

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

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Most individuals with chronic hepatitis B viral (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. We conducted a comprehensive search of multiple databases from 1988 to December 2, 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. In the 14 included studies, two 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 posttreatment follow-up <12 months, antiviral therapy compared to placebo improved alanine aminotransferase normalization (risk ratio [RR] = 2.3, 95% confidence interval [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 clearance (RR = 5.8, 95% CI 1.1-31.5). In RCTs with posttreatment follow-up ≥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), alanine aminotransferase 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 hepatitis B surface antigen clearance or seroconversion. *Conclusion:* In children with chronic HBV infection, antivirals compared to no antiviral therapy improve HBV DNA suppression and frequency of alanine aminotransferase normalization and HBeAg seroconversion. (HEPATOLOGY 2016;63:307-318)

Worldwide, most individuals with chronic hepatitis B viral (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 <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

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; RCT, randomized controlled trial; RR, risk ratio.

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antigen (HBeAg) in pregnant women. Perinatal transmission also occurs in nonendemic 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 <2% per year in children younger than 3 years of age and 4%-5% after age 3 and then rise during puberty. In contrast, children from nonendemic 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 none 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). HCC 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)- α 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 as much better agents are available, so they are less than ideal for children. Randomized phase 3 trials of pegylated IFN- α 2a and tenofovir in children with chronic HBV are under way. 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.

Materials and 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. The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses 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 coinfecting with hepatitis C, hepatitis D, or human immunodeficiency virus; patients receiving combination therapy, steroids, or chemotherapy/immunotherapy; liver transplant recipients; and hemodialysis patients. [Supporting Table S1](#) describes the detailed inclusion and exclusion criteria.

Search Strategy. The search strategy was designed and conducted by an experienced librarian (L.J.P.) 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 2, 2014. Controlled vocabulary supplemented with keywords was used to

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search for studies of antiviral therapy for hepatitis B in children. [Supporting Table S2](#) provides details of the search strategy. We conducted a manual search of bibliographies of the included studies and previous systematic reviews to identify relevant studies. Content experts from the American Association for the Study of Liver Diseases 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 texts of the included abstracts were retrieved and screened in duplicate. Disagreements were harmonized by consensus or arbitration by a third reviewer. We calculated interrater agreement (kappa) during the full text screening to observe the agreement between reviewers.

Data Extraction. Data extraction was done in duplicate 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, intervention 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. Quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation 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 (RRs) and 95% confidence intervals (CIs) using binomial distribution. We then pooled the log-transformed RRs using the DerSimonian and Laird¹⁴ random-effect method with the heterogeneity estimated from the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, we calculated the I^2 statistic, with $I^2 > 50\%$ 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

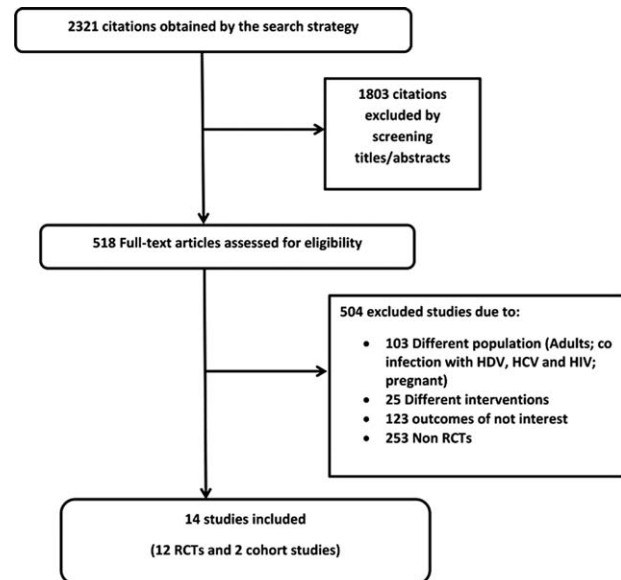


Fig. 1. The process of study selection.

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 (interrater agreement) for study selection was 0.75. Details of study selection and reasons for exclusion are described in Fig. 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- α with a 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).

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, eight studies evaluated IFN- α ¹⁹⁻²⁶ and one each evaluated lamivudine,²⁷ tenofovir,²⁸ adefovir,²⁹ and 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).

Any Antiviral Therapy Versus Control Results. Of the 12 RCTs that compared antiviral therapy to controls, five^{20,22,23,26,30} reported outcomes for both short (<12 months) and long (≥ 12 months) posttreatment follow-up durations, two^{19,25} included only longer (≥ 12 months) posttreatment follow-up, and five^{21,24,27-29} included only shorter (<12 months) follow-up. Two RCTs reported the

Table 1. Characteristics of Included Studies: Antiviral Versus Control Trials

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
Bortolotti et al., 1998 ¹⁷	Multicenter	IFN- α (3-5 MU/m ² three times/week for 3-6 months) Control	21	5.5 \pm 0.4	NR	NR	141.6 \pm 25.2	HBeAg-positive	Cohort
Fujisawa et al., 2004 ¹⁸	Japan	IFN- α (0.1 MU/kg/day \times 28 days)	117	5.5 \pm 0.4	NR	NR	153.6 \pm 38.4	HBeAg-positive	Cohort
Vajro et al., 1996 ¹⁹	Italy	IFN- α (10 MU/m ² body surface area intramuscularly, three times/week, in the evening, for 1 year)	13	6.9 \pm 2.4	7.2 \pm 7.1	238 \pm 197	48	HBeAg-positive	RCT
Barbera et al., 1994 ²⁰	Italy	Control IFN- α (7.5 MU/m ² three times/week for 6 months) IFN- α (3 MU/m ² three times/week for 6 months)	9 21 19	8.9 \pm 3.1 8.4 \pm 3.3 8.1 \pm 2.3	7.2 \pm 7 43% >6.7 21% >6.7	117 \pm 67 109.2 \pm 69 72.4 \pm 36	48 18 18	HBeAg-positive	RCT
Uttili et al., 1991 ²¹	Italy	Control IFN- α (3 MU intramuscularly three times/week for 12 months)	37 10	8.5 \pm 2.5 10 (6-14)	43% >6.7 6.3 (5.7-6.8)	72.4 \pm 37 138 \pm 95	18 18	HBeAg-positive	RCT
Ruiz-Moreno et al., 1991 ²²	Spain	Control IFN- α (10 MU three times/week for 24 weeks subcutaneously) IFN- α (5 MU three times/week for 24 weeks subcutaneously)	10 12 12	12 (6-14) 8.7 \pm 4.2 7.3 \pm 2.5	6.4 (5.7-6.6) 7.6 \pm 7.7 7.6 \pm 7.6	130 \pm 63 147 \pm 72 138 \pm 90	18 18 18	NR	RCT
Ruiz-Moreno et al., 1990 ²³	Spain	Control IFN- α (10 MU/m ² body surface, intramuscularly, three times/week for 3 months)	12 12	8.5 \pm 3.8 7.7 \pm 2.9	7.5 \pm 7.4 8.6 \pm 8.5	115 \pm 68 155 \pm 63	18 18	HBeAg-positive	RCT
Sokal et al., 1998 ²⁴	Multinational	Control IFN- α 2b (3 MU/m ² of body surface area three times/week for 1 week)	12 72	8.3 \pm 1.8 5.0 (1-17)	8.3 \pm 8.1 6.7 (<4.6-7.6)	149 \pm 122 3.2 (1.7-18.3)	18 48	HBeAg-positive	RCT
Lai et al., 1991 ²⁵	China	Control IFN- α (5×10^6 IU/m ² subcutaneously weekly for 16 weeks) Control	77 29 30	5.0 (1-17) 6.5 (4-16) 6 (3-15)	6.7 (<4.6-7.5) NR	3.7 (1.3-18.2) 12 (5-34) 9 (6-98)	48 24 24	HBeAg-positive	RCT

Table 1. Continued

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
Gregorio et al., 1996 ²⁶	Multicenter	IFN- α (5 MIU/m ² for 5 consecutive days during the induction phase, followed by three 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
Jonas et al., 2002 ²⁷	Multinational	Control	31	10.9 (2.5-15.1)	7.9 (6.7-9.04)	68 (35-266)	18	HBeAg-positive	RCT
		Control	9	8.9 \pm 3.1	7.2 \pm 7	117 \pm 67	48		
		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) \times UIN	24		
Murray et al., 2012 ²⁸	Europe and the United States	Control	191	8 (2-17)	8.3 (5.5-9.5)	2.3(0.3-22.1) \times UIN	24	HBeAg-positive	RCT
		Tenofovir (300 mg once daily for 72 weeks)	52	15.3 \pm 1.34	7.3 \pm 0.7	101 \pm 107.5	72		
Jonas et al., 2008 ²⁹	Multinational	Placebo	54	15.3 \pm 1.43	7.5 \pm 0.7	101 \pm 90	72	HBeAg-positive	RCT
		Adefovir dipivoxil (depend on the age and weight, dose not to exceed 10 mg/day)	115	10.8 \pm 4.3	8.04 \pm 0.2	111 \pm 81.6	6		
Jonas et al., 2015 ³⁰	Multinational	Placebo	58	10.7 \pm 3.9	7.9 \pm 0.3	99 \pm 52.8	6	HBeAg-positive	RCT
		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 \pm 0.45	8.1 \pm 0.1	107.1 \pm 5.4	24		
		Placebo	60	10.8 \pm 0.62	7.9 \pm 0.1	94.4 \pm 12.2	24		

Abbreviation: NR, not reported.

Table 2. Risk of Bias Assessment for RCTs: Antiviral Versus Control Trials

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
Vajro et al., 1996 ¹⁹	NR	NR	NR	Complete	None	None	High
Barbera et al., 1994 ²⁰	NR	NR	NR	Complete	None	None	High
Utili et al., 1991 ²¹	NR	NR	NR	Complete	None	None	High
Ruiz-Moreno et al., 1991 ²²	NR	NR	NR	Complete	None	None	High
Ruiz-Moreno et al., 1990 ²³	NR	NR	NR	Complete	None	None	High
Sokal et al., 1998 ²⁴	Random digit numbers	NR	NR	Complete	None	None	Moderate
Lai et al., 1991 ²⁵	NR	NR	NR	Complete	None	None	High
Gregorio et al., 1996 ²⁶	NR	NR	NR	Complete	None	None	High
Jonas et al., 2002 ²⁷	Centrally randomized	NR	Double blinded	Complete	None	None	Low
Murray et al., 2012 ²⁸	Centralized and stratified by age	Unclear	Unclear	Complete	None	None	Moderate
Jonas et al., 2008 ²⁹	Centrally randomized	NR	Double blinded	Complete	None	None	Low
Jonas et al., 2015 ³⁰	Sponsor-designated center through an interactive voice response system using a block size of 6	NR	Double blinded	Complete	None	None	Low

Abbreviation: NR, not reported.

short-term and long-term outcomes separately for lamivudine^{27,31} and adefovir.^{29,32}

In studies with posttreatment follow-up <12 months, meta-analysis (Fig. 2) demonstrated that antiviral therapy compared to placebo was more effective at improving ALT normalization (eight RCTs, RR = 2.3, 95% CI 1.7-3.2, $I^2 = 46.5\%$), HBeAg clearance/loss (seven RCTs, RR = 2.1, 95% CI 1.5-3.1, $I^2 = 0\%$), HBV DNA suppression (nine RCTs, RR = 3.3, 95% CI 1.9-6.1, $I^2 = 63.8\%$), HBeAg seroconversion (four RCTs, RR = 2.1, 95% CI 1.4-3.3, $I^2 = 0\%$), and HBsAg clearance (two RCTs, RR = 5.8, 95% CI 1.1-31.5, $I^2 = 0\%$). In studies with posttreatment follow-up ≥ 12 months (Fig. 3), antiviral therapy improved ALT normalization (two RCTs, RR = 1.4, 95% CI 1.1-1.7, $I^2 = 0\%$), HBeAg clearance/loss (five RCTs, RR = 2, 95% CI 1.9-3.2, $I^2 = 0\%$), HBV DNA suppression (seven RCTs, RR = 1.4, 95% CI 1.1-1.8, $I^2 = 0\%$), and HBeAg seroconversion (three RCTs, RR = 2.1, 95% CI 1.3-3.5, $I^2 = 0\%$). However, the short-term statistically significant difference did not persist after ≥ 12 months of follow-up for HBsAg clearance (two RCTs, RR = 3.3, 95% CI 0.4-27.8, $I^2 = 0\%$) and for HBsAg seroconversion (two 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.

Specific Antiviral Therapy Versus Control Results.

In studies (Fig. 4) with posttreatment follow-up <12 months, IFN- α compared to no treatment significantly improved HBeAg clearance/loss (four RCTs, RR = 3.2, 95% CI 1.8-5.7, $I^2 = 0\%$) and HBV DNA suppression (six RCTs, RR = 2.2, 95% CI 1.4-3.3, $I^2 = 0\%$) but did not significantly improve ALT normalization (four RCTs, RR = 1.4, 95% CI 0.9-2.3, $I^2 = 0\%$), HBeAg seroconversion (one RCT, RR = 2.8, 95% CI 0.8-9.4) or HBsAg clearance (one RCT, RR = 7.4, 95% CI 0.9-

58.6). In studies (Fig. 5) with posttreatment follow-up ≥ 12 months, IFN- α use was associated with improved HBeAg clearance/loss (five RCTs, RR = 2.0, 95% CI 1.9-3.2, $I^2 = 0\%$) and HBeAg seroconversion (two RCTs, RR = 3.1, 95% CI 1.2-8.1, $I^2 = 0\%$), but statistically significant differences were not observed for ALT normalization (one RCT, RR = 1.4, 95% CI 0.6-1.9), HBV DNA suppression (six RCTs, RR = 1.5, 95% CI 0.99-2.1, $I^2 = 7.6\%$), HBsAg clearance (two RCTs, RR = 3.3, 95% CI 0.4-27.8, $I^2 = 0\%$), or HBsAg seroconversion (two 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 (one RCT, RR = 4.5, 95% CI 2.3-9.1), HBeAg clearance/loss (one RCT, RR = 1.8, 95% CI 1-3.1), and HBV DNA suppression (one RCT, RR = 3.9, 95% CI 2.4-6.3) but not HBeAg seroconversion (two RCTs, RR = 1.7, 95% CI 0.96-3.2) or HBsAg clearance (one RCT, RR = 3.5, 95% CI 0.2-67.1) at the end of 48 weeks of 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.

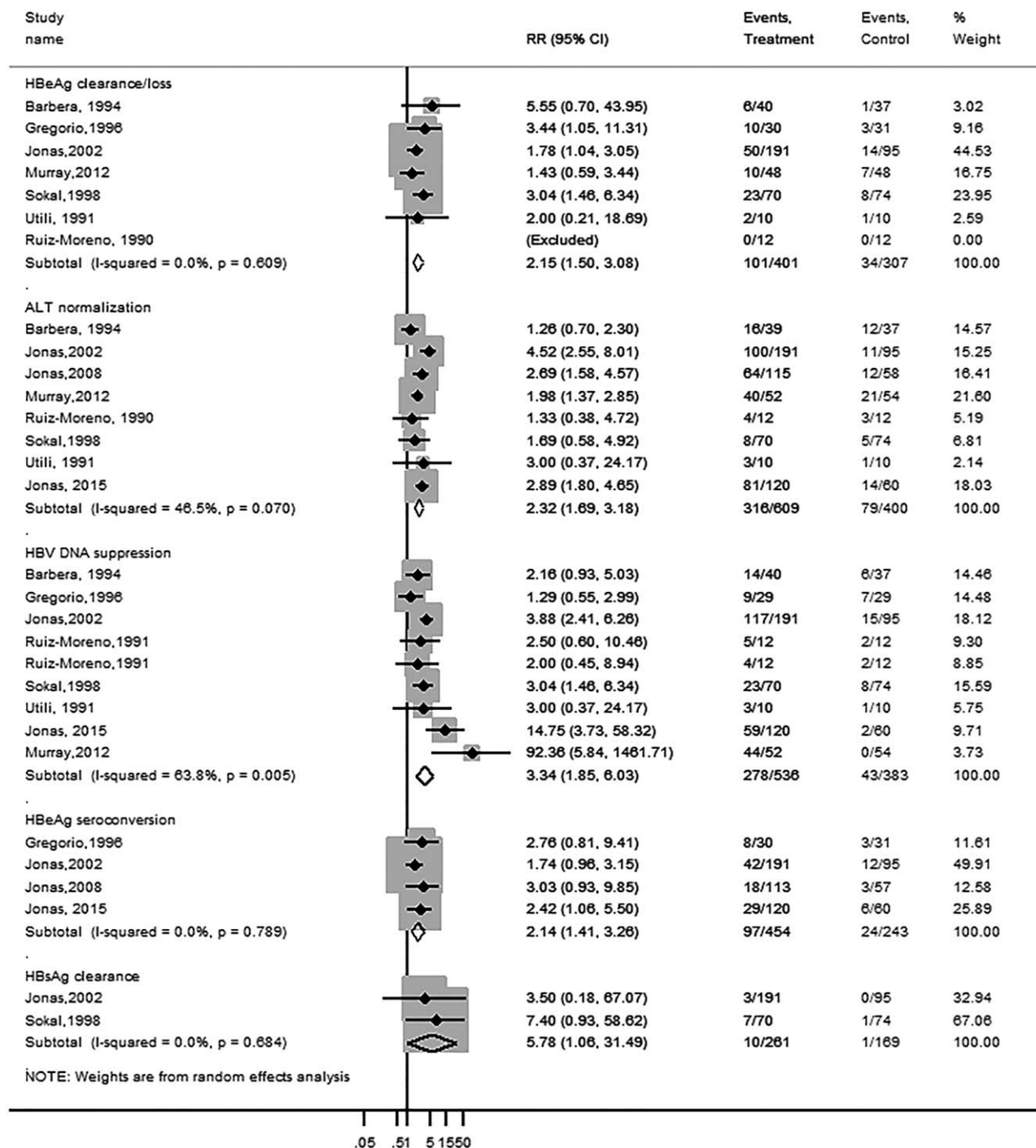


Fig. 2. Forest plot of intermediate outcomes for antiviral therapy compared to control at posttreatment follow-up <12 months.

One RCT²⁸ 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

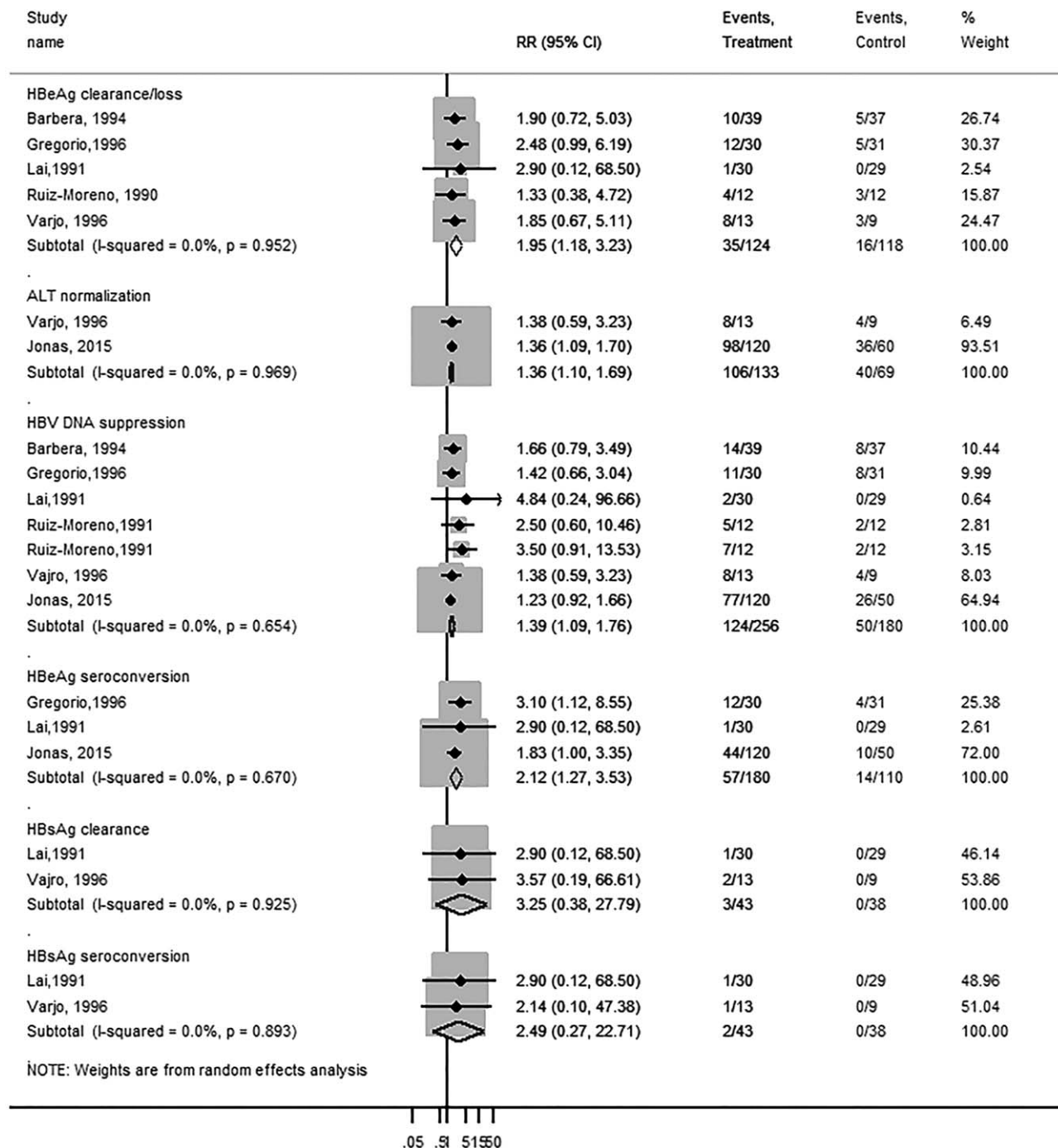


Fig. 3. Forest plot of intermediate outcomes for antiviral therapy compared to control at posttreatment follow-up ≥ 12 months.

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 [Supporting Table S3](#).

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

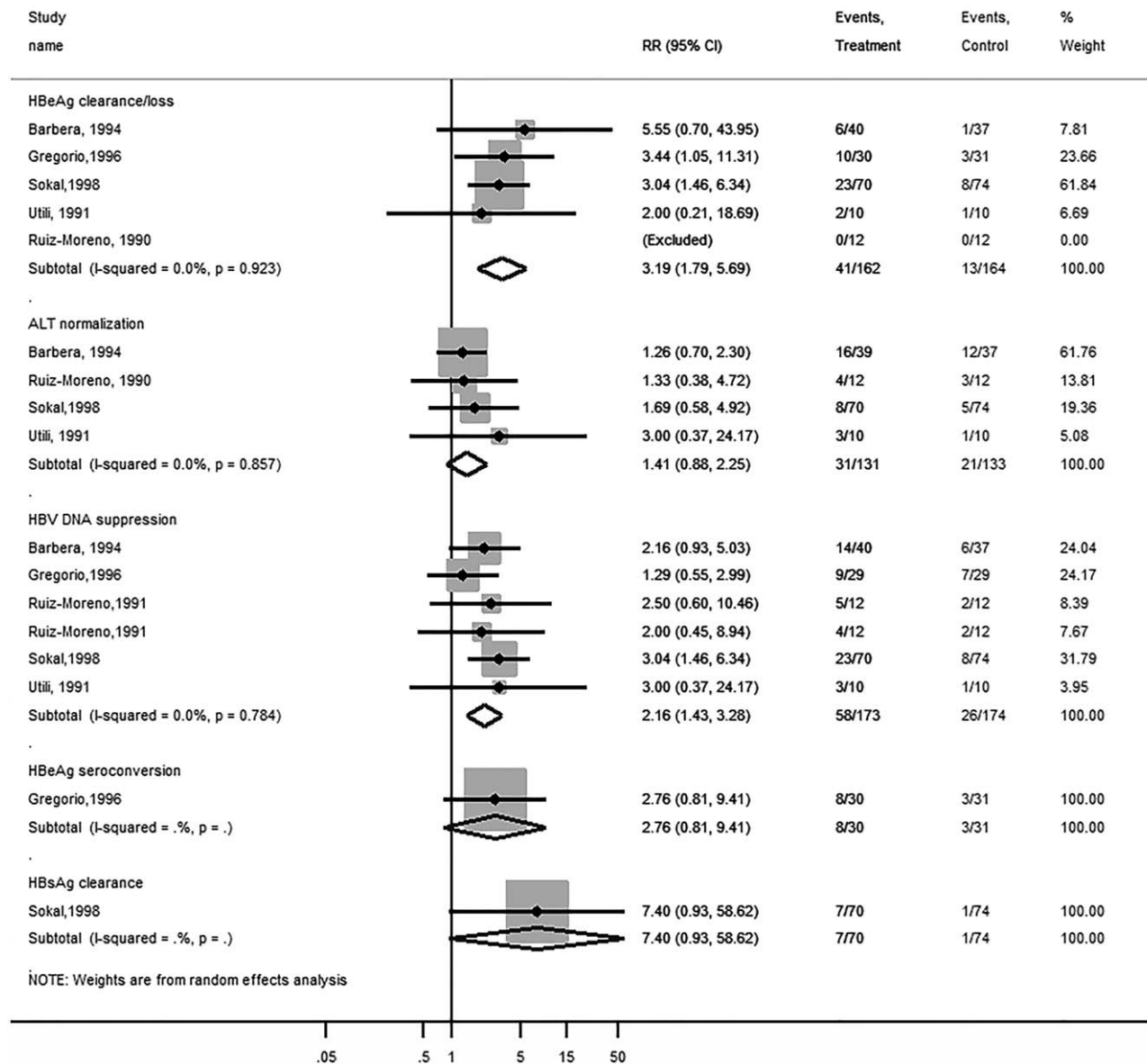


Fig. 4. Forest plot of intermediate outcomes for IFN-α compared to control at posttreatment follow-up <12 months.

confidence in this evidence is limited by the short duration of follow-up, certain methodological limitations that relate to randomization and blinding processes, and 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 as 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

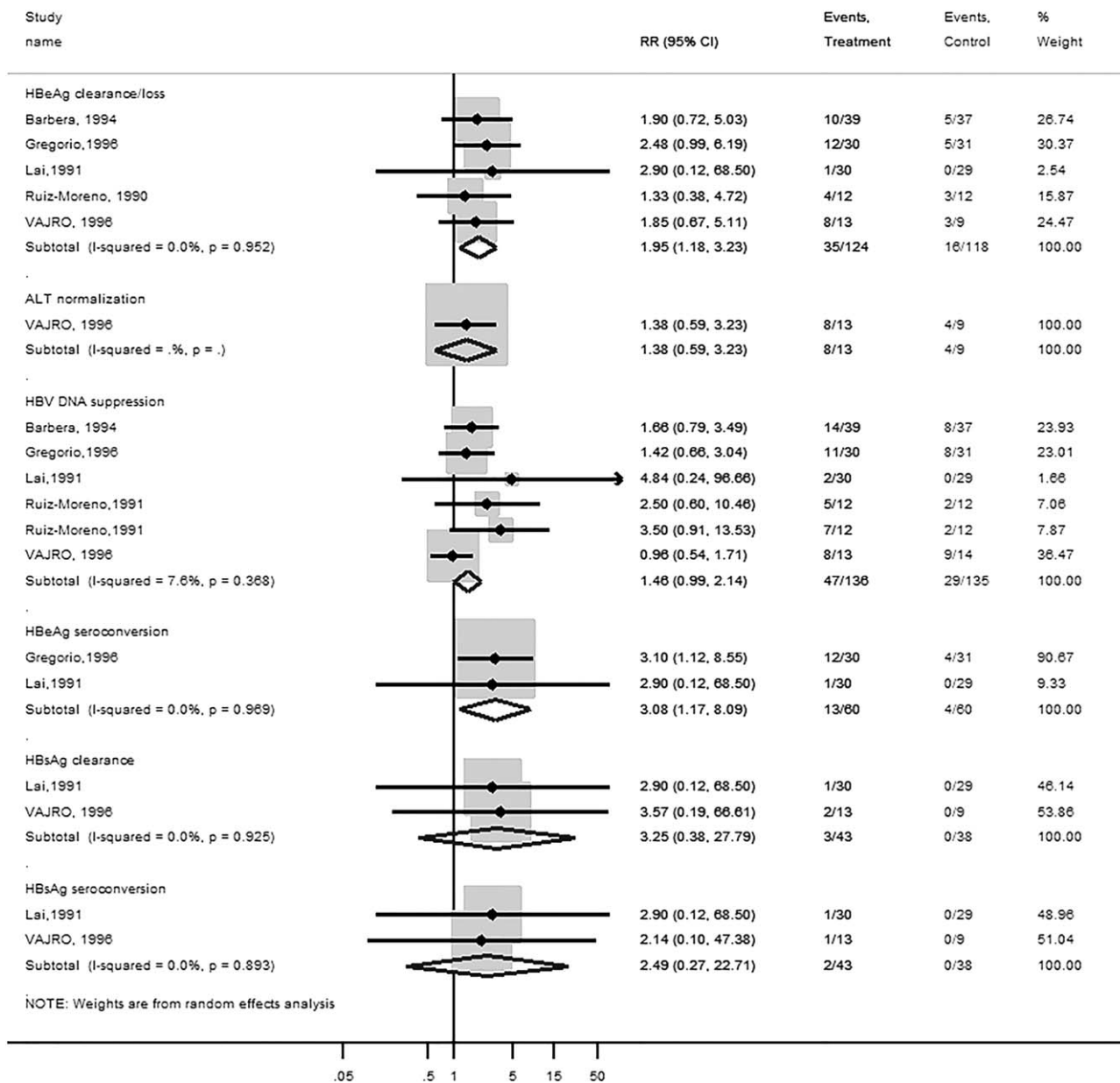


Fig. 5. Forest plot of intermediate outcomes for IFN-α compared to control at posttreatment follow-up ≥12 months.

side effect profile similar to that seen in adults, and transient effects on body weight and growth have been observed³³; 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,³⁰ 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 1.5-2 times the upper limit of normal 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 upper limit of normal 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 as entecavir has

recently been shown to be safe and effective in this population and data regarding pegylated IFN 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. Patients' and parents' values and preferences should be incorporated into shared decision-making about treatment. Prolonged treatment with nucleoside or nucleotide analogues in children who are in the immune-tolerant stage has not been associated with substantial benefit and carries a risk of developing antiviral drug resistance, both to the agent chosen and to 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.

References

- McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985;151:599-603.
- Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. *HEPATOLOGY* 1988;8:1130-1133.
- Bortolotti F, Cadrobbi P, Crivellaro C, Guido M, Rugge M, Noventa F, et al. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. *Gastroenterology* 1990;99:805-810.
- Bortolotti F, Calzia R, Cadrobbi P, Giacchini R, Ciravegna B, Armigliato M, et al. Liver cirrhosis associated with chronic hepatitis B virus infection in childhood. *J Pediatr* 1986;108:224-227.
- Cheah PL, Looi LM, Lin HP, Yap SF. Childhood primary hepatocellular carcinoma and hepatitis B virus infection. *Cancer* 1990;65:174-176.
- Giacchino R, Navone C, Facco F, Giambartolomei G, Pontisso P, Callea F. HBV-DNA-related hepatocellular carcinoma occurring in childhood. Report of three cases. *Dig Dis Sci* 1991;36:1143-1146.
- Hsu HC, Wu MZ, Chang MH, Su IJ, Chen DS. Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 51 cases strongly associated with rapid development of liver cirrhosis. *J Hepatol* 1987;5:260-267.
- Pontisso P, Basso G, Perilongo G, Morsica G, Cecchetto G, Ruvoletto MG, et al. Does hepatitis B virus play a role in primary liver cancer in children of Western countries? *Cancer Detect Prev* 1991;15:363-368.
- Tanaka T, Miyamoto H, Hino O, Kitagawa T, Koike M, Iizuka T, et al. Primary hepatocellular carcinoma with hepatitis B virus-DNA integration in a 4-year-old boy. *Hum Pathol* 1986;17:202-204.
- Livingston SE, Simonetti JB, McMahon BJ, Bulkow LR, Hurlburt KJ, Homan CE, et al. Hepatitis B virus genotypes in Alaska Native people with hepatocellular carcinoma: preponderance of genotype F. *J Infect Dis* 2007;195:5-11.
- Jonas MM, Block JM, Haber BA, Karpen SJ, London WT, Murray KF, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. *HEPATOLOGY* 2010;52:2192-2205.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med* 2009;3:e123-e130.
- Murad MH, Montori VM, Ioannidis JP, Jaeschke R, Devereaux PJ, Prasad K, et al. How to read a systematic review and meta-analysis and apply the results to patient care: users' guides to the medical literature. *JAMA* 2014;312:171-179.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-188.
- Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
- Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
- Bortolotti F, Jara P, Crivellaro C, Hierro L, Cadrobbi P, Frauca E, et al. Outcome of chronic hepatitis B in Caucasian children during a 20-year observation period. *J Hepatol* 1998;29:184-190.
- Fujisawa T, Inui A, Sogo T, Komatsu H. Long-term history of chronic hepatitis B virus infection in children. [in Japanese] *Nihon Rinsho* 2004;62(Suppl. 8):303-308.
- Vajro P, Tedesco M, Fontanella A, De Vincenzo A, Vecchione R, Ammendola R, et al. Prolonged and high dose recombinant interferon alpha-2b alone or after prednisone priming accelerates termination of active viral replication in children with chronic hepatitis B infection. *Pediatr Infect Dis J* 1996;15:223-231.
- Barbera C, Bortolotti F, Crivellaro C, Coscia A, Zancan L, Cadrobbi P, et al. Recombinant interferon-alpha 2a hastens the rate of HBeAg clearance in children with chronic hepatitis B. *HEPATOLOGY* 1994;20:287-290.
- Utili R, Sagnelli E, Galanti B, Aprea L, Cesaro G, Digilio L, et al. Prolonged treatment of children with chronic hepatitis B with recombinant alpha 2a-interferon: a controlled, randomized study. *Am J Gastroenterol* 1991;86:327-330.
- Ruiz-Moreno M, Rua MJ, Molina J, Moraleta G, Moreno A, Garcia-Aguado J, et al. Prospective, randomized controlled trial of interferon-alpha in children with chronic hepatitis B. *HEPATOLOGY* 1991;13:1035-1039.
- Ruiz Moreno M, Jimenez J, Porres JC, Bartolome J, Moreno A, Carreno V. A controlled trial of recombinant interferon-alpha in Caucasian children with chronic hepatitis B. *Digestion* 1990;45:26-33.
- Sokal EM, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. *Gastroenterology* 1998;114:988-995.
- Lai CL, Lin HJ, Lau JN, Flok AS, Wu PC, Chung HT, et al. Effect of recombinant alpha 2 interferon with or without prednisone in Chinese HBsAg carrier children. *QJM* 1991;78:155-163.
- Gregorio GV, Jara P, Hierro L, Diaz C, de la Vega A, Vegnente A, et al. Lymphoblastoid interferon alfa with or without steroid pretreatment in children with chronic hepatitis B: a multicenter controlled trial. *HEPATOLOGY* 1996;23:700-707.
- Jonas MM, Mizerski J, Badia IB, Areias JA, Schwarz KB, Little NR, et al. Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002;346:1706-1713. Erratum in: *N Engl J Med* 2002;347:955.
- Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *HEPATOLOGY* 2012;56:2018-2026.
- Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. *HEPATOLOGY* 2008;47:1863-1871.

30. Jonas MM, Chang M-H, Sokal E, Schwarz KB, Kelly D, Kim KM, et al. Randomized controlled trial of entecavir versus placebo in children with HBeAg-positive chronic hepatitis B. *HEPATOLOGY* 2015; doi: 10.1002/hep.28015.
31. Jonas MM, Little NR, Gardner SD; International Pediatric Lamivudine Investigator Group. Long-term lamivudine treatment of children with chronic hepatitis B: durability of therapeutic responses and safety. *J Viral Hepat* 2008;15:20-27.
32. Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, et al. Efficacy and safety of long-term adefovir dipivoxil therapy in children with chronic hepatitis B infection. *Pediatr Infect Dis J* 2012;31: 578-582.
33. Comanor L, Minor J, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, et al. Impact of chronic hepatitis B and interferon-alpha therapy on growth of children. *J Viral Hepat* 2001;8:139-147.
34. Sokal EM, Kelly DA, Mizerski J, Badia IB, Areias JA, Schwarz KB, et al. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. *HEPATOLOGY* 2006;43:225-232.

Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.28278/supinfo.