

Antiviral Therapy in Chronic Hepatitis B Viral Infection During Pregnancy: A Systematic Review and Meta-Analysis

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Perinatal or mother-to-child transmission (MTCT) of hepatitis B virus (HBV) remains the major risk factor for chronic HBV infection worldwide. In addition to hepatitis B immune globulin and vaccination, oral antiviral therapies in highly viremic mothers can further decrease MTCT of HBV. We conducted a systematic review and meta-analysis to synthesize the evidence on the efficacy and maternal and fetal safety of antiviral therapy during pregnancy. A protocol was developed by the American Association for the Study of Liver Diseases guideline writing committee. We searched multiple databases for controlled studies that enrolled pregnant women with chronic HBV infection treated with antiviral therapy. Outcomes of interest were reduction of MTCT and adverse outcomes to mothers and newborns. Study selection and data extraction were done by pairs of independent reviewers. We included 26 studies that enrolled 3622 pregnant women. Antiviral therapy reduced MTCT, as defined by infant hepatitis B surface antigen seropositivity (risk ratio = 0.3, 95% confidence interval 0.2-0.4) or infant HBV DNA seropositivity (risk ratio = 0.3, 95% confidence interval 0.2-0.5) at 6-12 months. No significant differences were found in the congenital malformation rate, prematurity rate, and Apgar scores. Compared to control, lamivudine or telbivudine improved maternal HBV DNA suppression at delivery and during 4-8 weeks' postpartum follow-up. Tenofovir showed improvement in HBV DNA suppression at delivery. No significant differences were found in postpartum hemorrhage, cesarean section, and elevated creatinine kinase rates. **Conclusions:** Antiviral therapy improves HBV suppression and reduces MTCT in women with chronic HBV infection with high viral load compared to the use of hepatitis B immunoglobulin and vaccination alone; the use of telbivudine, lamivudine, and tenofovir appears to be safe in pregnancy with no increased adverse maternal or fetal outcome. (HEPATOLOGY 2016;63:319-333)

Chronic hepatitis B viral (HBV) infection remains an important global health problem. Up to 600,000 of the approximately 240 million carriers worldwide die annually due to chronic hepatitis B (CHB)-related disease.¹ Perinatal or mother-to-child transmission (MTCT) is the most common form of transmission of HBV in many high-prevalence areas^{2,3} and may occur in up to 90% of mothers who are hepatitis B surface antigen (HBsAg)-positive and hepatitis B e antigen (HBeAg)-positive in the absence of

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; RCT, randomized controlled trial; RR, risk ratio.

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prophylaxis.⁴ This high rate of transmission may be partially due to the high proportion of mothers with active replication and HBeAg positivity during reproductive years,⁵⁻⁸ particularly in Asian countries and regions of the world where HBV genotype C is found⁹ as MTCT is associated with high maternal viral load (HBV DNA >10⁶ IU/mL).¹⁰⁻¹³ Universal prenatal testing of women is therefore recommended, as are hepatitis B vaccination and hepatitis B immunoglobulin administration starting at birth to prevent transmission to the newborn.

Women in their childbearing years with CHB may need antiviral therapy independent of its impact on MTCT if they have immune active HBV infection. Accordingly, data on the safety of antivirals during pregnancy, and especially their impact on potential teratogenicity, are of paramount importance when counseling pregnant patients with CHB on risks and benefits to their offspring.

Antiviral therapies for CHB have advanced markedly in the last decade. The newer, more potent nucleos(t)ide analogues durably suppress HBV viremia in most patients. Evolving data for CHB patients show low (0%-1%) rates of viral resistance and breakthrough after up to 6 years of entecavir or tenofovir monotherapy.^{14,15} The benefits of long-term viral suppression include slowing of liver disease progression and reversal of fibrosis and cirrhosis.¹⁶⁻¹⁸ Although no HBV therapies are currently approved for use in pregnancy, women being treated for CHB may become pregnant. Moreover, pregnant women in the immune tolerant phase of CHB with high HBV DNA levels (>10⁶ IU/mL) may want to be considered for antiviral therapy to reduce the HBV DNA level and decrease the risk of MTCT that can occur despite neonatal immunoprophylaxis.^{10,19} Safety data on the use of anti-HBV therapies are largely derived from human immunodeficiency virus (HIV)-positive mothers studied in the Antiretroviral Pregnancy Registry, which do not report any adverse impact of lamivudine or tenofovir use.²⁰ However, the use of antiviral therapies in pregnancy is controversial, and knowledge about the harm and benefit ratio is not widely disseminated among hepatologists and other providers including those specializing in women's health. Therefore, the American Association for the Study of Liver

Diseases (AASLD) made this issue a priority for clinical practice guideline development and evidence synthesis. We performed a systematic review and meta-analysis to compare the effect of oral HBV therapy (lamivudine, entecavir, telbivudine, or tenofovir) on MTCT prevention, HBV DNA suppression, and maternal and fetal safety including major birth defect rates.

Materials and Methods

This systematic review follows a protocol developed by a guideline writing group from the AASLD and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.²¹

Eligibility Criteria. We included controlled or comparative studies that enrolled pregnant women diagnosed with chronic HBV infection (characterized by the presence of HBsAg for more than 6 months), who received antiviral therapy and reported the outcomes of interest, including prevention of MTCT of HBV, clinical efficacy, and adverse outcomes from antiviral therapy to both mothers and newborns. Both English and non-English-language studies were included. We excluded studies that enrolled infants who did not receive immunization during the first week postpartum; studies of patients coinfecting with hepatitis C, hepatitis D, or HIV; patients receiving steroids, chemotherapy/immunotherapy, liver transplantation, and hemodialysis; and uncontrolled studies or studies published as abstracts only.

Search Strategy. A comprehensive search of Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus was conducted from early 1988 to September 11, 2014. The search strategy was designed and conducted by an experienced librarian (L.J.P.) with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of antivirals for hepatitis B in pregnancy. Details of the search strategy are available in [Supporting Table 1](#). A manual search of bibliographies of the included studies and relevant systematic reviews was conducted. Content experts from the AASLD were also queried for potential references.

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Study Selection. Two independent reviewers screened titles and abstracts for potential eligibility in duplicate using an online reference management system (DistillerSR; Evidence Partners, Inc.). Included abstracts were then reviewed in full text following the same procedure. Disagreements were reconciled by consensus or by a third reviewer.

Data Extraction. For each study, data extraction was done in duplicate using a standardized, pretested form. A third reviewer compared data and resolved inconsistencies by referring to the full text of the articles. We extracted the following data from each study: study characteristics, patient baseline characteristics, intervention details, and outcomes of interest.

Outcomes. We were interested in the following outcomes: infant outcomes including the risk of MTCT transmission, defined by HBsAg seropositivity at 6-12 months or HBV DNA positivity at 6-12 months; Apgar score (1 minute); prematurity rate; and congenital malformation rate. Maternal outcomes included HBV DNA suppression, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, cesarean section rate, postpartum hemorrhage rate, and elevated creatine kinase.

Risk of Bias Assessment. Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane Risk of Bias assessment tool and the Newcastle-Ottawa Scale for randomized controlled trials (RCTs) and observational studies, respectively. The 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.²²

Statistical Analysis. For dichotomized outcomes, we calculated the risk ratio (RR) and 95% confidence intervals (CIs) using binomial distribution. We then pooled the log-transformed RRs using the DerSimonian and Laird random-effect models and estimated heterogeneity using the Mantel-Haenszel model. For continuous outcomes, we calculated the weighted difference in means between the baseline and the longest duration of follow-up for each study and the pooled effect size using the DerSimonian and Laird random-effect model. To measure the overall heterogeneity across the included studies, we used the I^2 statistic, where $I^2 > 50\%$ suggests high heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). We planned to explore the impact of publication bias using the Egger regression asymmetry test

and constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low.²³

Results

The initial search resulted in 734 citations and three systematic reviews^{19,24,25} that included the China Biological Medicine Database and summarized additional studies published in Chinese. We eventually included 26 studies. The average weighted kappa for study selection was 0.82. The study selection process and reasons for exclusions are depicted in Fig. 1.

Characteristics of the Included Studies. Twenty-six studies that enrolled a total of 3622 pregnant women were included in the analysis: 10 studies²⁶⁻³⁵ were RCTs and 16 studies³⁶⁻⁵¹ were nonrandomized studies. Most of the studies (92%) were conducted in China, and none were conducted in the United States. Treatment started in the second or third trimester with an average baseline HBV DNA level of 7.63 log₁₀ IU/mL and an average baseline ALT level of 37.7 U/L. In these studies, all infants received hepatitis B vaccine at birth. Table 1 summarizes the characteristics of the studies.

Among the included studies, 11 compared lamivudine versus control, nine^{26,35,36,42-44,48,49,51} compared telbivudine versus control, two^{36,51} compared lamivudine versus telbivudine, three^{37,38,50} compared tenofovir versus control, and another³⁷ compared tenofovir versus lamivudine.

Five RCTs^{27-29,31,34} were considered to have low risk of bias, while five studies^{26,30,32,33,35} were considered to have a high risk of bias due to unclear/unreported methods of randomization, allocation concealment, blinding, or incomplete outcome data reporting. For nonrandomized studies, the overall methodological quality and features were adequate or appropriate as 60% of the studies reported adequate patient selection methods, comparable study groups, and adequate outcome measures and follow-up data. Tables 2 and 3 include detailed descriptions of the risk of bias assessment.

Infant Outcomes. Use of any antiviral therapy compared to control in pregnant women reduced the likelihood of MTCT as defined by infant HBsAg seropositivity (eight RCTs, RR = 0.3, 95% CI 0.2-0.4, $I^2 = 63.9\%$) or infant HBV DNA positivity (five RCTs, RR = 0.3, 95% CI 0.2-0.5, $I^2 = 47.2\%$) at 6-12 months (Fig. 2). Use of any antiviral compared to control reduced the risk of infant HBsAg seropositivity and HBV DNA positivity by 13.4% and 18.7%, respectively. The quality of evidence was moderate to low, rated down due to risk of bias. This significant reduction persisted when comparing individual drugs versus

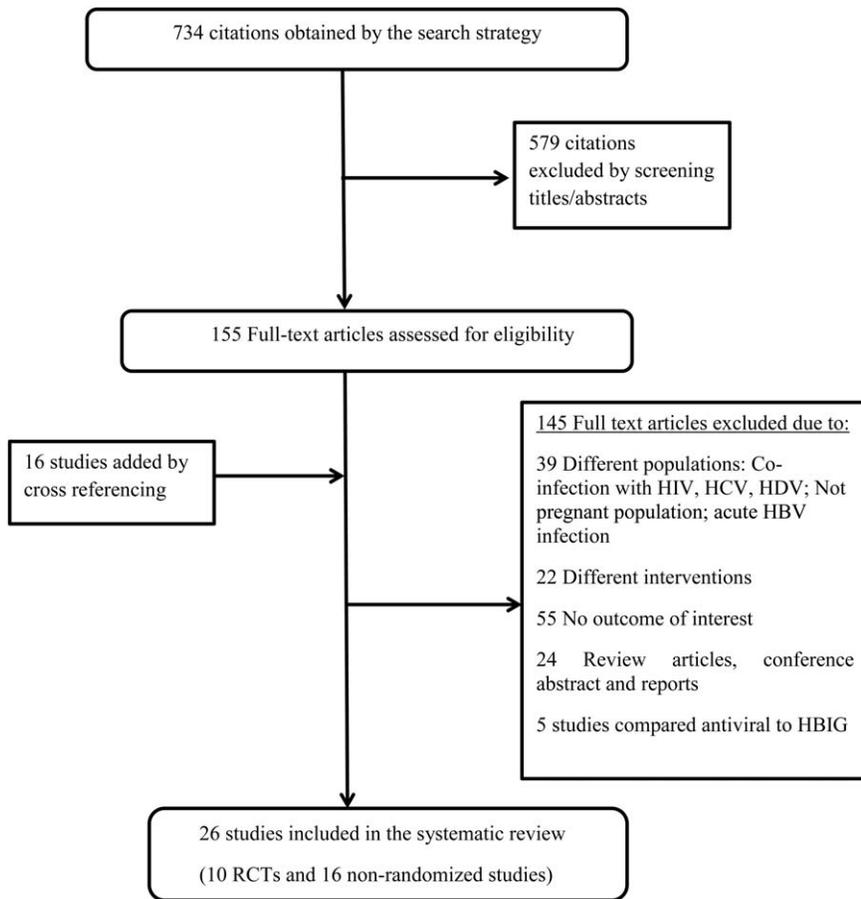


Fig. 1. The study selection process. Abbreviations: HBIG, hepatitis B immunoglobulin; HCV, hepatitis C virus; HDV, hepatitis D virus.

control at 6-12 months after birth. Lamivudine (Fig. 3) reduced infant HBsAg seropositivity by 11.7% (five RCTs, RR = 0.3, 95% CI 0.2-0.6, $I^2 = 42.4\%$) and infant HBV DNA positivity by 21.2% (three RCTs, RR = 0.3, 95% CI 0.2-0.6, $I^2 = 47.9\%$). Telbivudine also reduced infant HBsAg seropositivity by 15.8% (four RCTs, RR = 0.2, 95% CI 0.1-0.5, $I^2 = 0\%$) and infant HBV DNA positivity by 16.2% (two RCTs, RR = 0.1, 95% CI 0.03-0.6, $I^2 = 62.4\%$) compared to the control group (Fig. 4).

In three nonrandomized studies,^{37,38,50} tenofovir versus control (Fig. 5) reduced infant HBsAg seropositivity by 15.8% at 6-12 months' follow-up (RR = 0.2, 95% CI 0.1-0.7, $I^2 = 0\%$).

Compared to lamivudine, telbivudine (one study, RR = 1, 95% CI 0.7-1.5) and tenofovir (one study, RR = 2.93, 95% CI 0.12-70.08) showed no statistically significant reduction in infant HBsAg seropositivity at 6-12 months.

When comparing any antiviral therapy versus control for fetal harms, no statistically significant difference was found in any of the non-RCTs reporting on congenital malformation rate, prematurity rate, and Apgar scores (Fig. 6). The quality of the evidence of infant outcomes

was moderate to low, down-rated due to risk of bias and imprecision.

Maternal Outcomes. Compared to control, lamivudine improved maternal HBV DNA suppression before delivery (one cohort, RR = 57.1, 95% CI 3.5-921.4) and during 4-8 weeks' postpartum follow-up (two cohorts, RR = 70.9, 95% CI 8.5-590, $I^2 = 12.2\%$). No significant difference was found in maternal ALT normalization.

In studies comparing telbivudine versus control, telbivudine showed improved maternal HBV DNA suppression at delivery (three cohorts, RR = 52.8, 95% CI 10.7-261.8, $I^2 = 0\%$), at 4 weeks postpartum (two cohorts, RR = 102, 95% CI 14.4-722.8, $I^2 = 0\%$), and at 28 weeks postpartum (one cohort, RR = 1.5, 95% CI 1.2-1.8). When compared to control, pregnant women receiving telbivudine consistently had improved maternal ALT normalization at delivery (two cohorts, RR = 1.5, 95% CI 1.2-1.8, $I^2 = 0\%$), at 4 weeks postpartum (one cohort, RR = 1.6, 95% CI 1.1-2.3), and at 28 weeks postpartum (one cohort, RR = 1.3, 95% CI 1.04-1.6). Telbivudine also significantly increased maternal HBeAg loss at delivery (two cohorts, RR = 1.7, 95% CI 1.3-2.2, $I^2 = 0\%$), at 4 weeks postpartum

Table 1. Characteristics of the Included Studies

Author, Year	Interventions	Participants (Mothers) (N)	Country	Age (Years)	Baseline HBV DNA Level (Log ₁₀ IU/mL)	Baseline ALT Level (U/L)	Treatment Start (Gestational Weeks)	Treatment Discontinuation (Postpartum Weeks)	HBIG + Vaccine (Infants)	Study Design
Zhang and Wang, 2009 ²⁶	Telbivudine Control group	31 30	China	20-40 20-40	7.4 ± 0.8 7.5 ± 0.5	NR NR	32-36 NA	NR NA	All	RCT
Xu et al., 2009 ²⁷	Lamivudine	89	China	26 (19-32)	8.6 ± 0.2	0.4 (0.1-5.3) ×ULN	32	4	HBV vaccine with or without HBIG	RCT
	Control group	61		25 (20-36)	8.7 ± 0.2	0.4 (0.1-6) ×ULN	NA	NA		
Yang et al., 2008 ²⁸	Lamivudine	20	China	20-40	NR	NR	28	4	All	RCT
Li et al., 2003 ²⁹	Control group	20		20-40	NR	NR	NA	NA		
	Lamivudine	43	China	20-40	7.5 ± 0.5	NR	28	4	All	RCT
Zhang, 2010 ³⁰	Control group	52	China	20-40	7.1 ± 1.3	NR	NA	NA	All	RCT
	Lamivudine	50	China	NR	6.8 ± 0.9	NR	28	4	All	RCT
Shi et al., 2009 ³¹	Control group	50	China	NR	6.9 ± 1.7	NR	NA	NA	All	RCT
	Lamivudine	49	China	NR	7.2 ± 1.9	NR	28	4	All	RCT
Guo et al., 2008 ³²	Control group	43	China	NR	6.4 ± 2.1	NR	NA	NA	All	RCT
	Lamivudine	70	China	NR	NR	NR	28	4	All	RCT
Xiang et al., 2007 ³³	Control group	40	China	NR	NR	NR	NA	NA	All	RCT
	Lamivudine	21	China	NR	8.0 ± 1.2	NR	28	4	All	RCT
Shi et al., 2005 ³⁴	Control group	18	China	NR	7.2 ± 0.8	NR	NA	NA	All	RCT
	Lamivudine	21	China	NR	8.7 ± 0.7	NR	28	4	All	RCT
Guo et al., 2011 ³⁵	Control group	18	China	NR	8.9 ± 1.1	NR	NA	NA	All	RCT
	Telbivudine	28	China	NR	7.7 ± 4.6	NR	28	4	All	RCT
Zhang et al., 2014 ³⁶	Control group	26	China	NR	7.9 ± 3.5	NR	NA	NA	All	RCT
	Telbivudine	252	China	29.8 ± 6.3	6.9 ± 0.4	30.1 ± 27.9	28-30	4	All	Prospective, open-label, interventional trial
Greenup et al., 2014 ³⁷	Lamivudine	51	China	28.4 ± 7.1	6.9 ± 0.4	39.7 ± 26.4	28-30	4	All	
	Control group	352	Australia	28.9 ± 4.6	6.8 ± 0.5	29.5 ± 20.7	NA	NA	All	Cohort study
	Tenofovir	58		30.0 ± 8.5	7.9 ± 0.8	28 (22-36)	32	12	All	
	Lamivudine	52		28.0 ± 5.3	7.7 ± 0.6	22 (18-30)	32	4	All	
Celen et al., 2013 ³⁸	Control group	20	Turkey	28.0 ± 5.0	8 ± 0.04	25 (17-31)	NA	NA	All	Retrospective study
	Tenofovir	21		28.2 ± 4.1	8.3	56 (22-71)	18-27	4	All	
Jiang et al., 2012 ³⁹	Control group	24	China	26.9 ± 2.9	8.3	52 (19-77)	NA	NA	All	Cohort study
	Lamivudine	164	China	27.3 ± 4.4	7.8 ± 0.8	39.6 ± 26.0	24-32	At delivery	All	
Chen et al., 2012 ⁴⁰	Control group	92	China	26.4 ± 3.2	7.9 ± 0.6	42.2 ± 0.4	NA	NA	All	Cohort study
	Lamivudine	75	China	NR	7.7 ± 0.5	NR	24-32	4	All	
Yu et al., 2012 ⁴¹	Control group	28	China	NR	7.3 ± 0.4	NR	NA	NA	All	Cohort study
	Lamivudine	94	China	26.4 ± 4.2	6.9 ± 0.4	45.0	24-32	Continued for variable duration after delivery	All	Cohort study
Pan et al., 2012 ⁴²	Control group	91	China	25.8	7.0 ± 0.6	45.0	NA	NA	All	Prospective, non-randomized open-label trial
	Telbivudine	53	China	27 (21-34)	8.08 (6.6-9.4)	60.4 (41.4-422)	12-30	Continued for variable duration after delivery	All	
Han et al., 2012 ⁴³	Control group	35	China	27 (21-33)	8.1 (6.8-9.1)	63.2 (42.4-262.5)	NA	NA	All	Cohort study
	Telbivudine	120	China	26.0 ± 3.5	7.3 ± 0.5	31.0 ± 32.2	20-32	4	All	
Han et al., 2011 ⁴⁴	Control group	100	China	26.4 ± 3.2	7.3 ± 0.6	31.5 ± 35.1	NA	NA	All	Cohort study
	Telbivudine	135	China	27 (20-38)	7.4 ± 0.6	35.7 ± 43.4	20-32	4	All	Cohort study

Table 1. Continued

Author, Year	Interventions	Participants (Mothers) (N)	Country	Age (Years)	Baseline HBV DNA Level (Log ₁₀ IU/mL)	Baseline ALT Level (U/L)	Treatment Start (Gestational Weeks)	Treatment Discontinuation (Postpartum Weeks)	HBIG + Vaccine (Infants)	Study Design
Feng, 2007 ⁴⁵	Control group Lamivudine	94	China	26 (20-35)	7.3 ± 0.6	42.5 ± 40.1	NA	NA	All	RCT
Li et al., 2006 ⁴⁶	Control group Lamivudine	48 42	China	NR	8.3 ± 1.2	NR	28	4	All	RCT
Han et al., 2005 ⁴⁷	Control group Lamivudine	36 44	China	NR	8.3 ± 1.9	NR	28	4	All	RCT
Zhang, 2010 ⁴⁹	Control group Lamivudine	44 43	China	NR	6.9 ± 0.8	NR	28	4	All	RCT
Yao et al., 2011 ⁴⁸	Control group Telbivudine	35 60	China	NR	7.2 ± 0.9	NR	28	4	All	RCT
Chen et al., 2015 ⁵⁰	Control group Telbivudine	60 28	China	NR	> 5.6	NR	28	4	All	RCT
Yu et al., 2014 ⁵¹	Control group Telbivudine	30 62	Taiwan	NR	NR	NR	28	4	All	Open-labeled, nonrandomized controlled trial
	Tenofovir	56	China	32.5 ± 3.2	7.5 ± 0.6	NR	28	4	All	Cohort study
	Lamivudine	233	China	32.4 ± 3.1	7.5 ± 0.7	NR	28	4	All	
		154	China	26.8 ± 3.9	7.8 ± 0.8	57.6 ± 83.5	8-32	At delivery	All	
				26.7 ± 3.5	7.7 ± 0.7	56.3 ± 82.7	NA	NA	All	

Abbreviation: HBIG, hepatitis B immunoglobulin

Table 2. Risk of Bias Assessment for the Included RCTs

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel, and Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Risk of Bias
Zhang and Wang, 2009 ²⁶	Unclear	Unclear	Unclear	No missing outcome	All prespecified outcomes reported	No	Unclear
Xu et al., 2009 ²⁷	Unclear	Sequentially numbered drug containers of identical appearance	Adequate blinding	One arm of data missing forethics	All prespecified outcomes reported	No	Low
Yang et al., 2008 ²⁸	Random number table	Sequentially numbered drug containers of identical appearance	Adequate blinding	No missing outcome data	All prespecified	No	Low
Li et al., 2003 ²⁹	Computer random number generator	Unclear	Measurement not influenced by lack of blinding	No missing outcome data	All prespecified outcomes reported	No	Low
Zhang, 2010 ³⁰	Unclear	Unclear	Unclear	Missing outcome data no impact on effect size	None	None	Unclear
Shi et al., 2009 ³¹	Computer random number generator	Sequentially numbered drug containers of identical appearance	Adequate blinding	Missing outcome data no impact on effect size	All prespecified outcomes reported	No	Low
Guo et al., 2008 ³²	Adequate	Unclear	Unclear	No missing outcome	All prespecified outcomes reported	No	Unclear
Xiang et al., 2007 ³³	Adequate	Unclear	Unclear	No missing outcome	All prespecified outcomes reported	No	Unclear
Shi et al., 2005 ³⁴	Random table	Unclear	Measurement not influenced by lack of blinding	No missing outcome data	All prespecified outcomes reported	No	Low
Guo et al., 2011 ³⁵	Unclear	Unclear	No blinding	No missing outcome data	All prespecified outcomes reported	No	High/unclear

Table 3. Risk of Bias Assessment for the Observational Studies

Author, Year	Selection			Comparability			Outcome	
	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow-Up of Cohorts		
Zhang et al., 2014 ³⁶	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate		
Greenup et al., 2014 ³⁷	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate		
Celen et al., 2013 ³⁸	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate		
Jiang et al., 2012 ³⁹	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	Yes	Adequate		
Chen et al., 2012 ⁴⁰	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	No	Unclear		
Yu et al., 2012 ⁴¹	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate		
Pan et al., 2012 ⁴²	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate		
Han et al., 2012 ⁴³	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	Unclear	unclear		
Han et al., 2011 ⁴⁴	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate		
Feng, 2007 ⁴⁵	No description	No description	No description	No description	No description	No description		
Li et al., 2006 ⁴⁶	No description	No description	No description	No description	No description	No description		
Han et al., 2005 ⁴⁷	No description	No description	No description	No description	No description	No description		
Yao et al., 2011 ⁴⁸	No description	No description	No description	No description	No description	No description		
Zhang, 2010 ⁴⁹	No description	No description	No description	No description	No description	No description		
Chen et al., 2015 ⁵⁰	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate		
Yu et al., 2014 ⁵¹	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Independent blind assessment	Yes	Adequate		

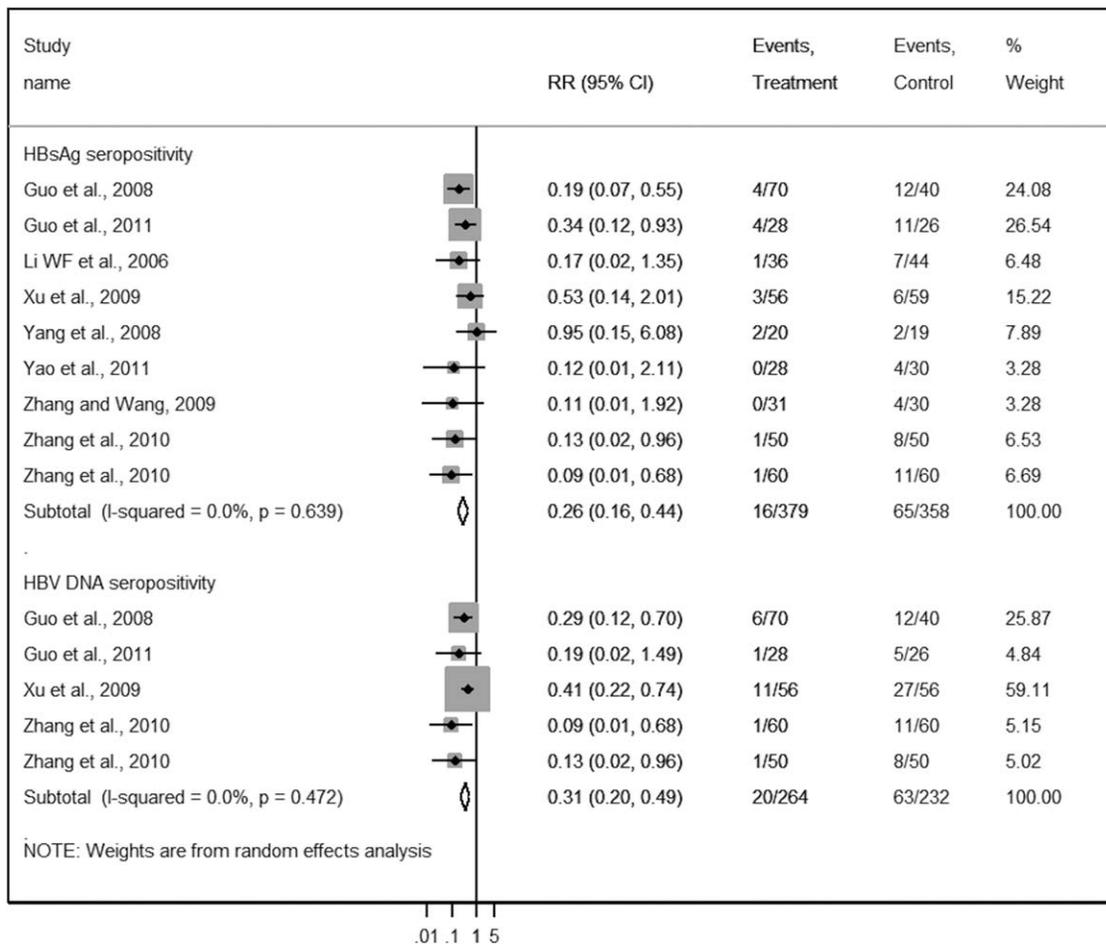


Fig. 2. Forest plots of infant outcomes for RCTs comparing any antiviral therapy versus control at 6-12 months follow-up.

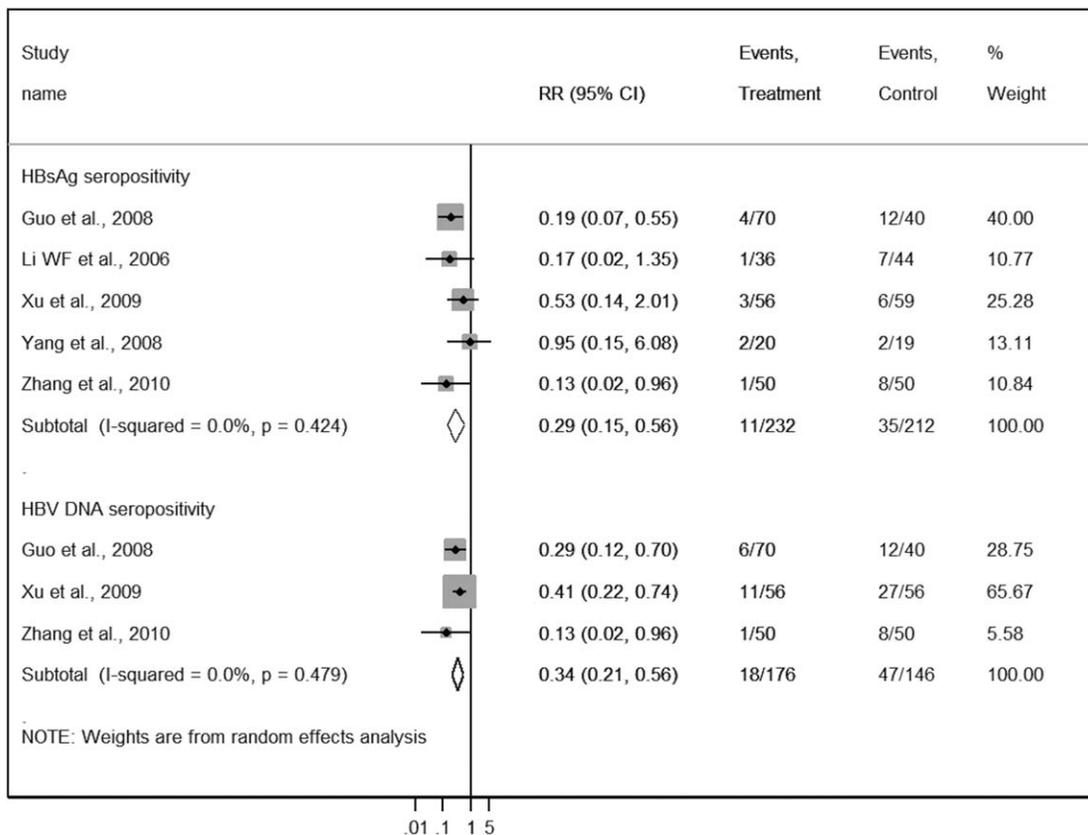


Fig. 3. Forest plots of infant outcomes for RCTs comparing lamivudine versus control at 6-12 months follow-up.

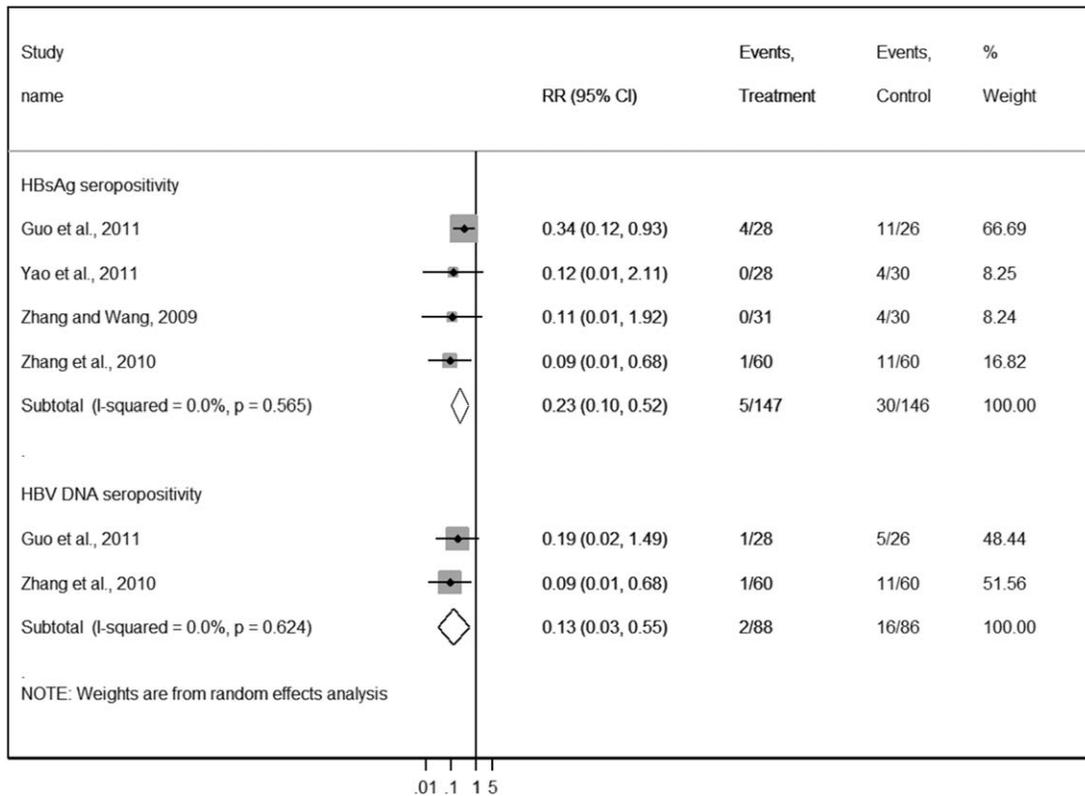


Fig. 4. Forest plots of infant outcomes for RCTs comparing telbivudine versus control at 6-12 months follow-up.

(one cohort, RR = 1.6, 95% CI 1.2-2.2), and at 28 weeks postpartum (one cohort, RR = 1.7, 95% CI 1.2-2.29). Tenofovir compared to control showed significant improvement in HBV DNA suppression at delivery

(two cohorts, RR = 45.4, 95% CI 9.3-222.5) but not ALT normalization or HBeAg seroconversion.

Compared to lamivudine, pregnant women treated with telbivudine had significantly greater HBV DNA

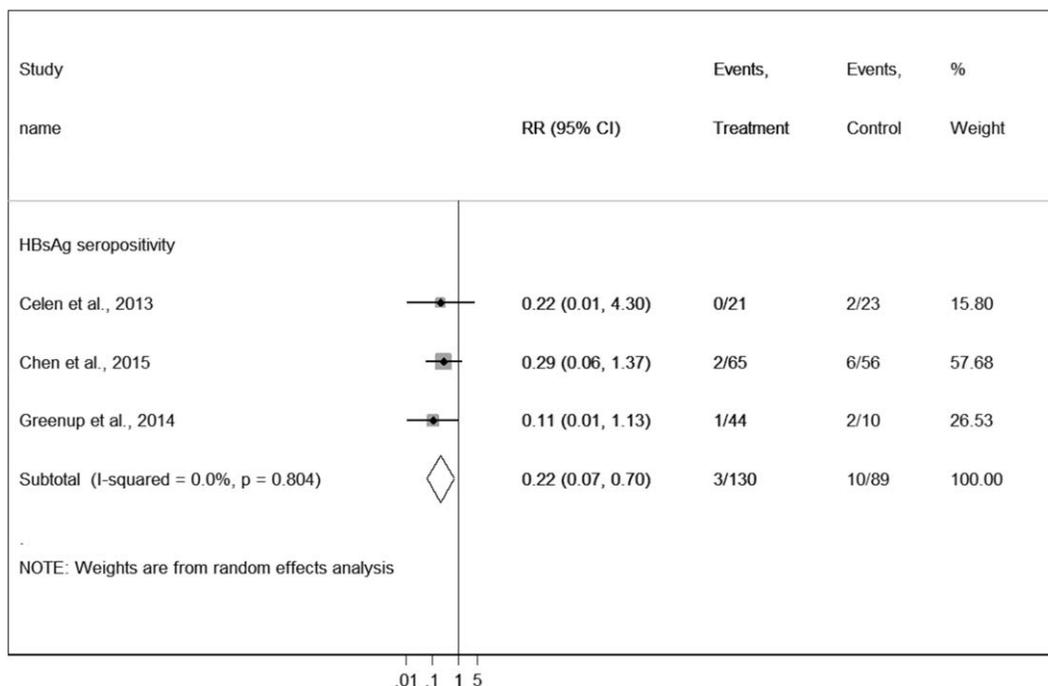


Fig. 5. Forest plots of infant outcomes for non-RCTs comparing tenofovir versus control at 6-12 months follow-up.

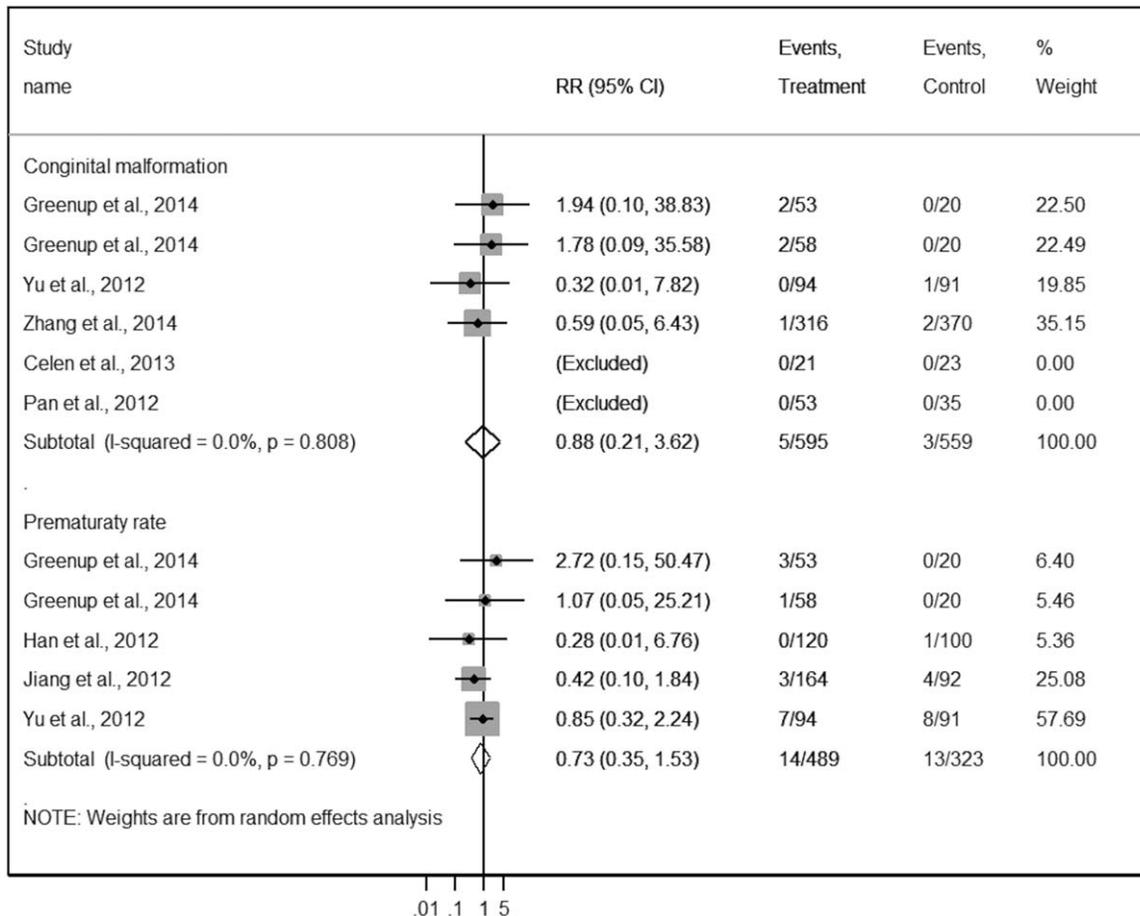


Fig. 6. Forest plot of congenital malformation and prematurity rates reported for studies comparing any antiviral therapy versus control.

suppression at delivery (one cohort, RR = 1.8, 95% CI 1.3-2.6) but not HBeAg loss (RR = 1.1, 95% CI 0.1-21.5) or seroconversion (RR = 0.6, 95% CI 0.03-15.2).

When comparing any antiviral therapy versus control for maternal harms, no statistically significant difference was found in postpartum hemorrhage rate, cesarean section rate, and elevated creatine kinase rate. The quality of the evidence in maternal outcomes was very low due to the observational nature of the studies, imprecision, and indirectness. Figures 7-9 show maternal outcomes reported at delivery in studies comparing lamivudine, telbivudine, and tenofovir treatment versus control group, respectively. [Supporting Table 2](#) summarizes the quality of evidence (Grading of Recommendations Assessment, Development, and Evaluation) for infant and maternal outcomes.

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

Discussion

For women who are or may become pregnant, consideration of the potential harms and benefits to the

fetus as well as the mother complicates medication treatment decisions, such as administering antiviral therapy for CHB during pregnancy. Although the benefit for antiviral therapy is unproven for the many women of childbearing age who are in the immune tolerant phase of CHB, these women have the highest risk of MTCT. Thus, characterizing the safety of these medications for the mother and fetus during pregnancy can help inform potential treatment choices for women of childbearing age. Even for women who are in the immune active phase of CHB infection antiviral treatment may be postponed until after completion of childbearing as long as they have compensated liver disease. Additionally, post-delivery neonatal combined immunoprophylaxis successfully prevents HBV infection in approximately 90% of infants. Thus, prevention of MTCT of HBV does not necessarily mandate antiviral treatment during pregnancy for most women. However, the current failure rate of postexposure neonatal immunoprophylaxis against MTCT of HBV may be unacceptably high (~9%) in women with high levels of viremia (serum HBV DNA >10⁶ copies/mL; ~2 × 10⁵ IU/mL).¹⁰

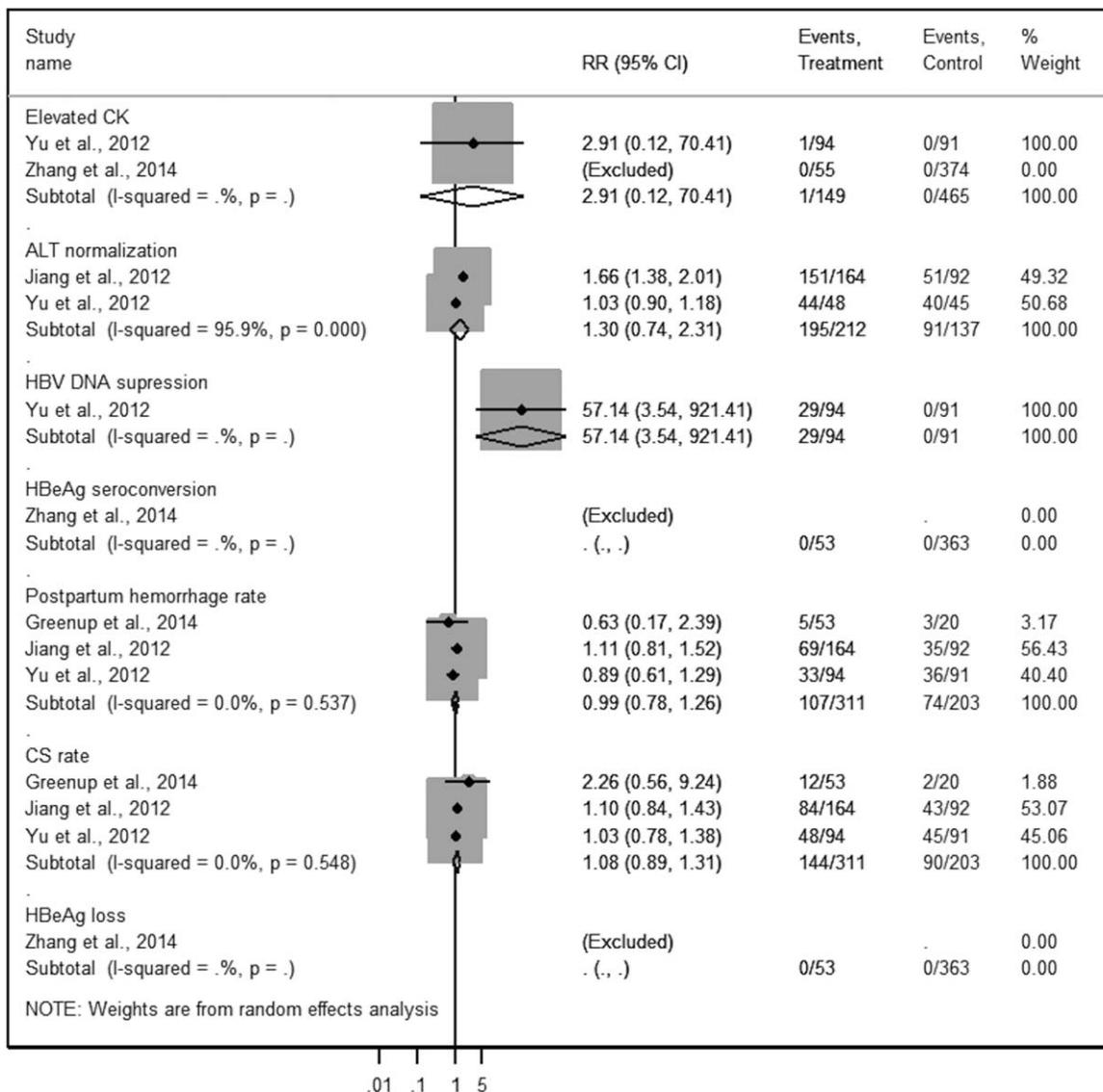


Fig. 7. Forest plot of maternal outcomes for non-RCTs comparing lamivudine versus control at delivery.

Among infants who received hepatitis B vaccine starting at birth, this meta-analysis found that antiviral therapy with lamivudine, telbivudine, or tenofovir in pregnant women with high levels of HBV DNA reduced MTCT rates, with over 70% reductions in the rates of infant HBsAg and HBV DNA positivity at 6-12 months postpartum. In non-head-to-head trials, telbivudine showed higher rates of HBV DNA suppression, ALT normalization, and HBeAg seroconversion than lamivudine. For tenofovir, there were insufficient controlled outcome data. No safety issues for maternal or fetal outcomes were identified in our meta-analysis of these studies. Thus, antiviral therapy in the third trimester for women who are HBeAg-positive with an HBV DNA level greater than 2×10^5 IU/mL to prevent MTCT seems warranted (see the accompanying AASLD Hepatitis B Treatment Guidelines for details).

Although lamivudine, telbivudine, and tenofovir are licensed for CHB and HIV treatment, none of these drugs are approved for use in pregnancy. Telbivudine and tenofovir are currently rated pregnancy category B, and lamivudine pregnancy category C, by the US Food and Drug Administration based primarily on animal data, with no clear evidence of harm in sparse human data. However, the substantial experience in the use tenofovir and lamivudine in HIV-infected pregnant women to prevent HIV transmission has not identified any significant safety concerns for either mother or newborn.²⁰ Recent data in women with HIV have reported lower bone mineral content in newborns exposed to tenofovir throughout pregnancy⁵²; but earlier data did not show any impact on early growth in infants exposed to tenofovir *in utero*,⁵³ so the significance of this finding is unclear. Additionally, initiating tenofovir, lamivudine, or

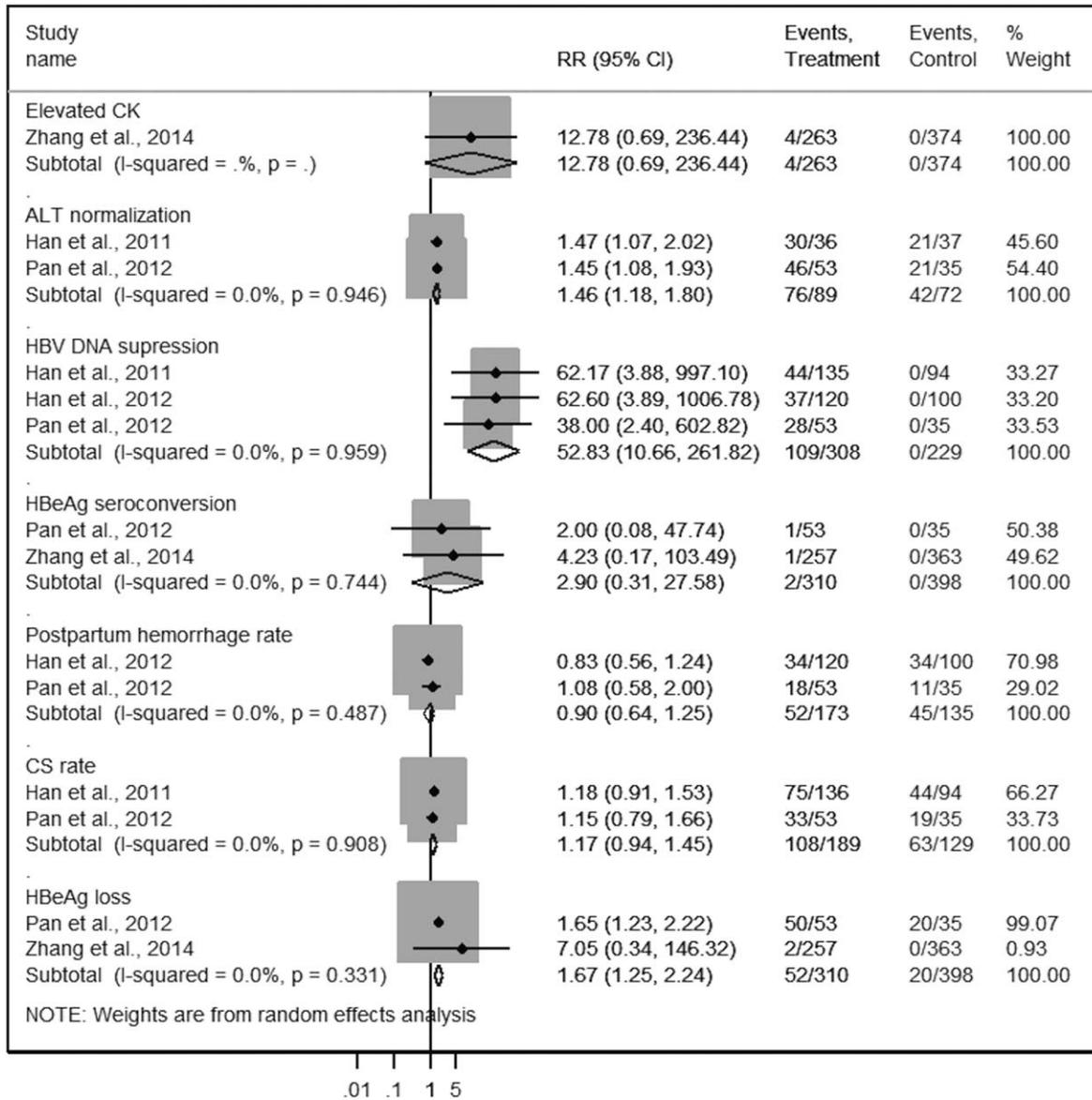


Fig. 8. Forest plot of maternal outcomes for non-RCTs comparing telbivudine versus control at delivery.

telbivudine for CHB during pregnancy may be less worrisome because the antiviral agents are usually started in the late second or early third trimester in mothers with high HBV DNA levels, to reduce maternal viremia and hence the risk of MTCT of HBV. Concern remains over the propensity to develop viral resistance to lamivudine or telbivudine⁵⁴ if it is used throughout the pregnancy or postpartum, rather than restricted to the late second or third trimester. On the other hand, tenofovir has a high resistance barrier with no resistance identified to date after up to 6 years of monotherapy for CHB.⁵⁵

The major limitation of this systematic review is the absence of studies warranting high confidence. With a paucity of RCTs, most of the data are derived from cohort studies, which are subject to significant biases,

especially selection bias. Additionally, despite a report from the Antiretroviral Pregnancy Registry finding no increased risk of birth defects for lamivudine or tenofovir,²⁵ data on fetal safety with antivirals remain limited, particularly for telbivudine. Recommendations for management of chronic HBV infection during pregnancy are provided in the updated AASLD guidelines.⁵⁶

In conclusion, in pregnant women with chronic HBV infection, the oral antiviral therapies lamivudine, telbivudine, and tenofovir lower HBV DNA levels as they do in nonpregnant women and reduce the rates of MTCT. These effects were demonstrated in women who are HBeAg-positive with high viral loads (>10⁶ copies or ~2 × 10⁵ IU/mL). The limited safety data suggest no increased risk of adverse maternal or fetal

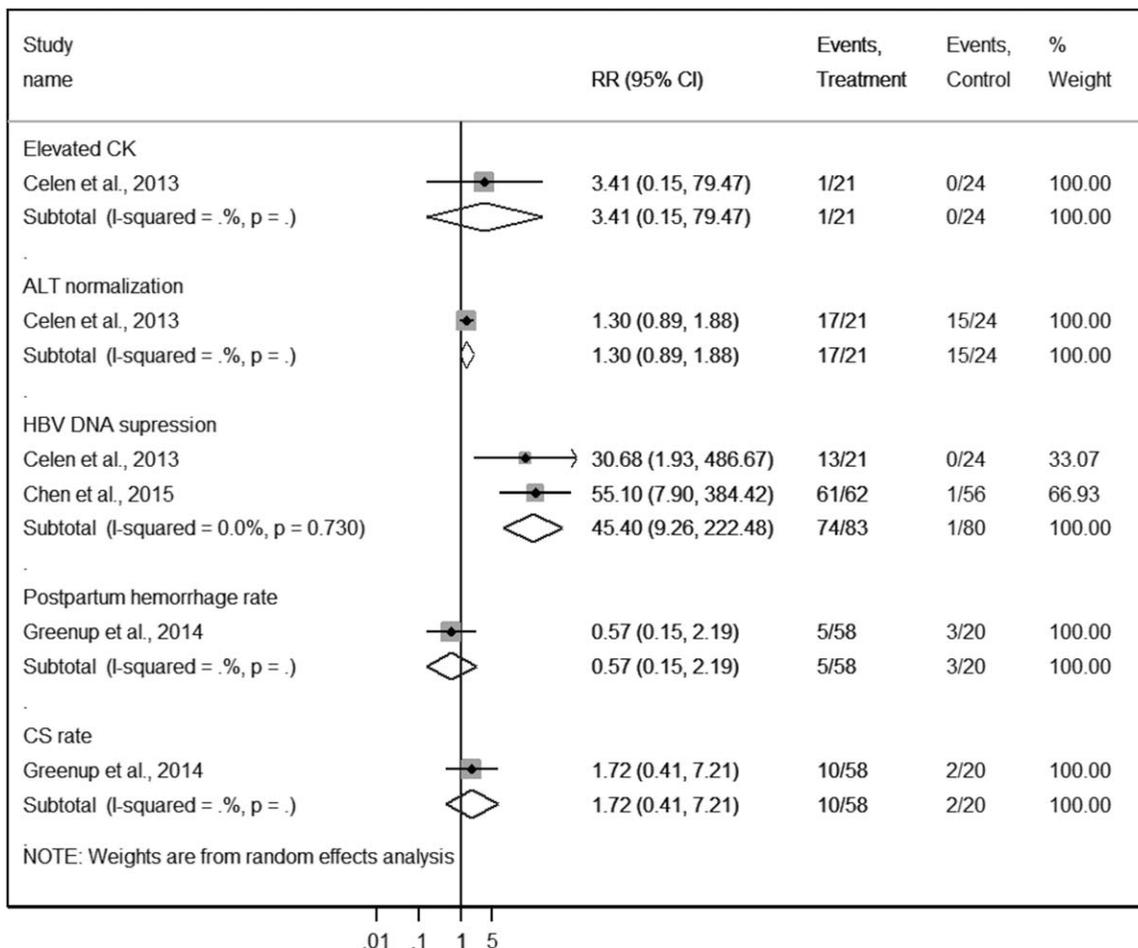


Fig. 9. Forest plot of maternal outcomes for non-RCTs comparing tenofovir versus control at delivery.

outcomes. Larger-scale RCTs of tenofovir are ongoing, and these results are eagerly awaited. In the meantime, the use of these agents in women who are HBeAg-positive and have HBV DNA >10⁶ copies/mL (200,000 IU/mL) in the third trimester to prevent MTCT is recommended.

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