

Antiviral Therapy in Management of Chronic Hepatitis B Virus Infection in Children: A
Systematic Review and Meta-analysis

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List of Abbreviations: Hepatitis B virus (HBV), Randomized Controlled Trials (RCTs), Hepatitis B e Antigen (HBeAg), Hepatitis B Surface Antigen (HBsAg), Alanine Aminotransferase (ALT), American Association for the Study of Liver Diseases (AASLD), Interferon (IFN).

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Conflict of Interest:

Maureen M. Jonas has received research grants from Bristol Myers Squibb, Roche and Gilead, and serves on a Data Safety Monitoring Board for Gilead.

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Abstract:

Introduction: Most individuals with chronic hepatitis B virus (HBV) infection acquired the infection around the time of birth or during early childhood. We aimed to synthesize evidence regarding the effectiveness of antiviral therapy in the management of chronic HBV infection in children. **Methods:** We conducted a comprehensive search of multiple databases from 1988 to December 2nd, 2014 for studies that enrolled children (< 18 years) with chronic HBV infection treated with antiviral therapy. We included observational studies and randomized controlled trials (RCTs). Two independent reviewers selected studies and extracted data. **Results:** In the 14 included studies, 2 cohort studies showed no significant reduction in the already low risk of hepatocellular carcinoma or cirrhosis, and 12 RCTs reported intermediate outcomes. In RCTs with post-treatment follow up < 12 months, antiviral therapy compared to placebo improved ALT normalization (RR 2.3 (95% CI, 1.7 - 3.2), hepatitis B e antigen (HBeAg) clearance/loss (RR 2.1 (95% CI, 1.5 - 3.1), HBV DNA suppression (RR 2.9 (95% CI, 1.8 - 4.6), HBeAg seroconversion (RR 2.1 (95% CI, 1.4 - 3.3) and hepatitis B surface antigen (HBsAg) clearance (RR 5.8 (95% CI, 1.1 - 31.5). In RCTs with post-treatment follow up \geq 12 months, antiviral therapy improved cumulative HBeAg clearance/loss (RR 1.9 (95% CI, 1.7 - 3.1), HBeAg seroconversion (RR 2.1 (95% CI, 1.3 - 3.5), ALT normalization (RR 1.4 (95% CI, 1.1 - 1.7) and HBV DNA suppression (RR 1.4 (95% CI, 1.1 - 1.8), but not HBsAg clearance or HBsAg seroconversion. **Conclusion:** In children with chronic HBV infection, antivirals compared to no antiviral therapy improve HBV DNA suppression and frequency of ALT normalization and HBeAg seroconversion.

Introduction:

Worldwide, most individuals with chronic hepatitis B virus (HBV) infection acquired their infections around the time of birth or during early childhood because the risk of chronic infection is 90% when infection occurs in infancy, 30% when occurring during the first 5-years of life and decreases to <5% when infection occurs in immunocompetent older children and adults (1). In countries where HBV is endemic, perinatal transmission remains the most important mode of infection because of the high prevalence of hepatitis B e antigen (HBeAg) in pregnant women. Perinatal transmission also occurs in non-endemic countries, including the United States, mostly in children of HBV-infected mothers who did not receive appropriate screening during pregnancy or HBV immunoprophylaxis at birth.

The natural history of chronic HBV infection in children varies, depending upon age at infection, mode of acquisition, and ethnicity. When HBV infection is acquired perinatally or horizontally during the first few years of life, children from HBV endemic countries usually become HBeAg-positive with high levels of viral replication (2). Spontaneous HBeAg seroconversion rates vary by age and are less than 2% per year in children younger than three years of age, 4 to 5% after age three, and then rise during puberty. In contrast, children from non-endemic countries are less likely to have acquired the infection perinatally and frequently undergo HBeAg seroconversion during the first two to three decades of life (3).

Cirrhosis is an infrequent complication of HBV infection during childhood. In one of the largest studies, involving 292 consecutive children with a mean age of 4.0 ± 3.3 years who were hepatitis B surface antigen (HBsAg) positive and who had elevated serum alanine aminotransferase (ALT) levels (4), 10 (3%) had cirrhosis at enrollment, but no child developed cirrhosis during

follow-up of 1-10 years. The risk of hepatocellular carcinoma (HCC) is related to the duration of infection, the degree of liver injury, and the replicative state of the virus (HBV DNA levels).

Hepatocellular carcinoma in children with chronic HBV infection has been described in both Asian and Western populations (5-9). Importantly, HCC may occur even in children who have undergone HBeAg seroconversion at a young age, indicating that risk for developing HCC persists even following reduced viral replication (10).

Management of children with chronic HBV infection involves education of the children and their parents on measures to prevent transmission of infection, regular follow-up to monitor viral replication and liver injury, and antiviral therapy and HCC surveillance in some cases(11). Few large trials of antiviral therapy in children exist to guide treatment decisions. In the United States, interferon (IFN)-alpha is approved for children beginning at 1 year of age, and lamivudine and entecavir are approved for use in children 2 years and older. Adefovir and tenofovir are approved for use in those 12 years of age and older. IFN, lamivudine and adefovir are no longer first line therapy in adults, since much better agents are available, so they are less than ideal for children. Randomized Phase III trials of entecavir, peginterferon-alpha2a and tenofovir in children with chronic HBV are underway. We conducted this systematic review and meta-analysis to synthesize existing evidence about effectiveness of antiviral therapy in the management of chronic HBV infection in children.

Methods:

This systematic review follows a predefined protocol that was developed by a guideline writing group from the American Association for the Study of Liver Diseases (AASLD). The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (12).

Eligibility criteria:

We included studies that enrolled children (< 18 years) with chronic HBV infection treated with antiviral therapy. Due to the anticipated limited number of randomized controlled trials (RCTs) evaluating patient important (clinical) outcomes, we included observational studies that evaluated such outcomes. Outcomes of interest were cirrhosis, decompensated liver disease, HCC, ALT normalization, HBV DNA suppression, HBeAg/ HBsAg seroconversion and HBeAg/ HBsAg loss. We included both English and non-English language studies. We excluded studies enrolling adults, patients co-infected with hepatitis C, D or HIV, patients receiving combination therapy, steroids, chemo/immunotherapy, liver transplant recipients and hemodialysis patients. Supplemental table 1 describes the detailed inclusion and exclusion criteria.

Search strategy:

The search strategy was designed and conducted by an experienced librarian (LJP) with input from the principal investigator. A comprehensive search of Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus was conducted from January 1988 to December 2nd, 2014. Controlled vocabulary supplemented with keywords was used to search for studies of antiviral therapy for hepatitis B in children. Supplemental table 2 provides the details of search strategy. We conducted a manual search of bibliographies of the included studies and previous systematic reviews to identify relevant studies. Content experts from AASLD were also queried for potential references.

Study selections:

Using an online reference management system (DistillerSR, Evidence Partners, Inc.), two reviewers independently screened titles and abstracts. Full text of the included abstracts were

retrieved and screened in duplicate. Disagreements were harmonized by consensus or through arbitration by a third reviewer. We calculated inter-rater agreement (Kappa) during the full text screening to observe the agreement between reviewers.

Data Extraction:

Data extraction was done in duplicates using a standardized, piloted form. A third reviewer compared the reviewers' entered data and resolved any inconsistencies by referring to the full text of the article. We extracted the following variables from each study: study characteristics, patient baseline characteristics, interventions details and outcomes of interest.

Risk of bias assessment:

Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane risk of bias tool and the Newcastle-Ottawa Scale for RCTs and observational studies; respectively. Quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity) and publication bias (13).

Statistical analysis:

For dichotomized outcomes, we calculated risk ratios and 95% confidence intervals using binomial distribution. We then pooled the log transformed risk ratios using the DerSimonian and Laird (14) random-effect method with the heterogeneity estimated from the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, we calculated I^2 statistic, where $I^2 > 50\%$ suggesting high heterogeneity (15). All statistical analyses were

conducted using STATA, version 13 (StataCorp LP, College Station, TX). We explored the impact of publication bias using the Egger regression asymmetry test and by constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low (16).

Results:

From the 2321 citations identified, with the primary search strategy, 14 studies that enrolled 1425 children were finally included. Two studies evaluated the clinical (patient important) outcomes of death, cirrhosis and HCC, and 12 studies reported intermediate outcomes. Average weighted kappa (inter-rater agreement) for study selection was 0.75. Details of study selection and reasons for exclusion are described in Figure 1.

1. Effect of antiviral therapy on clinical (patient-important) outcomes of cirrhosis and HCC:

Two cohort studies (17) (18) from Europe and Japan reported on 163 HBeAg positive patients treated with multiple interventions including IFN-alpha with mean follow up of 15 years. Characteristics of the included studies are described in Table 1. IFN treatment did not significantly reduce the risk of HCC (RR 0.3 (95% CI 0.01-156.2) or cirrhosis (RR 0.2 (95% CI 0.01-100.7)).

2. Effect of antiviral therapy on intermediate outcomes (ALT normalization, HBV DNA suppression, HBeAg/ HBsAg seroconversion and HBeAg/ HBsAg loss):

Among 12 RCTs reporting intermediate outcomes, 8 studies evaluated IFN-alpha (19-26) ; 1 each evaluated lamivudine (27), tenofovir (28), adefovir (29) or entecavir (30). Most of the

studies (74%) had a high risk of bias due to unreported or unclear randomization methods, allocation concealment and blinding (Table 2).

2.1 Any antiviral therapy vs control results:

In the 12 RCTs that compared antiviral therapy to controls, 5 (20, 22, 23, 26, 30) reported outcomes for both short (< 12 months) and long (\geq 12 months) post-treatment follow up durations, 2 (19, 25, 31) included only longer (\geq 12 months) post-treatment follow up and 5 (21, 24, 27-29) included only shorter (< 12 months) follow up. Two RCTs reported the short- and long-term outcomes separately for lamivudine (27,31) and adefovir (29, 32).

In studies with post-treatment follow up < 12 months, meta-analysis (Figure 2) demonstrated that antiviral therapy compared to placebo was more effective at improving ALT normalization (8 RCTs, RR 2.3 (95% CI, 1.7 - 3.2) $I^2=46.5\%$), HBeAg clearance/loss (7 RCTs, RR 2.1 (95% CI, 1.5 - 3.1) $I^2=0\%$), HBV DNA suppression (9 RCTs, RR 3.3 (95% CI, 1.9 - 6.1) $I^2=63.8\%$), HBeAg seroconversion (4 RCTs, RR 2.1 (95% CI, 1.4 - 3.3) $I^2=0\%$) and HBsAg clearance (2 RCT, RR 5.8 (95% CI, 1.1 - 31.5) $I^2=0\%$). In studies with post-treatment follow up \geq 12 months (Figure 3), antiviral therapy improved ALT normalization (2 RCTs, RR 1.4 (95% CI, 1.1 - 1.7) $I^2=0\%$), HBeAg clearance/loss (5 RCTs, RR 2 (95% CI, 1.9 - 3.2) $I^2=0\%$), HBV DNA suppression (7 RCTs, RR 1.4 (95% CI, 1.1 - 1.8) $I^2=0\%$) and HBeAg seroconversion (3 RCTs, RR 2.1 (95% CI, 1.3 - 3.5) $I^2=0\%$). However, the short-term statistically significant difference did not persist after \geq 12 months follow up for HBsAg clearance (2 RCTs, RR 3.3 (95% CI, 0.4 - 27.8) $I^2=0\%$) and for HBsAg seroconversion (2 RCTs, RR 2.5 (95% CI, 0.3- 22.7) $I^2=0\%$). The quality of evidence was low to very low due to high risk of bias and indirectness.

2.2 Specific antiviral therapy vs control results:

In studies (Figure 4) with post-treatment follow up < 12 months, IFN-alpha compared to no treatment significantly improved HBeAg clearance/loss (4 RCTs, RR 3.2, (95% CI, 1.8 - 5.7) $I^2=0\%$) and HBV DNA suppression (6 RCTs, RR 2.2(95% CI, 1.4 - 3.3) $I^2=0\%$) but did not significantly improve ALT normalization (4 RCTs, RR 1.4 (95% CI, 0.9 - 2.3) $I^2=0\%$), HBeAg seroconversion (1 RCT, RR 2.8 (95% CI, 0.8 - 9.4) or HBsAg clearance (1 RCT, RR 7.4 (95%CI, 0.9 - 58.6). In studies (Figure 5) with post-treatment follow up \geq 12 months, IFN alpha use was associated with improved HBeAg clearance/loss (5 RCTs, RR 2.0 (95% CI, 1.9 - 3.2) $I^2=0\%$) and HBeAg seroconversion (2 RCTs, RR 3.1 (95%CI, , 1.2 - 8.1) $I^2=0\%$), but statistically significant differences were not observed for ALT normalization (1 RCTs, RR 1.4 (95% CI, 0.6 - 1.9), HBV DNA suppression(6 RCTs, RR 1.5 (95% CI, 0.99 - 2.1) $I^2=7.6\%$), HBsAg clearance (2 RCTs, RR 3.3 (95% CI, 0.4 - 27.8) $I^2=0\%$) or HBsAg seroconversion (2 RCTs, RR 2.5 (95% CI, 0.3 - 22.7) $I^2=0\%$). The quality of evidence was low to very low due to risk of bias, indirectness and imprecision.

Lamivudine, when compared to placebo (27), was associated with significantly higher likelihood of ALT normalization (1 RCT, RR 4.5 (95% CI, 2.3 - 9.1), HBeAg clearance/loss (1 RCT, RR 1.8 (95% CI, 1 - 3.1) and HBV DNA suppression (1 RCT, RR 3.9 (95% CI, 2.4 - 6.3) but not HBeAg seroconversion (2 RCTs, RR 1.7 (95% CI, 0.96 - 3.2) or HBsAg clearance (1 RCT, RR 3.5 (95% CI, 0.2 - 67.1) at the end of 48 weeks treatment. The quality of evidence was moderate to low, due to indirectness and imprecision.

One RCT (29, 31) compared adefovir to placebo treatment. After 48 weeks of treatment, adefovir was associated with a higher rate of ALT normalization (RR 2.7 (95% CI, 1.6 - 4.6) and HBV DNA suppression (RR 11.1 (95% CI, 1.5 – 80.3) but not HBeAg seroconversion (RR 3 (95% CI, 0.9 - 9.9). Longer follow up (192 weeks) of the same cohort with open-label adefovir

treatment either alone or with lamivudine showed continued viral suppression and ALT normalization (32). The quality of evidence was moderate to low due to indirectness and imprecision.

One RCT (28) compared tenofovir to placebo treatment. After 72 weeks of treatment, tenofovir demonstrated significantly higher rates of ALT normalization (RR 2 (95% CI, 1.4 - 2.9)) and HBV DNA suppression (RR 92.4 (95% CI, 5.8-146.7)), but no statistically significant effect on HBeAg clearance/loss (RR 1.4 (95% CI, 0.6 - 3.4)). The quality of evidence was moderate to low due to indirectness and imprecision.

In one RCT (30), entecavir compared to placebo was associated with higher ALT normalization (RR 2.9 (95% CI, 1.8-4.7), HBV DNA suppression (RR 14.8 (95% CI, 3.7 – 58.3) and HBeAg seroconversion (RR 2.4 (95% CI, 1.1 – 5.5) at 48 weeks. Longer duration of treatment (96 weeks) resulted in persistently statistically significant HBeAg seroconversion (RR 1.8 (95% CI, 1.0 – 3.4) but not ALT normalization (RR 1.1 (95% CI, 0.9-1.4) and HBV DNA suppression (RR 1.2 (95% CI, 0.9 – 1.7). The quality of evidence was limited due to the use of surrogate outcomes.

A detailed summary of the assessment of quality of evidence is provided in Supplemental Table 3.

Publication bias: We were unable to evaluate publication bias due to the small number of studies for each outcome.

Discussion:

Main findings:

In this systematic review evaluating the effectiveness of antiviral therapy in children, we identified 14 studies. The current evidence demonstrates that antiviral therapy improves the frequency of surrogate outcomes (ALT normalization, HBeAg loss, HBV DNA suppression, HBeAg seroconversion and HBsAg loss) when compared to no or placebo treatment. The confidence in this evidence is limited by the short duration of follow-up, certain methodological limitations that relate to randomization and blinding processes, and the minimal data on patient-important outcomes such as cirrhosis and HCC.

Strengths and limitations: Although relatively few in number, some large, randomized trials of antiviral agents inform clinical decision-making in pediatric HBV infection. In general, the primary outcomes of these studies, including HBV DNA suppression, HBeAg loss and seroconversion, and ALT normalization, were used as surrogates for the clinical outcomes of cirrhosis, HCC and death, since the latter are quite rare during childhood. Despite this limitation, this is the reality of pediatric practice, and some data support the use of HBeAg seroconversion and viral suppression as therapeutic endpoints, particularly if these are durable. Going forward, future trials of antivirals in children should evaluate long-term durability of the surrogate outcomes. As for clinical outcomes; which require a very long follow up that may be challenging for randomized trials, we suggest the use of registries and large databases of treated children. Such observational studies can provide evidence on clinical outcome and can inform decision making if the studies had rigorous design features to protect from bias (e.g. prospective data entry, multivariable adjustment for prognostic factors and minimal loss to follow up).

Currently approved therapeutic agents have acceptable safety profiles in children and adolescents. IFN has a side effect profile similar to that seen in adults, and transient effects on body weight and growth have been observed (33), but no long-term safety issues have been

identified. Oral antivirals are both safe and well-tolerated, but viral resistance with lamivudine and adefovir develops at least as often in children as in adults (34). Development of viral resistance is less common with entecavir (22), as has been the case in adults.

Clinical and research implications: Some children with chronic HBV infection may benefit from treatment, at least with respect to the surrogate outcomes of HBV DNA suppression and HBeAg seroconversion. The effect of treatment in preventing serious sequelae, such as cirrhosis and HCC, in young adult life remains unproven. ALT levels less than 1.5 to 2 times the upper limit of normal (ULN) in a child who is HBeAg-positive with high HBV DNA levels (>10 million IU/ml) generally indicates that the child is in the immune tolerant phase of HBV infection. Such children are not typically candidates for treatment, because treatment with any of the currently available drugs has not been demonstrated to improve HBeAg seroconversion compared with no treatment. Children with ALT values greater than 10 times the ULN may be in the process of spontaneous HBeAg seroconversion and should be observed for several months before treatment is begun. Therapeutic choices for children with chronic hepatitis B have been limited but expanding, since entecavir has recently been shown to be safe and effective in this population, and data regarding peginterferon and tenofovir use in children are expected soon. Therefore, the choice of whether to treat now or to monitor depends on patient-specific characteristics that predict the efficacy of treatment, including persistently abnormal ALT levels or active disease on liver biopsy, as well as considerations regarding the likelihood of achieving appropriate therapeutic goals. Patient and parents' values and preferences should be incorporated into shared decision making about treatment. Prolonged treatment with nucleoside or nucleotide analogs in children who are in the immune tolerant stage has not been shown to be associated with substantial benefit and carry risk for developing antiviral drug resistance, both to the agent

chosen, and related drugs. An exception may be those immune tolerant children who will be undergoing immunosuppressive therapy, such as those who will be receiving chemotherapy, or stem cell or solid organ transplantation. Patient selection and timing of treatment are critical decisions, in order to avoid overtreatment, maximize therapeutic benefit while limiting duration of therapy, and minimize risk for antiviral drug resistance later in life.

Accepted Article

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Accepted Article

Table 1: Characteristics of included studies:

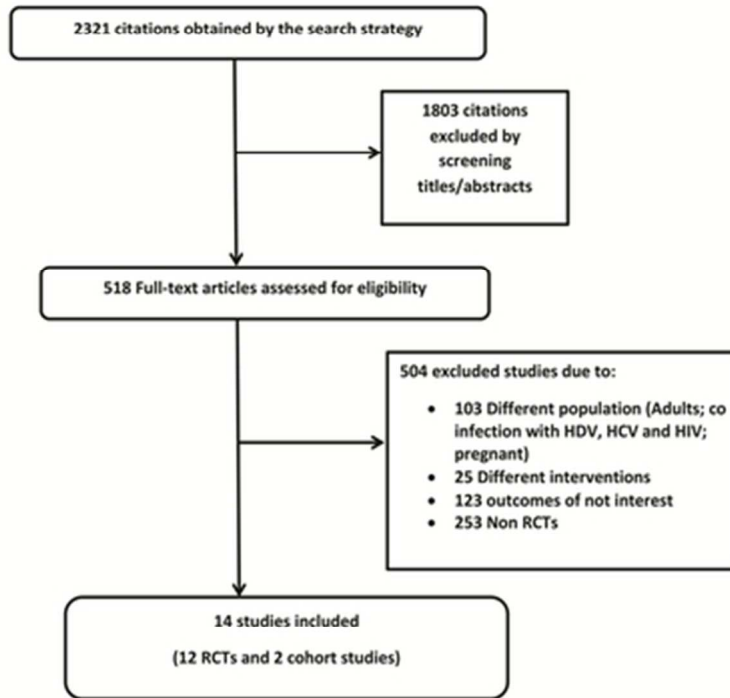
Author, year	Country	Interventions (dose)	Patients (N)	Age (Years)	Baseline HBV DNA level (log ₁₀ IU/mL)	Baseline ALT level (U/L)	Follow up (months)	HBeAg status at baseline	Study design
Antiviral vs control trails:									
Bortolotti, 1998(17)	Multicenter	IFN-alpha (3–5 MU/m ² thrice weekly for 3-6 months)	21	5.5±0.4	NR	NR	141.6±25.2	HBeAg positive	Cohort
		Control	117	5.5±0.4	NR	NR	153.6±38.4		
Fujisawa, 2004(18)	Japan	IFN-alpha (0.1 MU/kg/day x 28 days)	16	NR	NR	NR	216	HBeAg positive	Cohort
Vajro, 1996(19)	Italy	IFN-alpha (10 MU/ m ² body surface area intramuscularly, three times weekly, in the evening, for 1 year)	13	6.9 ± 2.4	7.2 ± 7.1	238±197	48	HBeAg positive	RCT
		Control	9	8.9 ± 3.1	7.2± 7	117± 67	48		
Barbera, 1994(20)	Italy	IFN-alpha (7.5 MU/ m ² three times weekly for 6 month)	21	8.4 ± 3.3	43%>6.7	109.2 ± 69	18	HBeAg positive	RCT
		IFN-alpha (3 MU/ m ² three times weekly for 6 month)	19	8.1 ± 2.3	21%>6.7	72.4 ± 36	18		
		Control	37	8.5 ± 2.5	43%>6.7	72.4 ± 37	18		
Utili, 1991(21)	Italy	IFN alpha (3 MU intramuscularly 3 times/ week for 12 months)	10	10(6-14)	6.3(5.7-6.8)	138 ± 95	18	HBeAg positive	RCT
		Control	10	12(6-14)	6.4 (5.7-6.6)	130 ± 63	18		
Ruiz-Moreno, 1991(22)	Spain	IFN-alpha (10 MU 3 times /week for 24 week subcutaneously)	12	8.7 ± 4.2	7.6 ± 7.7	147 ± 72	18	NR	RCT
		IFN alpha (5 MU 3 times /week for 24 week subcutaneously)	12	7.3 ± 2.5	7.6 ± 7.6	138 ± 90	18		
		Control	12	8.5 ± 3.8	7.5 ± 7.4	115 ± 68	18		
Ruiz-Moreno, 1990(23)	Spain	IFN alpha (10 MU/ m ² body surface, intramuscularly, 3 times/ week for 3 months)	12	7.7±2.9	8.6 ± 8.5	155 ±63	18	HBeAg positive	RCT
		Control	12	8.3±1.8	8.3 ± 8.1	149 ± 122	18		
Sokal, 1998(24)	Multinational	IFN-a2b (3 MU/ m ² of body surface area 3 times/ week for 1 week)	72	5.0 (1–17)	6.7 (<4.6–7.6)	3.2 (1.7–18.3)	48	HBeAg positive	RCT
		Control	77	5.0 (1–17)	6.7 (<4.6–7.5)	3.7 (1.3–18.2)	48		
Lai, 1991(25)	China	IFN-alpha	29	6.5 (4-16)	NR	12(5-34)	24	HBeAg	RCT

		(5x10 ⁶ u/m ² subcutaneously weekly for 16 weeks)						positive	
		Control	30	6(3-15)	NR	9(6-98)	24		
Gregorio,1996(26)	Multicenter	IFN-alpha (5 MU/ m ² for 5 consecutive days during the induction phase followed by 3 times/week for 11 weeks of maintenance therapy)	30	9.5(2.9-14.9)	8.3 (6.9 -9.01)	120 (49-620)	18	HBeAg-positive	RCT
		Control	31	10.9(2.5-15.1)	7.9 (6.7-9.04)	68 (35-266)	18		
		Control	9	8.9 ± 3.1	7.2± 7	117± 67	48		
Jonas, 2002(27)	Multinational	Lamivudine (3 mg/kg once daily for 52 weeks)	95	9(1-17)	8.3 (5.6 -9.8)	2.1(0.7-16.9) xULN	24	HBeAg-positive	RCT
		Control	191	8(2-17)	8.3(5.5-9.5)	2.3(0.3-22.1) xULN	24		
Murray, 2012(28)	Europe and the United State	Tenofovir (300 mg once daily for 72 weeks)	52	15.3± 1.34	7.3± 0.7	101 ±107.5	72	HBeAg-positive	RCT
		Placebo	54	15.3±1.43	7.5 ±0.7	101 ± 90	72		
Jonas, 2008(29)	Multinational	Adefovir dipivoxil (Depend on the age and weight, dose not to exceed 10 mg/day)	115	10.8 ± 4.3	8.04 ± 0.2	111 ±81.6	6	HBeAg-positive	RCT
		Placebo	58	10.7 ± 3.9	7.9 ± 0.3	99±52.8	6		
Jonas, 2015(30)	Multinational	Entecavir Weight-based at 0.015 mg/kg oral solution (0.05 mg/mL) once daily, up to a maximum of 0.5 mg/day.	120	10.5± 0.45	8.1 ± 0.1	107.1±5.4	24	HBeAg-positive	RCT
		Placebo	60	10.8± 0.62	7.9 ± 0.1	94.4 ±12.2	24		

Table 2: Risk of bias assessment for RCTs:

Author, year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel and Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall Risk of bias
Antiviral vs control trials:							
VAJRO, 1996(19)	NR	NR	NR	Complete	None	None	High
Barbera, 1994(20)	NR	NR	NR	Complete	None	None	High
Utili, 1991(21)	NR	NR	NR	Complete	None	None	High
Ruiz-Moreno, 1991(22)	NR	NR	NR	Complete	None	None	High
Ruiz-Moreno, 1990(23)	NR	NR	NR	Complete	None	None	High
Sokal, 1998(24)	Random digit numbers	NR	NR	Complete	None	None	Moderate
Lai, 1991(25)	NR	NR	NR	Complete	None	None	High
Gregorio, 1996(26)	NR	NR	NR	Complete	None	None	High
Jonas, 2002(27)	Centrally randomized	NR	Double blinded	Complete	None	None	Low
Murray, 2012(28)	Centralized and stratified by age	Unclear	Unclear	Complete	None	None	Moderate
Jonas, 2008(29)	Centrally randomized	NR	Double blinded	Complete	None	None	Low
Jonas, 2015 (30)	Sponsor-designated center via an Interactive Voice Response System (IVRS) using a block size of 6	NR	Double blinded	Complete	None	None	Low

Figure 1: The process of study selection:



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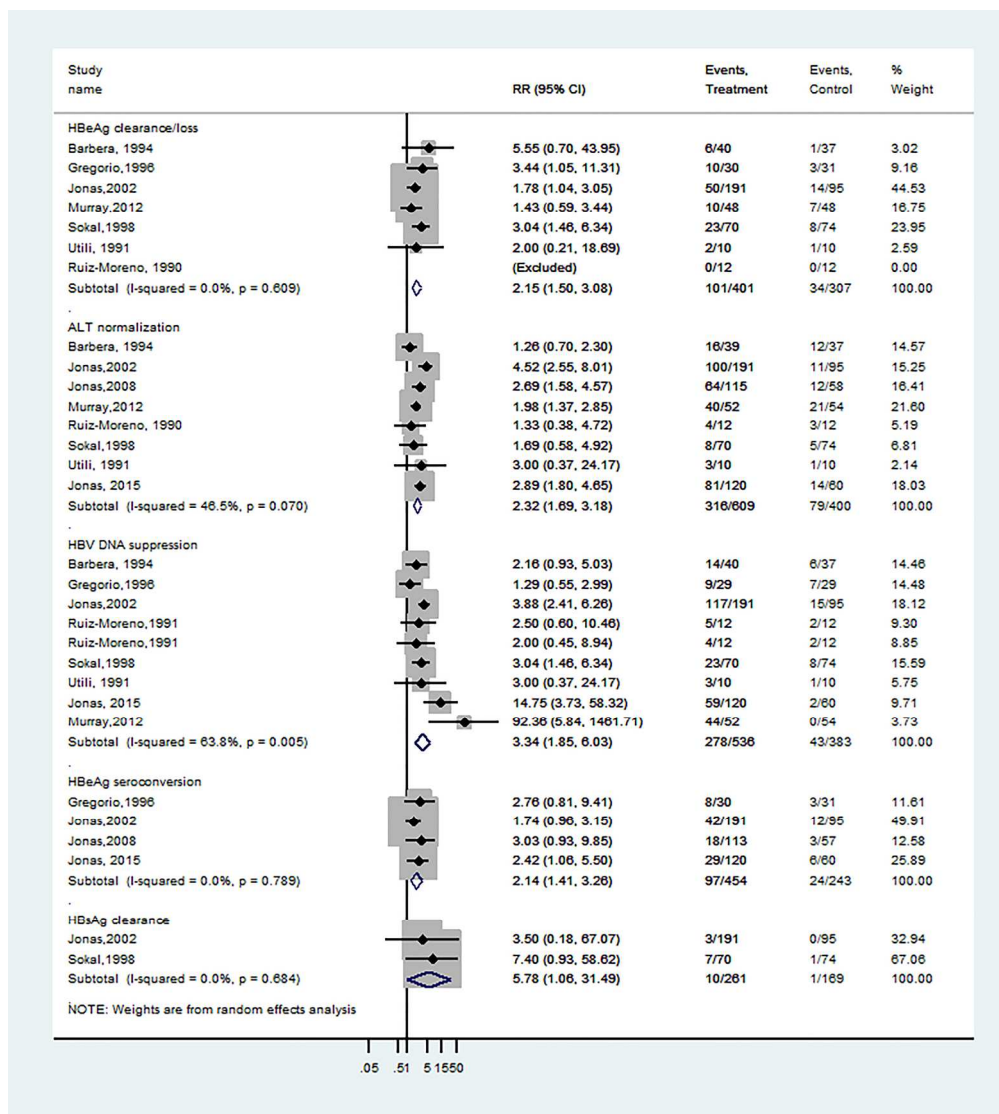


Figure 2: Forest plot of intermediate outcomes for antiviral therapy compared to control at post-treatment follow up < 12 months
277x307mm (300 x 300 DPI)



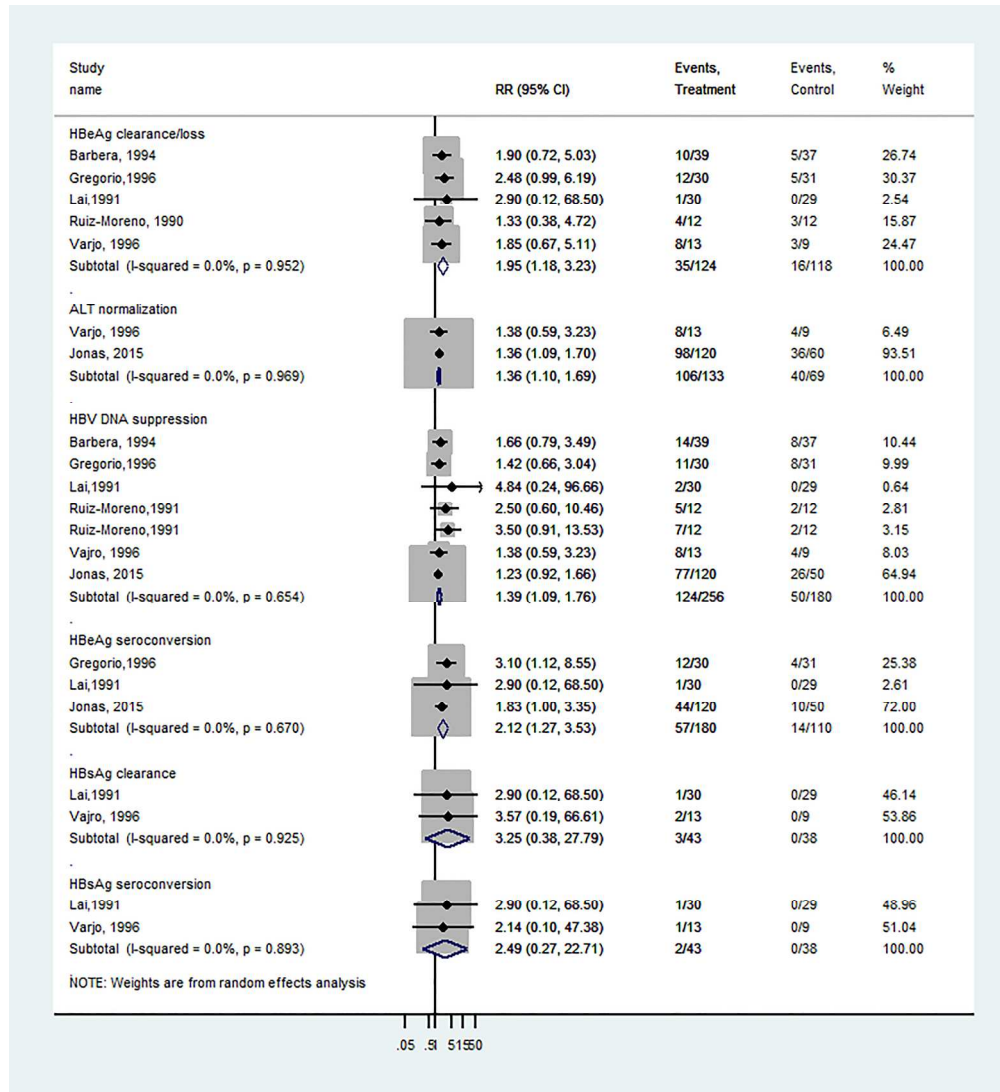


Figure 3: Forest plot of intermediate outcomes for antiviral therapy compared to control at post-treatment follow up ≥ 12 months
281x307mm (300 x 300 DPI)

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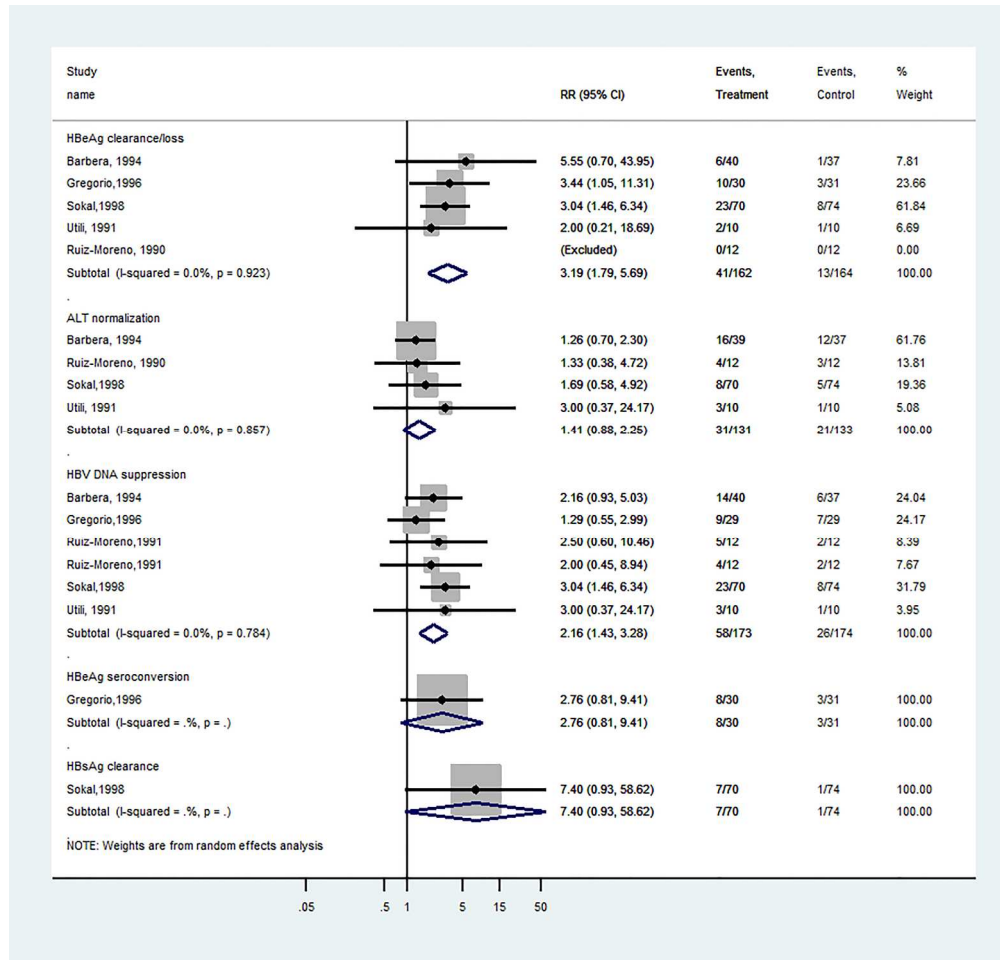


Figure 4: Forest plot of intermediate outcomes for IFN-alpha compared to control at post-treatment follow up < 12 months
324x310mm (300 x 300 DPI)

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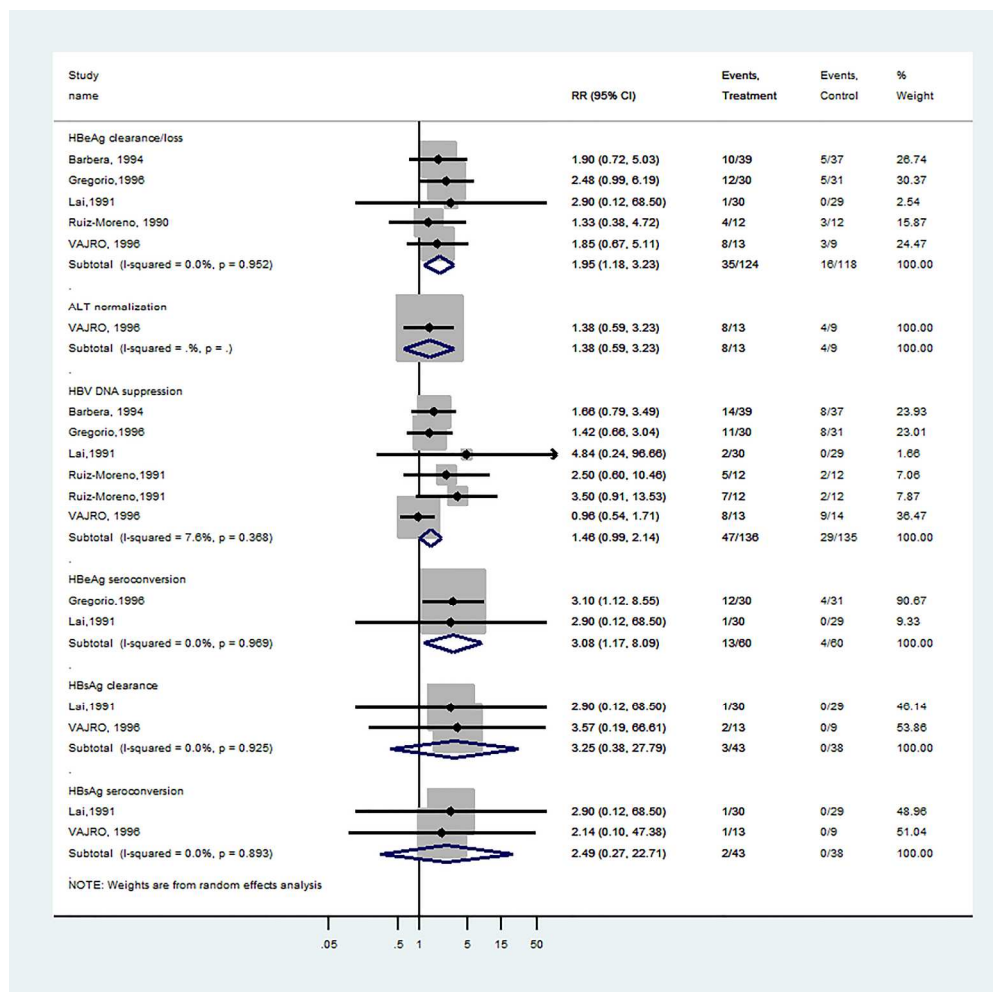


Figure 5: Forest plot of intermediate outcomes for IFN-alpha compared to control at post-treatment follow up ≥ 12 months
314x311mm (300 x 300 DPI)

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