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Comparative efficacy of antiviral therapy in preventing vertical transmission of hepatitis B: a network meta-analysis

Basile Njei[1,2], **Neil Gupta**[1], **Oforbuike Ewelukwa**[3], **Ivo Ditah**[4], **Munoh Foma**[5], and **Joseph K. Lim**[1]

Joseph K. Lim: joseph.lim@yale.edu

[1]Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, New Haven, CT, USA

[2]Investigative Medicine Program, Yale Center of Clinical Investigation, New Haven, CT, USA

[3]Gastroenterology and Hepatology, University of Florida, Gainesville, FL, USA

[4]Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

[5]Division of Clinical Pathology, University of Yaounde 1, Yaounde, Cameroon

Abstract

Background & Aims—Antiviral drugs are safe and effective in the third trimester to prevent intrauterine transmission of hepatitis B virus, and are recommended for hepatitis B virus (HBV) infected gravid mothers (between weeks 28 and 32) with high viral load, followed by postnatal hepatitis B immunization in the newborn. We estimated the comparative efficacy of antiviral drugs for prevention of vertical transmission of HBV, through a network meta-analysis of clinical trials.

Methods—We conducted a comprehensive search of MEDLINE, EMBASE and published proceedings from major liver meetings from January 1980 to November 2014. We conducted pair-wise meta-analyses and Bayesian framework using Markov chain Monte Carlo methods, combining direct and indirect evidence for any given pair of treatments.

Results—Seventeen clinical trials involving 2764 newborns of hepatitis B surface antigen seropositive mothers were eligible for analysis. There were no clinical trials involving tenofovir or entecavir. On pair-wise meta-analyses, telbivudine (hazard ratio, HR 0.12, 95% confidence interval (CI) 0.04–0.37; I^2 = 0%), and Lamivudine (HR 0.40, 95% CI 0.24–0.65; I^2 = 0%), were more effective than placebo in reducing vertical transmission of HBV in high viremic hepatitis B e antigen (HBeAg)-positive chronic Hepatitis B Chinese patients. Sensitivity analyses limited to studies with HBeAg seropositive mothers revealed similar results.

Conclusions—Based on a Bayesian network meta-analysis of clinical trials, combining direct and indirect treatment comparisons, telbivudine appears to be more effective than Lamivudine for

Correspondence: Joseph K. Lim, MD, Associate Professor of Medicine, Director, Yale Viral Hepatitis Program, 333 Cedar St, New Haven, CT 06520, USA Tel: +1 203 737 6063; Fax: +1 203 785 7273.

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preventing vertical transmission of HBV infection. Trials assessing the efficacy of tenofovir or entecavir compared to placebo or other antiviral drugs are lacking.

Keywords

antiviral therapy; hepatitis B; vertical transmission

Chronic hepatitis B virus (CHB) chronically infects over 350 million people worldwide (1). CHB can lead to end stage liver disease and hepatocellular cancer with significant morbidity and mortality (2). Infants born to mothers who are positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) have a 70–90% chance of acquiring perinatal hepatitis B virus (HBV) infection (3). Postnatal hepatitis B immunization (HBIG) plus HBV vaccine administered within 24 h of birth reduces vertical transmission in about 85–95% of recipients (3). The main causes of prophylaxis failure include high maternal viral load, HBeAg positivity, *in utero* infection, escape mutants and the immune status of the mother (4). Of these, high maternal serum viral load (HBV DNA level $>10^6$ copies/ml) appears to be the major cause of prophylaxis failure, with up to 3–9% of perinatal transmissions reported despite both active and passive immunizations (2, 5).

Antiviral drugs are safe and effective in the third trimester to prevent intrauterine transmission of hepatitis B virus and are recommended for CHB-infected gravid mothers (between weeks 28 and 32) with high viral load, followed by postnatal HBIG in the newborn (2, 5–9). Although all major liver society guidelines recommend third trimester antiviral therapy for women at higher risk of mother-to-child transmission of HBV, several areas of controversy remain, including the preferred antiviral drug, the optimal HBV viral load that warrants treatment, the gestational week at which to initiate therapy, and when to stop treatment after delivery (2, 5, 9). Antiviral therapies which have been used to decrease the HBV DNA levels during late pregnancy include nucleotide/nucleoside analogue polymerase inhibitors such as lamivudine (LAM), telbivudine (TBV), entecavir (ETV) and tenofovir (TDV) (1, 2, 4–18). Despite the benefits of adding an anitiviral agent to standard immunoprophylaxis, it is unknown whether one of these antiviral agents is superior to the other. Although clinical trials have evaluated each of these antiviral agents, no head-to-head comparison studies have been performed. In this study, we use a network meta-analysis design to compare the efficacy of the various antiviral drugs used in the prevention of vertical transmission of HBV.

Methods

Search strategy and outcomes

Two authors (BN and NG) independently conducted a comprehensive search of the Cochrane library, PUBMED, Scopus and published proceedings from major hepatology and gastrointestinal meetings from January 1980 to December 2014. The search was conducted using the key words ‘LAM or TBV’, ‘HBV or hepatitis B virus or chronic hepatitis B’ and ‘intrauterine or maternity or mother or pregnancy or pregnant’. All relevant articles irrespective of language, year of publication, type of publication or publication status were included. Clinical trials involving CHB-infected mothers with DNA $> 10^6$ copies/ml were

eligible for inclusion. Data from observational studies were excluded. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles. In the case of studies with incomplete information, the principal authors were contacted to obtain additional data.

Study outcomes included: newborn HBsAg status, newborn HBV DNA, and infant HBsAg seropositivity at age 6–12 months. Vertical transmission of HBV was defined as HBsAg positivity at age 6–12 months.

Assessment of risk of bias in included studies

The methodological quality of the trials, hence risk of bias, was assessed as follows: allocation sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and vested interest bias. We followed the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions and the Cochrane Hepato-Biliary Group Module (19, 20).

Data synthesis and statistical analysis

Two independent reviewers extracted data and scored publications; a third investigator adjudicated discrepancies. Kappa scores were measured to assess the agreement between the two initial reviewers in each step and interpreted as described (19, 20). We performed the review and meta-analyses following the recommendations of The Cochrane Collaboration. First, we conducted pair-wise meta-analyses with a random effects model to synthesize studies comparing the same pair of treatments. The data were analysed by intention-to-treat, including all patients irrespective of compliance or follow-up. The results were reported as pooled hazard ratios (HRs) with the corresponding 95% confidence interval (CI). Regression analyses were performed to estimate funnel plot asymmetry (19–21).

Heterogeneity was explored by the chi-squared test and I^2 test with significance limit set at a P value of 0.10. In the case of trials with zero events on any outcome event, we applied an empirical continuity correction of 0.5 in both arms to avoid overestimating a treatment effect. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement outline for reporting systematic reviews and meta-analyses was used to report this study (22). All pair-wise calculations were performed using REVIEW MANAGER version 5.3. (The Cochrane Collaboration, Copenhagen, Denmark).

Second, we built a random effects network within a Bayesian framework using Markov chain Monte Carlo methods in ADDIS 1.15 (23). We networked the translated binary outcomes within studies and specified the relations among the HRs across studies making different comparisons. This method combined direct and indirect evidence for any given pair of treatments. We used $P < 0.05$ and 95% CIs to assess significance.

We also estimated the probability that each treatment was the best regimen, or the second best, by calculating the HR for each drug compared with an arbitrary common control group, and counting the proportion of iterations of the Markov chain in which each drug had

the highest HR, the second highest, and so on. We ranked treatments in terms of efficacy with the same methods.

A variance calculation and a node-splitting analysis provided by the software ADDIS 1.15 were applied to evaluate the inconsistency within the network meta-analysis. If the difference between random effects variance and inconsistency variance was large or a $P < 0.05$ of disagreement between direct and indirect evidence was met, significant inconsistency was indicated. According to the quantitative estimation, we could adjust the study inclusion and ultimately obtain an ideal network with consistency. A sensitivity analysis limited to studies with HBeAg seropositive mothers was conducted.

Results

Characteristics of the studies

We identified 1922 citations through our searches, from which seventeen clinical trials involving 2764 newborns of HBsAg seropositive mothers (TBV vs control: seven trials; LAM vs control: eight trials; TBV vs LAM: two trials) were selected. There were no clinical trials involving TDF or ETV.

A PRISMA flow chart of the literature search and selection process is shown in Fig. S1. Of the studies included, 13 were RCTs while five were NRCTs. There was an excellent inter-reviewer agreement [Kappa = 0.92 (95% CI: 0.67–1.0)]. The characteristics of included studies are shown in Table 1. Figure S2 presents the consensus risk of bias assessments of the included trials.

Direct meta-analyses

Six studies (two RCT and four NRCTs) comparing TBV and placebo or no treatment demonstrated newborn HBsAg seropositivity at birth (1, 6, 15–18, 24). The newborn HBsAg positive rates were 4.3% (24/556) in the TBV group and 21.9% (65/240) in the control group (HR 0.27, 95% CI 0.15–0.49; $I^2 = 30\%$, Fig. 1). Subgroup analyses, based on study type (RCT or NRCT) showed similar results with a lower newborn HBsAg seropositivity in the TBV group compared to controls (RCT's: HR 0.07, 95% CI 0.01–0.30; $I^2 = 81\%$ vs NRCT's: HR 0.32, 95% CI 0.20–0.51; $I^2 = 0\%$).

Eight studies (all RCT) comparing LAM and placebo or no treatment demonstrated newborn HBsAg seropositivity at birth (2, 7, 8, 11, 13, 14, 17, 25–27). The newborn HBsAg positive rates were 12.0% (46/382) in the LAM group and 27.1% (101/373) in the control group (HR 0.41, 95% CI 0.24–0.73; $I^2 = 57\%$, Fig. 2). For HBV DNA outcomes, TBV (one RCT and three NRCTs) or LAM (six RCTs) had lower newborn HBV DNA seropositivity compared to controls (Figs S3 and S4).

At age 6–12 months, the infant HBsAg positive rates were 0.7% (2/281) in the TBV group and 12.2% (29/238) in the control group (1 RCTs and 4 NRCTs; HR 0.12, 95% CI 0.04–0.37; $I^2 = 0\%$, Fig. S5). Subgroup analyses, limited to the 4 NRCTs showed similar results with a lower infant HBsAg seropositivity in the TBV group compared to controls (HR 0.09, 95% CI 0.02–0.55; $I^2 = 0\%$).

At age 6–12 months, the infant HBsAg positive rates were 11.7% (18/154) in the LAM group and 31.1% (47/151) in the control group (3 RCTs; HR 0.40, 95% CI 0.24–0.65; I^2 = 0%, Fig. S6).

Publication bias

Visual inspection of funnel plots showed that the studies were well scattered with no suggestion of any publication bias. Indicators for publication bias: the Begg-adjusted rank correlation (P = 0.54) and Egger regression asymmetry tests (P = 0.43) indicated no significant publication bias (Fig. S7A,B).

Network meta-analyses

We established a network (Fig. 3), which also considered a sensitivity analyses (studies with only HBeAg seropositive mothers). Table 2 summarizes the results of the network meta-analysis for newborn HBsAg status, and infant HBsAg seropositivity at age 6–12 months (vertical transmission). Sensitivity analyses limited to studies with HBeAg seropositive mothers revealed similar results.

Figure S8 shows the rank probability to be the best treatment, or the second best treatment regimen. Agents with greater value in the histogram were associated with lower HR and higher efficacy in preventing mother-to-child transmission of hepatitis B.

Cumulative probabilities of being the most efficacious treatment were: TBV (75, 98, 92%) and LAM (25, 2, 8%), for newborn HBsAg status, HBV DNA, and infant HBsAg seropositivity at age 6–12 months respectively. There was no significant inconsistency within the network meta-analysis.

Discussion

Conventional meta-analysis cannot compare the relative effect of one drug to another unless they were compared to each other in the same study. In network meta-analysis, multiple treatment comparisons for a specific disease, which were not compared to each other, can be made simultaneously through a common comparator treatment (20, 21, 23). This analysis of 17 clinical trials shows that TBV is more effective than LAM for preventing vertical transmission of HBV infection in high viremic HBeAg-positive chronic Hepatitis B Chinese patients.

To the best of our knowledge, this is the first study that provides both direct and indirect evidence in terms of comparative effectiveness of available antiviral drugs for the prevention of vertical transmission of HBV. The superior efficacy of TBV compared to LAM for prevention of vertical transmission shown in this study has not been previously reported.

Lamivudine was the first antiviral drug used in HBV infected mothers to lower vertical transmission. LAM, a nucleoside analogue and reverse transcriptase inhibitor, can significant reduce the HBV viral load. FDA considers it a pregnancy Category C medication with no evidence of teratogenecity in animals. In 2014, Jackson *et al.* (28) published a study in which 45 women met criteria for LAM treatment, and no cases of perinatal transmission

occurred in infants born to mothers who received treatment. The authors concluded that LAM therapy in highly viremic CHB-infected pregnant women could help reduce the rate of vertical transmission. In 2011, a meta-analysis of randomized controlled trials of 1693 CHB-infected mothers showed LAM, initiated at 28 weeks of gestation, substantially reduced mother-to-child transmission of HBV compared to immunoprophylaxis using HBIG alone (1).

Telbivudine has anti-HBV activity without any known foetal toxic effects for reproductive women. Recently, Wu *et al.* (6) performed a prospective study of 450 HBeAg-positive pregnant woman with 279 woman receiving TBV and 171 women participating as controls. None of the infants whose mothers were given TBV tested positive for HBsAg at 6 months of age, compared to 14.7% of infants in the control group. The authors concluded that TBV was safe and significantly reduce vertical transmission of HBV from pregnant women to their infants. Han *et al.* reported a mother-to-child transmission rate of 0% for the TBV subgroup in an open-label trial of 229 women ages 20–40 years old who were HBeAg positive with HBV DNA > 7 log 10 copies per ml.

Both LAM and TBV have the major drawback of having high rates of resistance. Tenofovir, a nucleotide reverse transcriptase inhibitor, is a potent FDA category B with excellent resistance profile, but very limited data exists about its efficacy in reducing perinatal transmission of CHB. A recent small retrospective study showed 100% reduction in perinatal transmission of CHB compared to controls but no significant randomized controlled trial exists. A larger retrospective review of 48 women treated with TDF throughout pregnancy reported a rate of 0% with a spontaneous abortion rate of 6% in first trimester (29). However, such studies highlight the importance of larger studies needed to prove the efficacy and safety of TDF therapy in preventing the vertical transmission of HBV.

Entecavir, another nucleoside analogue that inhibits reverse transcription and DNA replication has an excellent resistance profile and comparable efficacy and safety with TDV for the treatment of CHB. However, it is an FDA category C and very limited data exists about its efficacy in pregnancy to reduce perinatal transmission, which makes consideration of an alternative agent advisable.

This is the first multiple treatment comparison for the currently available antiviral therapy in addition to standard immunoprophylaxis for prevention of vertical transmission of CHB. The novel finding that TBV was more effective than Lamividine may help guide clinicians in the decision-making process.

Our analysis has numerous strengths, including the use of a comprehensive and exhaustive search strategy, use of standardized guidelines on reporting systematic reviews according to PRIMSA, and treatment comparisons by Bayesian networks. These results, however, need to be interpreted with caution for several reasons.

First, there were no clinical trials assessing TDV and entecavir, which are widely used first line agents for CHB treatment. A large randomized controlled trial comparing TDV vs HBIG/vaccination in 200 HBeAg+ pregnant women with CHB in China is currently underway (NCT01488526) (30). Second, there was variation in the characteristics of

included patients and intervention regimens as a result there was some evidence of heterogeneity between the studies that was not explained by subgroup analysis. Third, there was some risk of bias in the original studies with regards to inadequate blinding. As a result of limited published studies, we expanded the search to include NRCTs. However, similar results were obtained in our subgroup analyses of RCTs and NRCTs. Finally, most of the included studies were performed in China. Therefore, more clinical studies performed in different populations and other regions are necessary to access the generalizability of the results.

In conclusion, based on a Bayesian network meta-analysis of clinical trials, TBV appears to be more effective than LAM for preventing vertical transmission of CHB infection. Published trials assessing the efficacy of TDF and ETV are lacking. Direct head-to-head and cost-effectiveness analyses comparing TBV, TDF, ETV and LAM are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CHB	chronic hepatitis B virus

d	days
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBVac	hepatitis B vaccine
HR	hazard ratio
Mo	months
PRISMA	preferred reporting items for systematic reviews and meta-analyses
Wk	weeks

Key points

- Antiviral drugs are recommended for hepatitis B virus (HBV) infected gravid mothers with high viral load.
- We estimated the comparative efficacy of antiviral drugs for prevention of vertical transmission of HBV, through a network meta-analysis of clinical trials.
- Telbivudine is more effective than Lamivudine for preventing vertical transmission of HBV infection in high viremic HBeAg-positive chronic Hepatitis B Chinese patients.
- Trials assessing the efficacy of tenofovir or entecavir compared to placebo are lacking.

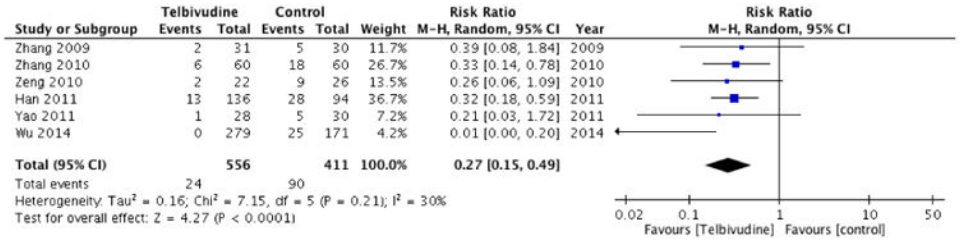

Fig. 1.

New born hepatitis B surface antigen seropositivity: telbivudine vs control.

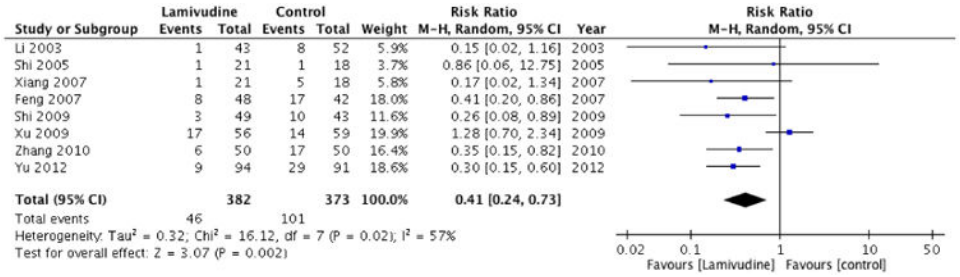

Fig. 2.

New born hepatitis B surface antigen seropositivity: lamivudine vs control.

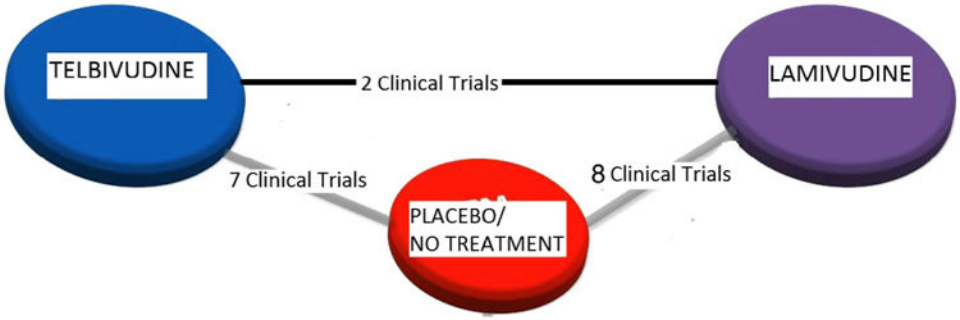

Fig. 3.
Network meta-analysis.

Table 1

Characteristics of the included clinical trials in this study

			Treatment		HBeAg positive/ HBeAg negative		HBVDNA level (log copies/ml)		Newborn immunization	
Study	Study design	Intervention/ control (*n*)	Intervention	Control	Intervention	Control	ntervention: mean (SD)	Control: mean (SD)	HBIG (IU)	HBV ac (mg)
Wu, 2015 (6)	RCT	279/171	TBV 600 from 24 to 32 wk of gestation up to delivery or 1 mo after delivery	No treatment	279/0	171/0	7.26 (0.50)	7.40 (0.65)	200 at birth and 15 d	20 at 0, 1, 6 mo
Han, 2011 (1)	NRCT	135/94	TBV 600 from 20 to 32 wk of gestation to 1 mo after delivery	No treatment	135/0	94/0	8.10 (0.56)	7.98 (0.61)	200 at birth and 15 d	20 at 0, 1, 6 mo
Yao, 2011 (15)	NRCT	28/30	TBV 600 from 28 wk of gestation to wk after delivery	No treatment	NA	NA	7.50 (0.60)	7.50 (0.70)	200 at birth	10 at 0, 1, 6 mo
Zhang, 2010 (17)	NRCT	60/60	TBV 600 from 28 wk of gestation to 1 mo after delivery	No treatment	60/0	60/0	7.66 (0.82)	6.86 (6.10)	200 at birth and 30 d	10 at 0, 1, 6 mo
Zeng, 2010 (16)	NRCT	22/26	TBV 600 from 28 wk of gestation to delivery	No treatment	22/0	26/0	7.66 (0.82)	7.13 (1.29)	200 at birth	10 at 0, 1, 6 mo
Zhao, 2010 (18)	RCT	30/30	TBV 600 from 28 wk of gestation to 1 mo after delivery	No treatment	30/0	30/0	NA	NA	200 at birth and 30 d	10 at 0, 1, 6 mo
Zhang, 2009 (24)	RCT	31/30	TBV 600 from 28 to 32 wk of gestation to 1 mo after delivery	No treatment	NA	NA	7.38 (0.81)	7.46 (0.45)	200 at birth and 30 d	10 at 0, 1, 6 mo
Yu, 2012 (25)	RCT	94/91	LAM 100 mg daily from week 24 to 32	No treatment	94/0	91/0	7.63 (0.54)	7.71 (0.71)	200 at birth and 15 d	10 at 0, 1, 6 mo
Zhang, 2010 (17)	RCT	50/50	LAM 100 mg daily from week 28	No treatment	NA	NA	6.83 (0.90)	6.87 (1.67)	200 at birth and 30 d	10 at 0, 1, 6 mo
Xu, 2009 (14)	RCT	63/62	LAM 100 mg from 32 wk of gestation to 1 mo after dellivery	Placebo	NA	NA	9.35 (0.21)	9.43 (0.21)	200 at birth	10 at 0, 1, 6 mo
Shi, 2009 (26)	RCT	49/43	LAM 100 mg from 28 wk of gestation to 1 mo after delivery	Placebo	NA	NA	7.24 (1.90)	6.40 (2.12)	100 at birth	10 at 0, 1, 6 mo
Xiang, 2007 (27)	RCT	21/18	LAM 100 mg from 28 wk of gestation to 1 mo after delivery	No treatment	NA	NA	8.02 (1.15)	7.16 (0.79)	200 at birth and 15 d	10 at 0, 1, 6 mo
Feng, 2007 (8)	RCT	48/42	LAM 100 mg from 28 wk of gestation to 1 mo after delivery	No treatment	NA	NA	8.34 (1.23)	8.26 (1.87)	100 at birth	10 at 0, 1, 6 mo
Shi, 2005 (13)	RCT	21/18	LAM 100 mg daily from week 28	No treatment	NA	NA	8.72 (0.69)	8.93 (1.12)	100 at birth	10 at 0, 1, 6 mo
Li, 2003 (11)	RCT	43/52	LAM 100 mg from 28 wk of gestation to 1 mo after delivery	No treatment. There were 56 patients in a HBIG comparative group	NA	NA	7.38 (1.17)	7.05 (1.29)	100 at birth	10 at 0, 1, 6 mo
Zhang, 2014 (4)	NRCT	252/51/345	TBV 600 from 28 wk of gestation to 4 wks after delivery	LAM 100 mg from 28 wk of gestation to 4 wks after delivery. 345 patients in the no treatment group	345/0	51/0	7.69 (0.44)	7.62 (0.37)	200 at birth and 15 d	20 at 0, 1, 6 mo
Yu, 2014 (7)	RTC	233/154	TBV 600 from 8 to 32 wks of gestation to delivery	LAM 100 mg daily from week 28 to delivery	233/0	154/0	7.77 (0.81)	7.66 (0.71)	200 at birth and 15 d	20 at 0, 1, 6 mo

Table 2

Multiple treatment comparison for efficacy of antiviral drugs for prevention of vertical transmission of CHB, based on network meta-analysis

	Comparator: new born HBsAg (+)			Comparator: infant HBsAg (+) at 6–12 months		
Intervention	**Control**	**Telbivudine**	**Lamivudine**	**Control**	**Telbivudine**	**Lamivudine**
Telbivudine	0.21 (0.09–0.46)	–	0.91 (0.23–3.75)	0.06 (0.02–0.23)	–	0.62 (0.13–3.11)
Lamivudine	0.31 (0.15–0.66)	1.14 (0.22–4.17)	–	0.22 (0.11–0.52)	1.56 (0.33–7.36)	–

Results presented as HR and 95% CI of event, comparing intervention in row, to comparator as reference in columns.