU/ mL	Mean: 2.79 (1.04) \log_{10} IU/ mL	<2000 IU/mL	Median: $9.95 \times 10^7 \mathrm{IU/mL}$	Median: 1.72×10^{8} IU/mL	≤20000 IU/ml	Mean: 5.26 (4.30–6.23) log _{io} IU/mL	Mean: 5.32 (4.41–6.41) log ₁₀ IU/mL	tenofovir disoproxil fum
Baseline	ALT			≤I X ULN		Mean: 0.6 ± 0.2 ULN	Mean: 0.6 ± 0.2 ULN	Mean: 26.9 (14.05) U/L	Mean: 26.2 (9.88) U/L	≤1 × ULN	Median: 27 (21–42) 11/1		Median: 30 (21–47) U/L	28.3 ± 9.0 IU/L 25.4 ± 8.4 IU/L	Median: 45 (28) U/ L		≤1 × ULN	Mean: 53 (45–63) U/L	Mean: 52 (46–66) U/L	V, entecavir; TDF,
HBeAg	pusitive (%)		100	100		31.8	42.9	98.4	100	100		0		0	100	100	0	16	26	dine; ET
Age (vears)	uge (jears)	Median: 34 (15–73)	Median: 32 (16–70)	Median: 34 (15–76)	Median: 35 (15–67)	Mean: 45±10	Mean: 42±12	Mean: 33 (9.5)	Mean: 33 (11.2)	Mean: 28.6	Mean: 44 (12)	Mean: 43 (12)	Mean: 41 (10)	38.8 ± 10.0 39.8 ± 10.6	Median: 7 (8)	Median: 8 (8)	21-75	Mean: 45 (39–54)	Mean: 43 (37–51)	; LAM, lamivu
Sex (male	(%)	78	81	71	80	59	55	48.4	50	0 0	61	47	60	66 65	65	57	NR	78	80	erventions
N included	in analysis	55	2	4	25	22	20	64	62	30 38	46	45	43	94 40	46	23	60 30	74	75	dies of int
Sample	size	55	2	4	25	22	20	64	62	30 38	46	45	43	94 40	46	23	60 30	62	81	nized stu
Interventions		LAM	IFN	LAM + IFN	Placebo	ETV	Placebo	TDF + placebo	TDF+FTC	LdT + CPIA LdT + placebo	PEG-IFN + ADV	PEG-IFN + TDF	No treatment	PEG-IFN/+ ADV No treatment	IFN/+ LAM	No treatment	PEG-IFN No treatment	TDF	Placebo	NRSI, nonrandor
Study	design		Е С	KU			RCT		KCI	NRSI		RCT		NRSI		RCT	RCT		KCI	d trial;
Geographic	locale		المسابية سنباسه	Multinational			Taiwan		Multinational	China		Netherlands		China		China	Singapore		laiwan	ed controlled
Vear	тсаг			7 7007			2014		2014 1	2014		2017		2017		2018	2019		2021	indomiza
First	authors		11: ת	Fernilo			Tseng	;	Chan	Lu		De Niet		Cao	i	Zhu	Lim		Hsu	RCT, ra

TABLE 1: Characteristics of included studies and subjects.

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Study or SubgroupEventsTotalEventsTotal(%)M-H, Fixed, 95% CIM-H, Fixed, 95% CICao 2017429414031.117.87 [2.55, 125.41]Image: constraint of the second	
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Zhu 2018104602314.710.72 [0.66, 175.30]Total (95% CI)383238100.012.22 [4.28, 34.95]Total events802Heterogeneity: $Chi^2 = 0.98$, $df = 4$ (P = 0.91); $I^2 = 0\%$ 238100.012.22 [4.28, 34.95]Test for overall effect: Z = 4.67 (P < 0.00001)	—
Total (95% CI) 383 238 100.0 $12.22 [4.28, 34.95]$ Total events 80 2 Heterogeneity: Chi ² = 0.98, df = 4 (P = 0.91); I ² = 0% 0.005 0.1 1 10 Test for overall effect: Z = 4.67 (P < 0.00001)	
Total events 80 2 Heterogeneity: $Chi^2 = 0.98$, $df = 4$ (P = 0.91); $I^2 = 0\%$ 0.005 0.1 1 10 10 Test for overall effect: Z = 4.67 (P < 0.00001)	
Heterogeneity: $Chi^2 = 0.98$, $df = 4$ (P = 0.91); $I^2 = 0\%$	
Test for overall effect: Z = 4.67 (P < 0.00001)	+-
(a) Favours Favours control antivirus	00
(a)	
antivirus therapy no treatment or placebo _{Weight} Risk Ratio Risk Ratio	
Study or Subgroup Events Total Events Total (%) M-H, Random, 95% CI M-H, Random, 95% CI	
1.2.1 HbeAg- HBV DNA≤20000 IU/mL	
Cao 2017 42 94 1 40 29.5 17.87 [2.55, 125.41]	
de Niet 2017 4 91 0 43 13.3 4.30 [0.24, 78.19]	
Lim 2019 16 60 1 30 28.8 8.00 [1.11, 57.4]	
Subtotal (95% CI) 245 113 71.5 9.93 [2.84, 34.67]	
Total events 62 2	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, $df = 2$ (P = 0.68); $I^2 = 0\%$ Test for overall effect: Z = 3.60 (P = 0.0003)	
1.2.2 HbeAg+ HBV DNA>20000 IU/mL	
Chan 2014 0 62 0 64 Not estimable	
Lu 2014 8 30 0 38 14.1 21.39 [1.28, 356.27]	—
Zhu 2018 10 46 0 23 14.3 10.72 [0.66, 175.30]	
Subtotal (95% CI) 138 125 28.5 15.11 [2.08, 109.69]	
Total events 18 0	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, $df = 1$ (P = 0.73); $I^2 = 0\%$	
Test for overall effect: $Z = 2.68 (P = 0.0007)$	
Total (95% CI) 383 238 100.0 11.19 [3.89, 32.22]	
Total events 80 2	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.98$, $df = 4$ (P = 0.91); $I^2 = 0\%$	+-
Test for overall effect: $Z = 4.48 (P < 0.00001)$ $0.005 0.1 1 10$	00
Test for subgroup differences: $Chi^2 = 0.12$, $df = 1$ (P = 0.73); $I^2 = 0\%$ Favours controlFavours antivirus	

(b) FIGURE 2: Continued.

	antivirus th	nerapy	no treatment or j	placebo	Weight	Risk Ratio	Risk R	atio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% Cl	I M-H, Rando	m, 95% CI	
1.3.1 with IFN									
Cao 2017	42	94	1	40	29.5	17.87 [2.55, 125.41]			→
de Niet 2017	4	91	0	43	13.3	4.30 [0.24, 78.19]		-	
Lim 2019	16	60	1	30	28.8	8.00 [1.11, 57.49]	-		
Lu 2014	8	30	0	38	14.1	21.39 [1.28, 356.27]		-	→
Zhu 2018	10	46	0	23	14.3	10.72 [0.66, 175.30]	+	-	→
Subtotal (95% CI)		321		174	100.0	11.19 [3.89, 32.22]			
Total events	80		2						
Heterogeneity: Tau ²	$= 0.00; Chi^2 =$	= 0.98, df	$= 4 (P = 0.91); I^2$	= 0%					
Test for overall effect	: Z = 4.48 (P	< 0.0000)						
1.3.2 without IFN									
Chan 2014	0	62	0	64		Not estimable			
Subtotal (95% CI)		62		64		Not estimable			
Total events	0		0						
Heterogeneity: Not a	pplicable								
Test for overall effect	: Not applica	ble							
Total (95% CI)		383		238	100.0	11 19 [3 89 32 22]			
Total events	80	000	2	200	10010	11117 [0103,02122]		-	
Heterogeneity: Tau ²	$= 0.00; Chi^2 =$	= 0.98, df	$= 4 (P = 0.91); I^2$	= 0%		F			
Test for overall effect	: Z = 4.48 (P	< 0.0000)			0.0	1 0.1 1	10	100
Test for subgroup dif	ferences: No	t applicat	le				Farroure	Favouro	
U I							control	antivirus	
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				(c)			D: 1 D		
	antivirus ti	herapy	no treatment or	placebo	Weight	Risk Ratio	Risk R	atio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% CI	M-H, Rando	m, 95% CI	
1.4.1 monotherapy									
Chan 2014				64					
Lim 2019	0	62	0	64		Not estimable		_	
	0 16	62 60	0 1	64 30	51.2	Not estimable 8.00 [1.11, 57.49]	-		
Subtotal (95% CI)	0 16	62 60 122	0 1	64 30 94	51.2 51.2	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49]	-		
Subtotal (95% CI) Total events	0 16 16	62 60 122	0 1 1	64 30 94	51.2 51.2	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49]	-		
Subtotal (95% CI) Total events Heterogeneity: Not a	0 16 16 pplicable	62 60 122	0 1 1	64 30 94	51.2 51.2	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49]	-		
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect	0 16 pplicable : Z = 2.07 (P	$62 \\ 60 \\ 122 = 0.04)$	0 1 1	64 30 94	51.2 51.2	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49]	-		
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs	0 16 pplicable : Z = 2.07 (P	$62 \\ 60 \\ 122 = 0.04)$	0 1 1	64 30 94	51.2 51.2	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49]	-	•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017	0 16 pplicable : Z = 2.07 (P 4	62 60 122 = 0.04) 91	0 1 1 0	64 30 94 43	51.2 51.2 23.7	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19]	-	•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014	0 16 pplicable : Z = 2.07 (P 4 8	$62 \\ 60 \\ 122 = 0.04)$ $91 \\ 30$	0 1 1 0 0	64 30 94 43 38	51.2 51.2 23.7 25.2	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27]		•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI)	0 16 pplicable : Z = 2.07 (P 4 8	62 60 122 = 0.04) 91 30 121	0 1 1 0 0	64 30 94 43 38 81	51.2 51.2 23.7 25.2 48.8	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03]		•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events	0 16 pplicable : Z = 2.07 (P 4 8	62 60 122 = 0.04) 91 30 121	0 1 1 0 0 0	64 30 94 43 38 81	51.2 51.2 23.7 25.2 48.8	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03]		•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ²	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² :	62 60 122 = 0.04) 91 30 121 = 0.62, df	$\begin{array}{c} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ (P = 0.43); I^2 \end{array}$		51.2 51.2 23.7 25.2 48.8	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03]		•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03)	$ \begin{array}{c} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ P = 0.43); I^{2} \end{array} $		51.2 51.2 23.7 25.2 48.8	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03]	-	•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI)	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03) 243	$ \begin{array}{c} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ P = 0.43); I^{2} \end{array} $		51.2 51.2 23.7 25.2 48.8	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03] 8.85 [2.16, 36.27]		•	_
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI) Total events	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P 28	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03) 243	$ \begin{array}{c} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ = 1 (P = 0.43); I^{2} \\ 1 \\ \end{array} $		51.2 51.2 23.7 25.2 48.8	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03] 8.85 [2.16, 36.27]	-	•	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ²	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P 28 = 0.00; Chi ²	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03) 243 = 0.63, df	$\begin{array}{c} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\$		51.2 51.2 23.7 25.2 48.8 100.0	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03] 8.85 [2.16, 36.27]			-
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² Test for overall effect	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P 28 = 0.00; Chi ² : Z = 3.03 (P	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03) 243 = 0.63, df = 0.002)	$0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ $		 51.2 51.2 23.7 25.2 48.8 100.0 	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03] 8.85 [2.16, 36.27]			— +- 00
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Test for overall effect	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P 28 = 0.00; Chi ² : Z = 3.03 (P ferences: Chi	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03) 243 = 0.63, df = 0.002) i2 = 0.02, i2 = 0.02,	$\begin{array}{c} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0$		51.2 51.2 23.7 25.2 48.8 100.0	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03] 8.85 [2.16, 36.27] - 0.		10 20 Favours	 +000
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 1.4.1 IFN plus NAs de Niet 2017 Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Test for subgroup dif	0 16 16 pplicable : Z = 2.07 (P 4 8 12 = 0.00; Chi ² : Z = 2.22 (P 28 = 0.00; Chi ² : Z = 3.03 (P ferences: Chi	62 60 122 = 0.04) 91 30 121 = 0.62, df = 0.03) 243 = 0.63, df = 0.002) i2 = 0.02,	$0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ $		51.2 51.2 23.7 25.2 48.8 100.0	Not estimable 8.00 [1.11, 57.49] 8.00 [1.11, 57.49] 4.30 [0.24, 78.19] 21.39 [1.28, 356.27] 9.83 [1.31, 74.03] 8.85 [2.16, 36.27] - 0.1		10 20 Favours antivirus	 +000

(d)

FIGURE 2: The outcomes of HBsAg loss. (a) Pooled risk ratio for HBsAg loss between the antiviral therapy group and control group. (b) Subgroup analysis stratified by patients' baseline parameters (the status of HBeAg and the level of HBV DNA). (c) Subgroup analysis stratified by therapeutic regimen with or without IFN. (d) Subgroup analysis stratified by monotherapy and combined therapy (IFN plus NAs). NAs, nucleos(t)ide analogs; IFN, interferon; CI, confidence interval; monotherapy exclusively included NAs or IFN. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate.

	antivirus t	herapy	no treatment or	placebo	Weight	Risk Ratio	Risk I	Ratio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Fixed, 95% CI	M-H, Fixe	d, 95% CI	
Cao 2017	36	94	0	40	51.3	31.51 [1.98, 501.07]			
Chan 2014	0	62	0	64		Not estimable			
Hsu 2021	0	74	0	75		Not estimable			
Tseng 2014	0	21	0	18		Not estimable			
Zhu 2018	7	46	0	23	48.7	7.66 [0.46, 128.52]			
Total (95% CI)		297		220	100.0	19.90 [2.75, 144.09]			
Total events	43		0						
Heterogeneity: Chi2 :	= 0.55, df = 1	(P = 0.46)	5); $I^2 = 0\%$			-			
Test for overall effect	t: Z = 2.96 (P	= 0.003)				0.002	0.1 1	10	500
							Favours control	Favours antivirus	
				(a)					
	antivirus tł	herapy	no treatment or 1	olacebo	147 - 1 - 1 - 4	Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% CI	M-H, Rand	lom, 95% CI	
1.6.1 with IFN									
Cao 2017	36	94	0	40	51.0	31.51 [1.98, 501.07]			\rightarrow
Zhu 2018	7	46	0	23	49.0	7.66 [0.46, 128.52]			→
Subtotal (95% CI)		140		63	100.0	15.75 [2.19, 113.47			
Total events	43		0			•			
Heterogeneity: Tau ² :	= 0.00; Chi ² =	= 0.55, df	$= 1 (P = 0.46); I^2$	= 0%					
Test for overall effect	: Z = 2.74 (P	= 0.006)							
1.6.2 wthout IFN									
Chan 2014	0	62	0	64		Not estimable			
Hsu 2021	0	74	0	75		Not estimable			
Tseng 2014	0	21	0	18		Not estimable			
Subtotal (95% CI)		157		157		Not estimable			
Total events	0		0						
Heterogeneity: Not a	pplicable								
Test for overall effect	: Not applica	ble							
Total (95% CI)		297		220	100.0	15.75 [2.19, 113.47]			
Total events	43	277	0	220	100.0	10.70 [2.17, 110.17]			
Heterogeneity: Tau ² :	= 0.00; Chi ² :	= 0.55, df	$I = 1 (P = 0.46): I^2$	= 0%		H		 	
Test for overall effect	: Z = 2.74 (P	= 0.006)	()) -			0.01	0.1	1 10	100

Test for subgroup differences: Not applicable

(b)

FIGURE 3: The outcomes of HBsAg seroconversion. (a) Pooled risk ratio for HBsAg seroconversion between the antiviral therapy group and control group. (b) Subgroup analysis stratified by therapeutic regimen with or without IFN. IFN, interferon; CI, confidence interval. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate.

a significantly higher incidence of HBeAg seroconversion (RR = 8.79, 95% CI: 1.68–45.95, P = 0.010). In contrast, in studies that adopted interferon-free regimen, there was no significant difference in HBeAg seroconversion between the two groups (RR = 0.90, 95% CI: 0.15–5.38, P = 0.910). Subgroup analysis showed no significant difference between IFN-based subgroup and IFN-free subgroup (P = 0.070) (Figure 5(b)). Both combination therapy (RR = 2.75, 95% CI: 0.68-11.00, P = 0.150) and monotherapy (RR = 0.71, 95% CI: 0.17–2.95, P = 0.630) exhibited the same effect of HBsAg loss compared with the control one. Moreover, the difference between the two subgroups (monotherapy subgroup and combination treatment subgroup) was not significant (P = 0.180) (Figure 5(c)). In addition, stratified by treatment duration, subgroup analysis showed that there was a significant difference between the two subgroups (long-term subgroup and short-term subgroup) (P = 0.006). Only in the short-term subgroup, antiviral therapy exhibited a superior effect of HBeAg seroconversion than that of the control one (RR = 6.34, 95% CI: 1.51–26.52, P = 0.010) (Figure 5(d)). Generally, only patients who underwent IFN-based antiviral therapy were more inclined to have HBeAg seroconversion. Besides, the extension of the treatment duration did not promote the occurrence of HBeAg seroconversion.

Favours

control

Favours

antivirus

2.8. Undetectable HBV DNA. Compared with nonantiviral treatment, antiviral therapy was associated with a significantly higher incidence of undetectable HBV DNA (RR = 11.89, 95% CI: 2.44–57.89, P = 0.002; with a noticeable heterogeneity $I^2 = 92\%$) (Figure 6(a)). Sensitivity analysis with removing Chan's study (2014) for

0, 1, 0, 1				T (1	Weight		CT	MILD 1		
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95%	CI	M-H, Rand	lom, 95% CI	
Chan 2014	1	62	4	63	26.6	0.25 [0.03, 2.21]				
Hsu 2021	1	12	4	19	27.1	0.40 [0.05, 3.13]				
Lu 2014	17	30	0	38	23.5	44.03 [2.76, 703.60]			
Perrillo 2002	3	61	0	25	22.7	2.94 [0.16,54.84]				
Total (95% CI)		165		145	100.0	1.68 [0.14, 19.67]				
Total events	22		8	_				1		
Heterogeneity: $Tau^2 =$	4.70; $Chi^2 = 1$	12.13, df =	= 3 (P = 0.007); I	$^{2} = 75\%$			0.01	0.1	1 10	10
Test for overall effect: 2	Z = 0.41 (P =	0.68)					0.01	0.1	1 10	10
								Favours	Favours	
								control	antiviru	S
				(a)						
	antivirus	therapy	no treatment of	r placebo	Weight	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95%	CI	M-H, Rand	lom, 95% CI	
1.8.1 with IFN					. ,					
Lu 2014	17	30	0	38	19.2	44 03 [2,76, 703,60	1			
Perrillo with IFN 2002	1	6	0	25	17.8	11.14 [0.51,244.86	í	-		
Subtotal (95% CI)		36		63	37.0	23.86 [3.03, 187.80	j			
Total events	18		0							
Heterogeneity: $Tau^2 =$ Test for overall effect: 2	$0.00; Chi^2 = 0$ Z = 3.01 (P =	0.52, df = 0.003)	$1 (P = 0.47); I^2 =$	= 75%						
1.8.2 without IFN										
Chan 2014	1	62	4	63	22.2	0.25 [0.03, 2.21]			+	
Hsu 2021	1	12	4	19	22.7	0.40 [0.05, 3.13]			<u>+</u>	
Perrillo without IFN 20	002 2	55	0	25	18.2	2.32 [0.12, 46.65]				
Subtotal (95% CI)		129	0	107	63.0	0.47 [0.12, 1.81]				
Total events	4	1 42 16	8	00/						
Test for overall effect: 2	$0.00; Chi^2 = 1$ Z = 1.09 (P =	1.43, df = 1 0.28)	2 (P = 0.49); 1 ² =	= 0%						
Total (95% CI)		165		170	100.0	2.21 [0.28, 17.67]				
Total events	22		8							
Heterogeneity: $Tau^2 =$	$3.84; Chi^2 = 1$	13.10, df =	$= 4 (P = 0.01); I^2$	= 69%			0.00)5 0 1	1 10	200
Test for overall effect: 2	L = 0.75 (P = 0.75)	0.45)	1 (D 0.002).	12 00 70/			0.00	0.1	1 10	200
l est for subgroup diffe	rences: Chi ²	= 9./5, df	= 1 (P = 0.002);	$1^2 = 89.7\%$				Favours	Favours	
								control	antivirus	
	antivirus	therapy	no treatment o	(b) r placebo		Dick Datio		Dick	Patio	
Charles an Carle announ	E	Tetel	E	T placebo	Weight	M II Dandama 0500	CI	MILD	1 0.50/ CI	
Study or Subgroup	Events	1 otal	Events	Total	(70)	M-H, Random, 95%	CI	M-H, Kano	10m, 95% CI	
1.9.1 monotherapy		(2)		(2)	140					
Chan 2014	1	62	4	63	16.9	0.25 [0.03, 2.21]			<u> </u>	
Perrillo monothrapy 20	1002 24	201	4	84	27.0	251[0.90, 7.01]			⊢ ∎−−	
Subtotal (95% CI)	002 21	275	1	166	61.5	0.80 [0.17, 3.86]				
Total events	26		12							
Heterogeneity: Tau ² = Test for overall effect: Z	1.16; $Chi^2 = 5$ Z = 0.27 (P =	5.03, df = 1 0.78)	2 (P = 0.08); I^2 =	= 60%						
191 JEN plue NAe										
Lu 2014	17	30	0	38	12.9	44.03 [2.76, 703.6()]			
Perrillo plus 2002	7	57	4	84	25.6	2.58 [0.79, 8.41]	.1			
Subtotal (95% CI)		87		122	38.5	8.66 [0.34, 222.33]			
Total events	24		4							
Test for overall effect: 2	$4.42; Chi^2 = 4$ Z = 1.30 (P =	4.74, df = 0.19)	$1 (P = 0.03); I^2 =$	= 79%						
Total (95% CI)		362		288	100.0	1.79 [0.50, 6.45]				
Total events	50		16							
Heterogeneity: Tau ² =	1.30; Chi ² = 1	11.82, df =	$= 4 (P = 0.02); I^2$	= 66%			+			
Test for overall effect: 2	Z = 0.89 (P =	0.37)		2			0.005	0.1	1 10	200
Test for subgroup diffe	erences: Chi ²	= 1.67, df	= 1 (P = 0.20); I	$^{2} = 40.2\%$				Favours	Favours	
								control	antivirus	S

8

(c) FIGURE 4: Continued.

	antivirus th	nerapy	no treatment or pla	icebo	Weight	Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% CI	M-H, Rando	om, 95% CI	
1.10.1 Long duration:	>96 weeks								
Chan 2014	1	62	4	63	26.6	0.24 [0.03, 2.23]		_	
Hsu 2021	1	12	4	19	26.2	0.34 [0.03, 3.49]			
Subtotal (95% CI)		74		82	52.8	0.28 [0.06, 1.42]		-	
Total events	2		8						
Heterogeneity: Tau ²	= 0.00; Chi ² =	= 0.04, di	$f = 1 (P = 0.83); I^2 = 0$	0%					
Test for overall effects	: Z = 1.53 (P	= 0.13)							
1.10.2 Short duration	≤96 weeks								
Lu 2014	17	30	0	38	23.9	99.81 [5.61, 1775.77]			
Perrillo 2002	3	61	0	25	23.4	3.05 [0.15, 61.25]		-	
Subtotal (95% CI)	U	91	Ū	63	47.2	17.91 [0.56, 570.63]			
Total events	20		0						
Heterogeneity: Tau ²	= 3.99; Chi ² =	= 2.77, di	$f = 1 (P = 0.10); I^2 = 0$	64%					
Test for overall effect	: Z = 1.63 (P	= 0.10)							
Total (95% CI)		165		145	100.0	2.01 [0.12, 32.78]			
Total events	22		8						
Heterogeneity: Tau ² =	= 6.33; Chi ² =	= 14.06, 0	$df = 3 (P = 0.003); I^2$	= 79%		H			
Test for overall effect:	: Z = 0.49 (P	= 0.62)				0.01	0.1 1	10	100
Test for subgroup dif	ferences: Chi	i ² = 4.52,	$df = 1 (P = 0.03); I^2$	= 77.9%	,		Favours	Favours	
							control	antivirus	
				(d)					

FIGURE 4: The outcomes of HBeAg loss. (a) Pooled risk ratio for HBeAg loss between the antiviral therapy group and control group. (b) Subgroup analysis stratified by therapeutic regimen with or without IFN. (c) Subgroup analysis stratified by monotherapy and combined therapy (IFN plus NAs). (d) Subgroup analysis stratified by therapy duration with threshold of 96 weeks. NAs, nucleos(t)ide analogs; IFN, interferon; CI, confidence interval; monotherapy group exclusively included NAs or IFN. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate.

	antivirus th	nerapy	no treatment or	placebo	Weight	Risk Ratio		R	isk Ra	atio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% C	I	M-H, Ra	andor	n, 95% C	
Chan 2014	0	62	3	63	17.2	0.15 [0.01, 2.75]		-		—	
Hsu 2021	1	12	4	19	23.8	0.40 [0.05, 3.13]				_	
Perrillo 2002	2	58	0	25	16.8	2.20 [0.11, 44.31]					-
Tseng 2014	2	7	0	18	17.3	11.88 [0.64, 220.58]			+		\rightarrow
Zhu 2018	15	46	1	23	24.8	7.50 [1.05, 53.32]			_		_
Total (95% CI)		185		148	100.0	1.66 [0.32, 8.60]					
Total events	20		8								
Heterogeneity: Tau ²	= 1.84; Chi ² =	= 8.54, d	$f = 4 (P = 0.07); I^2$	= 53%			+				
Test for overall effect	:: Z = 0.61 (P	= 0.54)					0.01	0.1	1	10	100
								Favours control		Favours antiviru	s S

(a) FIGURE 5: Continued.

	antivirus tł	nerapy no	o treatment o	r placebo	Weight	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95%	6 CI	M-H, Rand	om, 95% CI	
1.12.1 with IFN										
Perrillo with IFN 2002	1	5	0	25	14.1	13.00 [0.60, 281.4	6]			
Zhu 2018 Subtotal (95% CI)	15	46 51	1	23 48	21.6 35.7	7.50 [1.05, 53.32 8.79 [1.68, 45.95]			•
Total events	16		1				1		-	
Heterogeneity: $Tau^2 = 0.0$	0; $Chi^2 = 0$.	09, $df = 1$ ($P = 0.76$; $I^2 =$	= 0%						
Test for overall effect: Z =	2.58 (P = 0	.010)								
1.12.2 without IFN										
Chan 2014	0	62	3	63	14.9	0.15 [0.01, 2.75]	-		<u> </u>	
Hsu 2021	1	12	4	19	20.8	0.40 [0.05, 3.13]	1		_	_
Perrillo without IFN 2002	1	53	0	25	13.6	1.44 [0.06, 34.26			-	
Subtotal (95% CI)	2	134	0	18	15.0 64.3	11.88 [0.64, 220.5 0.90 [0.15, 5.38]	8]			,
Total events	4	101	7	125	01.5	0.50 [0.15, 5.50]				
Heterogeneity: $Tau^2 = 1.3$	8; Chi ² = 5.	14, $df = 3$ ($P = 0.16$; $I^2 =$	= 42%						
Test for overall effect: Z =	0.11 (P = 0	.91)								
Total (95% CI)		185		173	100.0	2.09 [0.46, 9.50]				
Total events	20		8							
Heterogeneity: $Tau^2 = 1.7$	5; Chi ² = 10).04, df = 5	$(P = 0.07); I^2$	= 50%			<u> </u>			
Test for overall effect: Z =	0.96 (P = 0	.34)					0.01	0.1	1 10	100
Test for subgroup differen	ices: Chi ² =	3.36, df =	1 (P = 0.07); I	$[^2 = 70.2\%]$				Favours	Favours	
								control	antivirus	6
				(b)						
	antivirus tl	nerapy n	o treatment o	or placebo	Weight	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	(%) 1	M-H, Random, 95% C	CI	M-H, Rand	om, 95% CI	
1.13.1 monotherapy										
Chan 2014	0	62	3	63	11.6	0.15 [0.01, 2.75]			<u> </u>	
Hsu 2021	1	12	4	19	19.9	0.40 [0.05, 3.13]				
Perrillo monothrapy 2002	. 12	191	3	84	36.2	1.76 [0.51, 6.07]				
Total events	12	205	10	100	07.0	0.71 [0.17, 2.95]				
Heterogeneity: $Tau^2 = 0.6$	15 3: Chi ² = 3	24. $df = 2.0$	$P = 0.20$; I^2	= 38%						
Test for overall effect: Z =	0.47 (P = 0	0.63)		0070						
1.13.2 IFN plus NAs										
Perrillo plus 2002	5	51	3	84	32.4	2.75 [0.68, 11.00]		-		
Subtotal (95% CI)	-	51	2	84	32.4	2.75 [0.68, 11.00]		-		
Total events	5		3							
Heterogeneity: Not applic	able									
Test for overall effect: Z =	1.43 (P = 0)	0.15)								
Total (95% CI)		316		250	100.0	1.13 [0.38, 3.40]				
Total events	18		13							
Heterogeneity: $Tau^2 = 0.4$	7; $Chi^2 = 4$.85, df = 3 ($(P = 0.18); I^2 =$	= 38%			+			+
Test for overall effect: Z =	0.22 (P = 0	.83)					0.01	0.1	1 10	100
Test for subgroup differer	nces: Chi ² =	1.78, df =	1 (P = 0.18);	$I^2 = 43.8\%$				Favours	Favours	
								control	antivirus	

(c) FIGURE 5: Continued.

	antivirus th	nerapy	no treatment or p	lacebo	Weight	Risk Ratio		Risk	k Ratio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95%	CI	M-H, Ran	dom, 95%	CI
1.14.1 Long duration:	>96 weeks									
Chan 2014	0	62	3	63	17.2	0.15 [0.01, 2.75]	_	-	<u> </u>	
Hsu 2021	1	12	4	19	23.8	0.40 [0.05, 3.13]			+-	
Subtotal (95% CI)		74		82	41.0	0.28 [0.05, 1.54]				
Total events	1		7							
Heterogeneity: Tau ² :	= 0.00; Chi ² =	= 0.31, di	$f = 1 (P = 0.58); I^2 =$	0%						
Test for overall effect	: Z = 1.46 (P	= 0.14)								
1.14.2 Short duration	≤96 weeks									
Perrillo 2002	2	58	0	25	16.8	2.20 [0.11, 44.31]				
Tseng 2014	2	7	0	18	17.3	11.88 [0.64, 220.58]	1			
Zhu 2018	15	46	1	23	24.8	7 50 1 05 53 321				
Subtotal (95% CI)	10	111	-	66	59.0	6.34 [1.51, 26.52]				
Total events	19		1							
Heterogeneity: Tau ²	= 0.00; Chi ² =	= 0.68, df	$f = 2 (P = 0.71); I^2 =$: 0%						
Test for overall effect	: Z = 2.53 (P	= 0.01)	(- •)))-							
Total (95% CI)		185		148	100.0	1.66 [0.32, 8.60]				
Total events	20		8							
Heterogeneity: Tau ² =	= 1.84; Chi ² =	= 8.54, di	$f = 4 (P = 0.07); I^2 =$	53%			+	1	1 1	
Test for overall effect	: Z = 0.61 (P	= 0.54)					0.005	0.1	1 10	200
Test for subgroup dif	ferences: Chi	i ² = 7.54,	df = 1 (P = 0.006);	$I^2 = 86.7^{\circ}$	%			Favoure	For	211176
								control	1'dVC	virue
								control	antiv	11 45

(d)

FIGURE 5: The outcomes of HBeAg seroconversion. (a) Pooled risk ratio for HBeAg seroconversion between the antiviral therapy group and control group. (b) Subgroup analysis stratified by therapeutic regimen with or without IFN. (c) Subgroup analysis stratified by monotherapy and combined therapy (IFN plus NAs). (d) Subgroup analysis stratified by therapy duration with threshold of 96 weeks. NAs, nucleos(t)ide analogs; IFN, interferon; CI, confidence interval; monotherapy group exclusively included NAs or IFN. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate.

	antivirus th	nerapy	no treatment or p	lacebo	Weight	Risk Ratio		Ris	sk Ra	atio	
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95%	CI	M-H, Ra	ndor	n, 95% CI	
Cao 2017	49	49	0	17	13.3	35.64 [2.32, 548.21]					
Chan 2014	43	62	29	64	22.0	1.53 [1.12, 2.10]					
Hsu 2021	63	74	9	75	21.4	7.09 [3.82, 13.19]					
Lu 2014	28	30	0	38	13.3	71.71 [4.56, 1128.43]				
Tseng 2014	16	21	0	18	13.3	28.50 [1.83, 443.91]				-	
Zhu 2018	34	46	1	23	16.7	17.00 [2.48, 116.49]					
Total (95% CI)		282		235	100.0	11.89 [2.44, 57.89]					
Total events	233		39								
Heterogeneity: Tau ² =	= 2.94; Chi ² =	= 63.97, d	lf = 5 (P < 0.00001)	; $I^2 = 929$	6		+				+
Test for overall effect:	: Z = 3.06 (P	= 0.002)					0.002	0.1	1	10	500
								Favours control		Favours antivirus	



	antivirus tl	nerapy	no treatment or	placebo	Weight	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	(%)	M-H, Random, 95% C	CI M-H, Random, 95% CI
1.16.1 with IFN							
Cao 2017	49	49	0	17	13.3	35.64 [2.32, 548.21]	_
Lu 2014	28	30	0	38	13.3	71.71 [4.56, 1128.43]	_
Zhu 2018	34	46	1	23	16.7	17.00 [2.48, 116.49]	
Subtotal (95% CI)		125		78	43.3	29.14 [7.43, 114.28]	
Total events	111		1				
Heterogeneity: Tau ² Test for overall effect	= 0.00; Chi ² = : Z = 4.84 (P	= 0.75, df < 0.0000	= 2 (P = 0.69); I ² l)	= 0%			
1.16.1 without IFN							
Chan 2014	43	62	29	64	22.0	1.53 [1.12, 2.10]	+
Hsu 2021	63	74	9	75	21.4	7.09 [3.82, 13.19]	
Tseng 2014	16	21	0	18	13.3	28.50 [1.83, 443.91]	
Subtotal (95% CI)		157		157	56.7	4.93 [0.96, 25.41]	
Total events	122		38				
Heterogeneity: Tau ²	= 1.67; Chi ² =	= 29.94, d	f = 2 (P < 0.00001)); $I^2 = 93\%$			
Test for overall effect	: Z = 1.91 (P	= 0.06)	,				
Total (95% CI)		282		235	100.0	11.89 [2.44, 57.89]	
Total events	233		39				
Heterogeneity: Tau ²	= 2.94; Chi ² =	= 63.97, d	f = 5 (P < 0.00001)); $I^2 = 62.4$	%		+ + + + + +
Test for overall effect	: Z = 0.96 (P	= 0.34)					0.005 0.1 1 10 200
Test for subgroup dif	ferences: Chi	$i^2 = 2.66$,	df = 1 (P = 0.10);	$I^2 = 62.429$	ó		Equation Equation
0 1							ravours ravours
							control antivirus
				(b)			
	antivirus tl	nerapy	no treatment or	(b) placebo	Weight	Risk Ratio	Risk Ratio
Study or Subgroup	antivirus tl Events	nerapy Total	no treatment or Events	(b) placebo Total	Weight (%)	Risk Ratio M-H, Random, 95% C	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup	antivirus tl Events	nerapy Total	no treatment or Events	(b) placebo Total	Weight (%)	Risk Ratio M-H, Random, 95% C	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014	antivirus tl Events 43	nerapy Total 62	no treatment or Events 29	(b) placebo Total 64	Weight (%) 32.5	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021	antivirus tl Events 43 63	nerapy Total 62 74	no treatment or Events 29 9	(b) placebo Total 64 75	Weight (%) 32.5 31.5	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014	antivirus tl Events 43 63 16	Total 62 74 21	no treatment or Events 29 9 0	(b) placebo Total 64 75 18	Weight (%) 32.5 31.5 18.1	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI)	antivirus tl Events 43 63 16	nerapy Total 62 74 21 157	no treatment or Events 29 9 0	(b) placebo Total 64 75 18 157	Weight (%) 32.5 31.5 18.1 82.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events	antivirus tl Events 43 63 16 122	62 74 21 157	no treatment or Events 29 9 0 38	(b) placebo Total 64 75 18 157	Weight (%) 32.5 31.5 18.1 82.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect	antivirus th Events 43 63 16 122 = 1.67; Chi ² = : Z = 1.91 (P	nerapy Total 62 74 21 157 = 29.94, d = 0.06)	no treatment or Events 29 9 0 38 f = 2 (P < 0.00001	(b) placebo Total 64 75 18 157 1); I ² = 93%	Weight (%) 32.5 31.5 18.1 82.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs	antivirus tl Events 43 63 16 122 = 1.67; Chi ² : : Z = 1.91 (P	nerapy Total 62 74 21 157 = 29.94, d = 0.06)	no treatment or Events 29 9 0 38 f = 2 (P < 0.00001	(b) placebo Total 64 75 18 157 1); I ² = 93%	Weight (%) 32.5 31.5 18.1 82.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect 1.17.2 IFN plus NAs Lu 2014	antivirus th Events 43 63 16 122 = 1.67; Chi ² : Z = 1.91 (P 28	nerapy Total 62 74 21 157 = 29.94, d = 0.06) 30	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0	(b) placebo Total 64 75 18 157 1); I ² = 93% 38	Weight (%) 32.5 31.5 18.1 82.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI)	antivirus tl Events 43 63 16 122 = 1.67; Chi ² : : Z = 1.91 (P 28	nerapy Total 62 74 21 157 = 29.94, d = 0.06) 30 30	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43]	Risk Ratio EI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events	antivirus th Events 43 63 16 122 = 1.67; Chi ² = : Z = 1.91 (P 28 28 28	$ \frac{1}{10000000000000000000000000000000000$	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38 38	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43]	Risk Ratio EI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not appendix to the second s	antivirus th Events 43 63 16 122 = 1.67; Chi ² : : Z = 1.91 (P 28 28 pplicable	$\frac{1}{10000000000000000000000000000000000$	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0 0 0	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43]	Risk Ratio EI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not ay Test for overall effect	antivirus tl Events 43 63 16 122 = 1.67; Chi ² = : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P	$\frac{1}{10000000000000000000000000000000000$	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0 0	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect Total (95% CI)	antivirus tl Events 43 63 16 122 = 1.67; Chi ² : : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P	$\frac{62}{74}$ $= 29.94, d$ $= 0.060$ $\frac{30}{30}$ $= 0.002)$ 187	no treatment or Events 29 9 0 38 f = 2 (P < 0.00001 0 0	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38 38 195	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0 18.0 100.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43] 8.40 [1.48, 47.86]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not aj Test for overall effect Total (95% CI) Total events	antivirus tl Events 43 63 16 122 = 1.67; Chi ² : : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P 150	nerapy Total 62 74 21 157 = 29.94, d = 0.06) 30 30 30 = 0.002) 187	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0 0 0 38	(b) placebo Total 64 75 18 157 l); $I^2 = 93\%$ 38 38 38 195	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0 18.0 100.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43] 8.40 [1.48, 47.86]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not ay Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² =	antivirus th Events 43 63 16 122 = 1.67; Chi ² = : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P 150 = 2.40; Chi ² =	$\frac{1}{10000000000000000000000000000000000$	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0 0 0 $38 \\ f = 3 (P < 0.00001)$	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38 195 1); I ² = 93%	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43] 8.40 [1.48, 47.86]	Risk Ratio CI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not ay Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	antivirus th Events 43 63 16 122 = 1.67; Chi ² = : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P 150 = 2.40; Chi ² = : Z = 2.40 (P	$\begin{array}{c} \text{herapy} \\ \hline \text{Total} \\ \hline \\ 62 \\ 74 \\ 21 \\ 157 \\ = 29.94, d \\ = 0.06) \\ \hline \\ 30 \\ 30 \\ = 0.002) \\ \hline \\ 187 \\ = 45.09, d \\ = 0.02) \end{array}$	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001)$ 0 0 0 0 1 f = 3 (P < 0.00001)	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38 195 1); I ² = 93%	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43] 8.40 [1.48, 47.86]	Risk Ratio 21 M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect Total events Heterogeneity: Tau ² = Test for overall effect	antivirus th Events 43 63 16 122 = 1.67; Chi ² : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P 150 = 2.40; Chi ² : : Z = 2.40 (P	$\begin{array}{c} \text{herapy} \\ \hline \text{Total} \\ \hline \\ 62 \\ 74 \\ 21 \\ 157 \\ = 29.94, d \\ = 0.06) \\ \hline \\ 30 \\ 30 \\ = 0.002) \\ 187 \\ = 45.09, d \\ = 0.02) \\ ^2 = 2.68, \end{array}$	no treatment or Events $29 \\ 9 \\ 0 \\ 38 \\ f = 2 (P < 0.00001) \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 16 = 3 (P < 0.00001) \\ df = 1 (P = 0.10);$	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38 195 1); I ² = 93% I ² = 93% I ² = 93% I ² = 93%	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0 18.0 18.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43] 8.40 [1.48, 47.86]	Risk Ratio EI M-H, Random, 95% CI
Study or Subgroup 1.17.1 monotherapy Chan 2014 Hsu 2021 Tseng 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 1.17.2 IFN plus NAs Lu 2014 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect Total events Heterogeneity: Tau ² = Test for overall effect	antivirus th Events 43 63 16 122 = 1.67; Chi ² : : Z = 1.91 (P 28 28 pplicable : Z = 3.04 (P 150 = 2.40; Chi ² : : Z = 2.40 (P	$\begin{array}{c} \text{herapy} \\ \hline \text{Total} \\ \hline \\ 62 \\ 74 \\ 21 \\ 157 \\ = 29.94, d \\ = 0.06) \\ \hline \\ 30 \\ 30 \\ = 0.002) \\ \hline \\ 187 \\ = 45.09, d \\ = 0.02) \\ \hline \\ 2^2 = 2.68, \end{array}$	no treatment or Events 29 = 9 = 0 38 = 100 = 100000000000000000000000000000	(b) placebo Total 64 75 18 157 1); I ² = 93% 38 38 195 1); I ² = 93% I ² = 93% I ² = 93%	Weight (%) 32.5 31.5 18.1 82.0 18.0 18.0 18.0 100.0	Risk Ratio M-H, Random, 95% C 1.53 [1.12, 2.10] 7.09 [3.82, 13.19] 28.50 [1.83, 443.91] 4.93 [0.96, 25.41] 71.71 [4.56, 1128.43] 71.71 [4.56, 1128.43] 8.40 [1.48, 47.86]	Risk Ratio EI M-H, Random, 95% CI

(c)

FIGURE 6: The outcomes of undetectable HBV DNA. (a) Pooled risk ratio for undetectable HBV DNA between the antiviral therapy group and control group. (b) Subgroup analysis stratified by therapeutic regimen with or without IFN. (c) Subgroup analysis stratified by monotherapy and combined therapy (IFN plus NAs). NAs, nucleos(t)ide analogs; IFN, interferon; CI, confidence interval; monotherapy group exclusively included NAs or IFN. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate.

undetectable HBV DNA revealed consistent results with the primary meta-analysis, while heterogeneity was reduced to a degree where it was not significant (Supplementary Figure 3). In studies that adopted IFN-based treatment, antiviral therapy was associated with a significantly higher incidence of undetectable HBV DNA (RR = 29.14, 95% CI: 7.43–114.28,

P < 0.001); whereas in studies that adopted IFN-free regimen, there was no significant difference between the two groups in undetectable HBV DNA (RR = 4.93, 95% CI: 0.96–25.41, P =0.06). No significant difference was found between the two subgroups (IFN-based subgroup and IFN-free subgroup) (P = 0.10) (Figure 6(b)). In order to explore whether there was a synergy between IFN and NAs on undetectable HBV DNA, subgroup analysis of monotherapy and combined therapy was conducted. Only in the combined treatment subgroup, antiviral therapy exhibited a superior effect than that of the control one (RR = 71.71, 95% CI: 4.56–1128.43, P = 0.002). However, the difference between the two subgroups (monotherapy subgroup and combination treatment subgroup) was insignificant (P = 0.100) (Figure 6(c)). Collectively, patients who underwent antiviral treatment were inclined to have undetectable HBV DNA.

3. Discussion

In this systematic review, we evaluated the proportion of HBsAg loss with or without the seroconversion to HBsAb in CHB patients with only normal or minimally elevated ALT levels. It was revealed that antiviral therapy increased the rate of achieving HBsAg loss, HBsAg seroconversion, and undetectable HBV DNA compared with no or placebo treatment. IFN exhibited a more important role in HBsAg loss with or without HBsAg seroconversion than NAs. Besides, no synergism was found between IFN and NAs in virological response.

There was a consensus that antiviral therapy should be actively administered in patients with elevated ALT levels (>2 ULN), cirrhosis, and liver cancer, while there was a controversy over antiviral therapy in CHB patients with normal or mildly elevated ALT levels. Studies have suggested that CHB patients with normal or low ALT levels have a certain histological damage, and they may eventually develop liver failure, cirrhosis, or HCC [22, 23]. A retrospective cohort study found that long-term antiviral therapy reduced the incidence of liver cancer in patients with CHB, with no significant association with ALT levels [24]. In addition, a meta-analysis indicated that the rate of fibrosis is more than 40% in patients with CHB and minimal increased ALT levels [25]. Combined with the results of our study, it is likely to conclude that given the possibility of liver disease progression and the available benefits of antiviral therapy, the threshold for the initiation of treatment must be individualized.

For CHB patients with normal or minimally increased ALT levels, the overall treatment goal is to inhibit and even eliminate hepatitis B virus infection, alleviate necrosis and inflammation, and suppress the disease progression. IFN and NAs are two effective antiviral drugs for CHB patients to delay the disease progression and to improve the longstanding prognosis. A meta-analysis included 24 studies and found that combination therapy took an advantage on promoting HBsAg loss [26]. Another research demonstrated that NAs combined with IFN strategy could improve efficacy on HBeAg seroconversion compared to monotherapy with NAs [27]. However, our study found the equivalence of combination therapy and monotherapy in achieving virological response. Considering the high heterogeneity and small sample size, additional RCTs are required to verify the synergy between IFN and NAs on virological response.

NAs can suppress the replication of hepatitis B virus effectively, while IFN has dual functions on viral inhibition and immunomodulation. In clinical practice, for the vast majority

of CHB patients, long-term NA therapy is the top choice for them, apart from the few achieved HBsAg clearance or the conversion to HBsAb. IFN, compared with NAs, is inferior in preventing the virus from replicating itself, while it is superior in achieving HBeAg seroconversion and HBsAg loss [28, 29]. The present study revealed that CHB patients with ALT levels <2 ULN can benefit from IFN-based treatment in achieving primary outcomes. Besides, there was a significant difference in HBeAg clearance, and it could be due to immunomodulatory effects of IFN. Previous studies have demonstrated that IFNbased treatment was associated with greater sustained virological and serological responses and a higher chance of HBsAg loss, and the induced functional cure was durable [30, 31]. However, our research indicated that IFN-based therapy was not superior to IFN-free therapy in achieving HBeAg seroconversion and undetectable HBV DNA, which might be attributed to the same reason as mentioned above.

A previous prospective cohort study revealed that the rate of HBeAg seroconversion increased along with the prolonged treatment [32]. In the subgroup analysis stratified by the treatment duration, short-term treatment, compared with long-term treatment, could improve the efficacy of HBeAg loss and HBeAg seroconversion. The possible reason for the difference was that all the studies included in the long-term treatment subgroup adopted IFN-free strategy and tenofovir treatment, while most of the studies in the short-term treatment subgroup adopted IFN-based strategy, and the difference might stem from IFN treatment.

The present study exhibited the following deficiencies. Firstly, several factors might influence patients' response to the therapy, including demographic characteristic, HBV genotype, HBeAg status, HBV DNA levels, and with or without history of undergoing antiviral treatment. However, the limitation of the available studies impeded further subgroup analysis to explore the influences of the abovementioned factors. Secondly, because the unknown approach for measuring ALT and ULN was not mentioned in some articles, and it was infeasible to evaluate the efficacy of antiviral therapy for CHB patients with normal ALT level. Thirdly, high heterogeneity and limited research studies in each subcohort restricted us from exploring optimal antiviral strategies for CHB patients with ALT level <2 ULN. Fourthly, the small quantity of the available studies and certain methodological limitations, which were related to randomization and blinding processes, diminished the quality of our study.

In general, for CHB patients with ALT level <2 ULN, antiviral therapy could significantly improve the HBsAg loss rate. Through the immune modulatory function of IFN and our results, IFN is highly recommended to CHB patients with ALT level <2 ULN for achieving the objective of functional treatment.

4. Methods

This study was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study protocol was registered in the PROSPERO database (Registration No. CRD42020209639).

4.1. Data Sources and Searches. On October 3, 2020, the relevant studies were retrieved by searching four English language databases, such as MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science, from January 1990 to October 2020. The following strategy was applied: ((("Hepatitis B"(Mesh)) OR ("Hepatitis B virus"(Mesh))) OR ("Hepatitis B, Chronic"(Mesh))) AND ((alanine aminotransferase (Title/Abstract)) OR ("Alanine Transaminase"[Mesh))). To avoid missing potentially relevant articles, the additional citations of all retrieved articles were also searched manually.

4.2. Study Selection. Studies fulfilling the following specific criteria were considered for inclusion in the primary analysis: (i) patients: both infected with hepatitis B virus and with ALT level ≤2 ULN (ULN shall be subjected to each article reported); (ii) treatment strategy: patients were divided into antiviral therapy group (treated with nucleos(t)ide analogs (NAs) or interferon (IFN)) and control group (no treatment or placebo); and (iii) outcomes: including rates of undetectable HBV DNA, HBeAg loss, HBeAg seroconversion, HBsAg loss, or HBsAg seroconversion. We excluded studies where study cohorts included patients with (i) coinfection with hepatitis C virus, hepatitis D, or human immunodeficiency virus; (ii) remarkable alcohol abuse; or (iii) other liver diseases. Then, four of the authors (C. X. Y, Z. X. R, W. H. W, and Z. B. X) reviewed the articles independently. Information about the source or author of the report was not blinded to the investigators. However, when a decision was made on which studies should be included, two observers (C. X. Y and Z. B. X) analyzed in parallel and without interference. In case of the occurrence of any disagreement, they conferred with other two authors (W. H. W and Z. X. R). The final decision was confirmed by four observers and the senior author (X. C). The decision to include these data was not influenced by the results of the recruited study.

4.3. Data Extraction and Study Quality. The modified Newcastle-Ottawa Scale was applied to assess the risk of bias in cohort studies by two reviewers (C. X. Y and Z. B. X) separately. The included studies in the meta-analysis were rated on a scale of zero to 9 points. Only studies that scored six or higher points were regarded as good quality. For each study considered for being included, the following data were fetched from them: (i) study characteristics (first author's name, year of publication, geographic locale, study design, sample size, number of patients included in analysis, and quality score); (ii) patients' demographics (age, gender, HBeAg-positive rate, baseline HBV DNA level, and baseline ALT level); (iii) inclusion and exclusion criteria; (iv) treatment details (i.e., antiviral agent, treatment duration, lower limit of detection of HBV DNA, and data collected at timepoints).

4.4. Statistical Analysis. Using the Mantel-Haenszel method, the pooled outcome was calculated as risk ratio (RR) or risk difference (RD) with 95% confidence interval (CI) for

various indicators reported as dichotomous variables, involving undetectable HBV DNA, HBsAg loss, HBsAg seroconversion, HBeAg loss, and HBeAg seroconversion. The χ^2 test was applied for the exploration of heterogeneity, and statistical significance was set to P < 0.05. To quantify heterogeneity, I^2 statistic was taken, with a maximum of 50% that was defined as low heterogeneity, while >50% indicated significant heterogeneity. If there was a high degree of heterogeneity, the random-effects model was used, otherwise, the fix-effects model was utilized. The Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK) was used to calculate RRs and draw the forest plots to display the results of the meta-analysis. The squares around the estimates were proportional to the weights used in the meta-analysis, with horizontal lines that represented 95% CI. Sensitivity analysis was performed by leave-one-out analysis to test the influences of individual studies on aggregate estimates. The following subgroup analyses were carried out, wherever possible: therapeutic strategy (combination therapy (NAs and IFNs), NAs-monotherapy, and IFN-monotherapy; patients who were treated with two or more types of NAs were divided into the monotherapy group), treatment duration, baseline HBeAg status, and baseline HBV DNA level. Once a significant difference was found between the subgroups (test for interaction, P < 0.05), the results were reported separately. A formal test was also performed for subgroup interactions.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Xiyao Chen and Xingrong Zheng are the co-first authors of the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

X. C and P. L conceived and supervised the study; X. C and P. L designed the study; X. C and P. L designed the study search terms; C. X. Y, Z. X. R, Z. B. X, and W. H. W identified studies for inclusion; C. X. Y and Z. X. R designed data extraction template; C. X. Y, Z. B. X, Z. X. R, and W. H. W conducted data extraction; C. X. Y, Z. B. X, Z. X. R, and W. H. W assessed data quality; C. X. Y and Z. X. R analyzed and/or interpreted data; C. X. Y drafted the manuscript. All the authors critically reviewed or revised the manuscript and approved the final version of the manuscript.

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Supplementary Materials

Supplementary Figure 1: risk difference was used for HBsAg loss under subgroup analysis stratified by therapeutic regimen with or without IFN. CI, confidence intervals. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate. Supplementary Figure 2: risk difference was used for HBsAg seroconversion under subgroup analysis stratified by therapeutic regimen with or without IFN. CI, confidence intervals. The size of square represents the weight of each study, and the vertical dotted line represents the weight of each study, and the vertical dotted line represents the pooled rate. Supplementary Figure 3: sensitivity analysis. (A) HBeAg loss. (B) HBV DNA undetectable. CI, confidence intervals. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate. Supplementary Figure 3: sensitivity analysis. (A) HBeAg loss. (B) HBV DNA undetectable. CI, confidence intervals. The size of square represents the weight of each study, and the vertical dotted line represents the pooled rate. *Supplementary Materials*)

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