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Telbivudine or Lamivudine Use in Late Pregnancy Safely Reduces Perinatal Transmission of Hepatitis B Virus in Real-Life Practice

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Little observational data exist describing telbivudine (LdT) or lamivudine (LAM) use in late pregnancy for preventing hepatitis B mother-to-child transmission (MTCT) in real-world settings. During the period of January 2009 to March 2011, we enrolled hepatitis B e antigen–positive mothers with HBV DNA >6 $\log_{10}$ copies/mL in China. At gestation week 28, the mothers received LdT or LAM until postpartum week 4 or no treatment (NTx). The study endpoints were the safety of LdT/LAM use and MTCT rates. Of the 700 mothers enrolled, 648 (LdT/LAM/NTx = 252/51/345) completed the 52-week study with 661 infants (LdT/LAM/NTx = 257/52/352). On treatment, viral rebound occurred in 1.6% of mothers, all resulting from medication noncompliance. There was no genotypic mutation detected. At delivery, significantly lower HBV DNA levels were noted in mothers who received LdT or LAM versus NTx. Alanine aminotransferase flares were observed in 17.1% of treated mothers versus 6.3% of untreated mothers ($P < 0.001$). At birth, hepatitis B surface antigen (HBsAg) was detected in 20% and 24% of newborns in the treated and NTx groups, respectively. At week 52, an intention-to-treat analysis indicated 2.2% (95% confidence [CI]: 0.6-3.8) of $HBsAg^+$ infants from the treated group versus 7.6% (95% CI: 4.9-10.3) in the NTx group ($P = 0.001$) and no difference of $HBsAg^+$ rate between infants in the LdT and LAM groups (1.9% vs. 3.7%; $P = 0.758$). On-treatment analysis indicated 0% of $HBsAg^+$ infants in the treated group versus 2.84% in the NTx group ($P = 0.002$). There were no differences for gestational age or infants' height, weight, Apgar scores, or birth defect rates between infants from the treated and untreated groups. *Conclusions*: LdT and LAM use in late pregnancy for highly viremic mothers was equally effective in reducing MTCT. The treatment was well tolerated with no safety concerns identified. (HEPATOLOGY 2014;60:468-476)

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Chronic hepatitis B (CHB) virus infection is an epidemic that is associated with cirrhosis and liver cancer.[1] Management of CHB during pregnancy remains a challenge, with unique issues that involve prevention of MTCT and safe use of antiviral therapy. Previous studies indicate that mothers with CHB pose a risk of vertical transmission of hepatitis B virus (HBV) to infants.[2,3] Without intervention, 80%-90% of infants who are born to hepatitis B e antigen (HBeAg)-positive mothers may develop CHB infection.[3,4] Use of HBV vaccine and immunoglobulin G (HBIg) within 12 hours of birth, followed by two additional HBV vaccination inoculations, has been demonstrated to reduce the mother-to-child transmission (MTCT) rate from 90% to approximately 5%-10%.[5] However, despite appropriate passive-active immunoprophylaxis, MTCT remains a concern and has been reported in approximately 8%-15% of infants who are born to highly viremic mothers, resulting in a significant incidence of infant chronic infection and adding to the large pool of patients with CHB in Asia.[6-8] Previous

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; APR, antiretroviral pregnancy registry; CHB, chronic hepatitis B; CI, confidence interval; CK, creatine kinase; HBeAg, hepatitis B e antigen; HBIg, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; MTMC, mother-to-child transmission; SAEs, severe AEs; SD, standard deviation; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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studies indicate that use of lamivudine (LAM) or telbivudine (LdT) during late pregnancy in highly viremic mothers can reduce MTCT, although long-term fetal and infant safety has not been established.[7,9,10] Currently, tenofovir disoproxil fumarate (TDF) is not approved for treatment of hepatitis B in China. A recent U.S. report suggested that TDF might be used in the third trimester of pregnancy in preventing MTCT.[11] However, real-life observational data are lacking on the use of antiviral therapy in late pregnancy for preventing MTCT. In addition, the sample size in the currently published prospective trials for antiviral treatment in pregnancy involves only approximately 100 subjects in the treatment arm, which may not be large enough to capture the uncommon adverse events (AEs). We conducted a prospective study with a sample size of 700 patients to assess the safety and efficacy of third-trimester use of LdT or LAM versus no treatment, based on the patient-physician decision in a real-life MTCT prevention setting.

Patients and Methods

Study Design. This was a prospective, open-label, interventional trial, in which patients were recruited from a tertiary care hospital (the Beijing Youan Hospital in China) between January 2009 and March 2011. The trial was approved by the institutional ethics review committee and registered with ClinicalTrials.gov (no.: NCT01743079). All subjects consented before screening for the study. Pregnant subjects were screened for the following eligibility criteria: age between 20 and 40 years, gestational age between 26 and 28 weeks, hepatitis B surface antigen (HBsAg) and HBeAg positivity, HBV DNA levels above 6 $\log_{10}$ copies/mL, and alanine aminotransferase (ALT) below the upper limit of normal (ULN; 40 IU/mL). Key exclusion criteria werethe following: coinfection with hepatitis C, D, or E or human immunodeficiency virus (HIV); evidence of hepatocellular carcinoma or cirrhosis; concurrent treatment with immune modulators, cytotoxic drugs, or steroids; clinical signs of threatened miscarriage in early pregnancy; use of antiviral therapy before or during pregnancy; evidence of fetal deformity by ultrasound examination; or if the biological father of the child had CHB.[12] We did not enroll patients with elevated ALT because LdT or LAM treatment as a monotherapy was not considered the optimal treatment for maternal active CHB. Pregnant women fulfilling the inclusion and exclusion criteria were offered participation in the study. Investigators explained the following key information to the patient and her family before the mother made a decision: (1) The standard MTCT prevention method is to administer HBIg and vaccine on time, which have approximately 90% successful rates. (2) To further reduce the MTCT rate in highly viremic mothers, antiviral therapy may be used, but there is a lack of long-term safety data. In addition, there is no guarantee of successful outcomes. (3) If the mother would like to be enrolled and receive antiviral treatment after week 28 of pregnancy, only LdT or Lam may be taken. LdT was more potent than LAM in reducing HBV DNA in a large, registration clinical trial, but included only nonpregnant female patients. Thus, safety in pregnant women has not been well established. LAM has much more short-term safety data in HBV monoinfected mothers and a larger database for HIV-infected mothers and infants. However, antiviral resistance is more common in LAM-treated patients. After discussing the risks and benefits of LdT or LAM therapy during the third trimester with standard immunization to infants versus clinical observation (no antiviral treatment) during pregnancy with standard immunization to infants, pregnant mothers were enrolled in the treatment or observation group based on patient's informed decision. Those who opted for antiviral therapy started on oral LdT 600 mg or LAM 100 mg (as per patients' wishes) daily between gestational weeks 28 and 30. Tenofovir treatment was not discussed with patients in this study because it was not an approved CHB therapy in mainland China during the study period. With adherence to our standard of care, mothers receiving no treatment (NTx) also had the same follow-up schedule before delivery as those who received antiviral therapy. After delivery, mothers taking LdT or LAM treatment discontinued treatment

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at postpartum week 4 and received follow-up every 4 weeks for 12 weeks or until ALT returned to normal if subjects had elevated ALT after cessation of antiviral therapy, whichever was longer. Mothers were instructed not to breastfeed infants during antiviral therapy because the concentration of LAM or LdT in the breast milk has not been fully studied. As the standard of care for all subjects, prenatal visits were scheduled as follows: baseline; every 2 weeks until the 36th week; and then weekly until delivery. Tests for HBV serologic status, ALT, and HBV DNA were repeated in 4-week intervals before the due date. Paired infants had the following prophylaxis schedule: 200 IU of HBIg intramuscular (Chengdu Institute of Biological Products, Chengdu, China; or Hualan Biological Engineering Inc., Xinxiang, China), and the first dose of 10 μg of recombinant HBV vaccine (Hansenula yeast vaccine; Dalian Hissen BioPharm Inc., Dalian, China) was administered within 6 hours of birth. The second injection of the same dose of HBIg was administered at 2 weeks of age. The second and third doses of recombinant HBV vaccines were given at 1 and 6 months of age, respectively. The infant's HBV serologic status and HBV DNA were tested at birth (before immunization) and again at week 52.

Outcome Measures and Endpoints. The two primary outcomes were (1) the safety and tolerability of LdT and LAM in mothers and infants, which included all AEs and drug discontinuation in patients who received at least one dose of a study drug. Data of mothers and infants who were lost to follow-up after delivery were still included for antepartum analysis of drug safety. AEs were graded according to the Common Terminology Criteria for Adverse Events (version 3.0). As per protocol, ALT flares (>5 times baseline level or >10 times ULN) were considered severe AEs (SAEs). The direct genome sequencing method was used for resistance surveillance of viral genotypic mutation(s) only in patients with virological breakthrough on antiviral therapy (defined as >1 $\log_{10}$ increase from nadir). Perinatal and partum complications (e.g., hypertensive disorders in pregnancy, gestational diabetes mellitus, fetal growth retardation, premature delivery, premature rupture of membrane, and postpartum hemorrhage) were included in the safety analysis. Safety reports for infants were tabulated using data acquired from infant follow-up visits (e.g., reports of birth defects and Apgar scores, measurements from growth charts, and development milestones).[2] MTCT rates in the treated and untreated groups were an endpoint, which was defined as detectable levels of HBV DNA or HBsAg in peripheral serum samples of infants at age 52 weeks. Secondary measurements were antiviral effects of LdT and LAM during the third trimester of pregnancy on controlling HBV viremia, defined as the percentage of mothers having predelivery serum HBV DNA reduction to levels of either partial control (<6 $\log_{10}$ copies/mL) or complete control (<500 copies/mL, polymerase chain reaction; range of detection: 500 copies; 8 × $\log_{10}$ copies/mL; Shanghai Kehua Bioengineering, Co., Ltd., Shanghai, China), maternal HBeAg loss/seroconversion and HBsAg loss/seroconversion rate (enzyme-linked immunosorbent assay; Shanghai Kehua Bioengineering). In addition, infant HBsAg status and titers at birth and age 28 weeks were also tested against the comparison of their status at the age of 52 weeks. For infants' HBsAg titers at birth, 5 IU has been recommended by our central laboratory system as a cut-off level for significance and high specificity.

Statistical Analysis. Intention to treat (ITT) was defined as an analysis performed in all enrolled patients, including those with protocol deviations, but patients who withdrew consent before treatment were excluded. Patients lost to follow-up during the study were counted as treatment failures in ITT analyses. On-treatment analysis was defined as analysis performed for all enrolled patients, including those with protocol deviations, but those who withdrew consent before treatment, who were lost to follow-up, or who discontinued the study for any other reason(s) were excluded. ITT and on-treatment analysis of baseline characteristics and all endpoints were performed. Baseline characteristics and laboratory results were summarized for the three groups by means of descriptive statistics, including percentage, means ± standard deviation (SD), and 95% CI. For the quantitative variable, the t test was used to compare group differences. For categorical variables, the chi-square test was used for group comparisons. Significance level was set at $P < 0.05$; all data were analyzed by SPSS 17.0 (SPSS, Inc., Chicago, IL).

Results

Study Population. Among 700 mothers enrolled, eight subjects withdrew consents before the baseline visit. Forty-four subjects were lost to follow-up after baseline, which included 19 mothers before delivery and 25 during the postpartum period, resulting in 648 mothers with a 52-week follow-up (LdT/LAM/NTx = 252/51/345). Patient disposition is shown in Fig. 1. At least one dose of LdT was administered in 263 patients and one dose of LAM was administered to 55 patients, resulting in 318 patients in the treated group at the baseline visit. The rest of the 374 subjects received no antiviral treatment and served as the control group. Baseline characteristics of the three study arms were similar and are shown

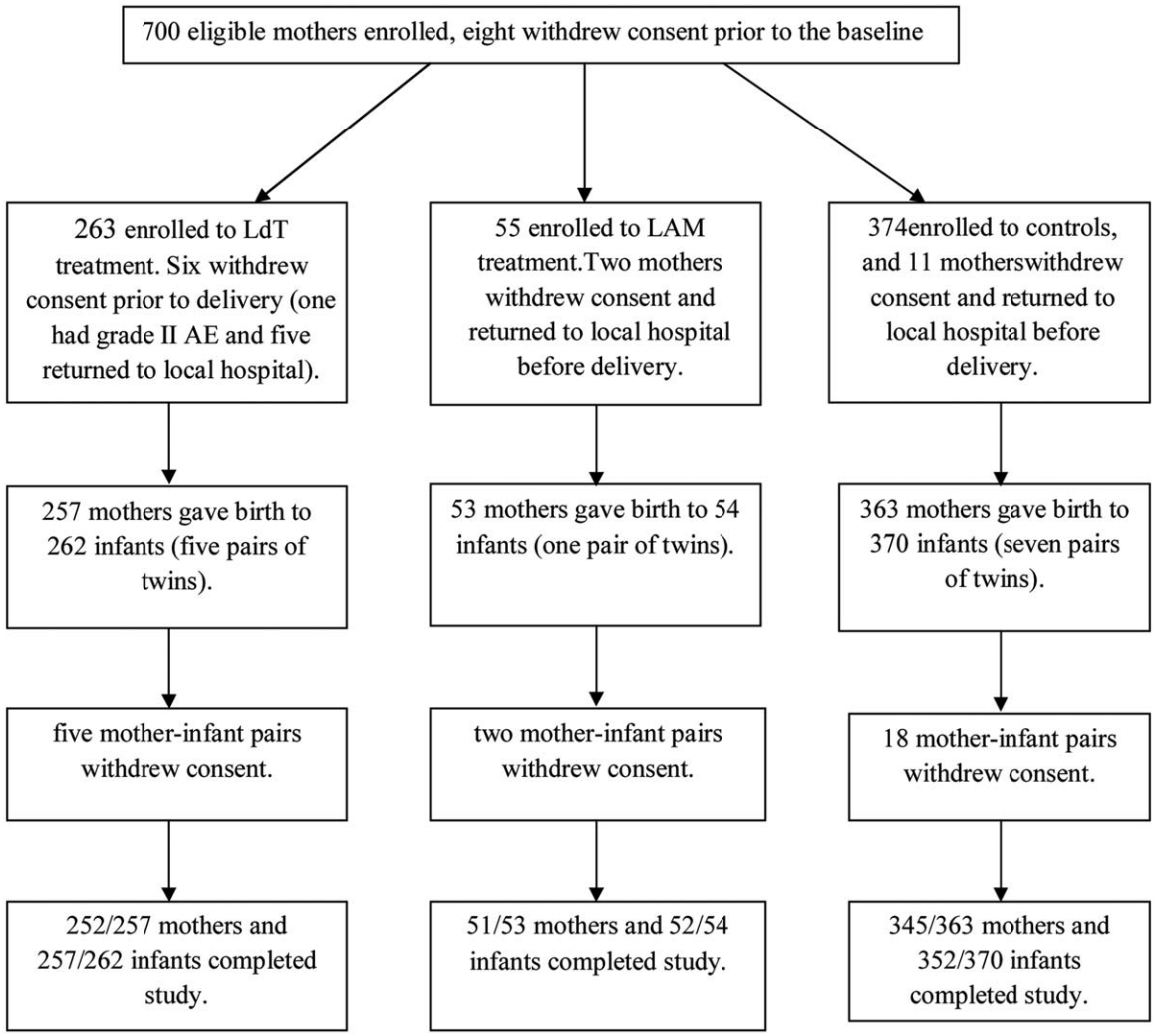

Fig. 1. Disposition of mothers and infants.

in Table 1. After the baseline visit, there were 8 mothers in the treatment group and 11 in the control group who withdrew from the study before the delivery. There were 686 infants born from 673 mothers (LdT/LAM/NTx = 257/53/363) in this cohort with 13 pairs of twins, and 661 infants completed the 52-week follow-up. There were no significant differences in baseline demographics, and the clinical characteristics of the infants in the three study arms are shown in Table 1. The mean (+SD) duration of treatment was 10.38 (+1.02) and 10.53 (+0.89) weeks for patients who received LdT and LAM therapy, respectively.

Safety of Mothers and Infants. Treatment with LdT or LAM was generally well tolerated by pregnant women. During the treatment period, 8 mothers (LdT/LAM = 6/2) in the treatment group withdrew from the study after receiving the first dose of medication. All withdrawals were for because of family relocation to other cities, except for 1 patient who experienced grade II AE (mild skin rash and a few episodes of vomiting) and voluntarily withdrew from the study. There were 20 itemized AEs, including maternal symptoms and laboratory abnormalities, reported in this study, and they are shown in Table 2. However, there were no maternal severe AEs observed in this study, and all AEs reported were grade I-II. Certain AEs occurred more often in patients in the treatment group, compared to those in the untreated group, which included headache, diarrhea, nausea, arthralgia, dizziness, dyspepsia, abdominal pain, insomnia, and ALT elevation. The earliest case with ALT elevation was observed at 4 weeks after starting antiviral therapy, and all patients' ALT elevations were within the range of 1.3-4.5 × ULN (grade I AE: ALT = 1.25-2.50 × ULN; grade II AE: ALT = 2.51-5.00 × ULN). Asymptomatic mild creatine kinase (CK) elevation (<2 × ULN) with normal electrocardiography (EKG) was reported in 1.5% (n = 4 of 263) of

Table 1. Maternal and Infant Baseline Values

Median (range)	LdT Treated	Lam Treated	All Treated	Nontreated	x^2 or t	*P* Value (All Treated vs. Nontreated)
Mothers	(n = 263)	(n = 55)	(n = 318)	(n = 374)		
Age, years	29.78 ± 6.31	28.42 ± 7.12	29.56 ± 4.78	28.97 ± 4.59	1.25	0.372
Previous pregnancy (delivery)	1.42 ± 0.31	1.22 ± 0.81	1.32 ± 0.71	1.35 ± 0.69	1.36	0.567
HBV DNA-Log, copies/mL	7.69 ± 0.44	7.62 ± 0.37	7.65 ± 0.41	7.58 ± 0.45	1.48	0.632
ALT U/L (normal <40)	30.06 ± 27.86	39.65 ± 26.37	34.85 ± 27.17	29.53 ± 20.72	1.72	0.767
Infants	(n = 262)	(n = 54)	(n = 316)	(n = 370)		
Gestational age, weeks	38.53 ± 1.23	38.17 ± 1.63	38.23 ± 1.72	38.59 ± 1.61	1.21	0.234
Delivery with cesarean section, %	52.53	52.83	52.58	53.72	0.087	0.768
Infants' height, cm	50.32 ± 2.37	50.05 ± 2.57	50.21 ± 2.62	49.83 ± 2.61	1.15	0.321
Infants' weight, kg	3.48 ± 1.07	3.36 ± 0.37	3.43 ± 0.91	3.39 ± 0.89	1.27	0.197
Apgar score (1 min)	7.89 ± 2.07	7.69 ± 1.97	7.85 ± 2.09	7.83 ± 2.16	1.16	0.289
$HBsAg^+$ at birth, %	19.46	20.37	19.62	24.32	2.19	0.139

patients receiving LdT (CK range: 198-347 U/L; normal, 34-170), and all were normalized postpartum after medication cessation. There were no patients in the LAM group or untreated group with CK elevation. In addition, direct genome sequencing was performed on all patients in the treatment group who had viral breakthrough (n = 5), and there was no genotypic mutation detected in these patients. All 5 cases had a history of medication noncompliance preceding the breakthrough. When mothers in the treated versus untreated groups were compared, there were no significant differences in gestational weeks (38.23 vs. 38.59; $P > 0.05$), incidence of postpartum hemorrhaging (1.56% [95% CI: 0.18-2.94] vs. 1.28% [95% CI: 0.12-2.44]; with $P > 0.05$), and rates of cesarean section (52.58% [95% CI: 46.43-57.56] vs. 53.72% [95% CI: 48.87-59.13]; with $P > 0.05$), respectively. As per protocol, 303 patients (LdT/LAM; n = 252:51) in the treatment group stopped antiviral therapy at postpartum week 4. Among them, 5.28% (16 of 303) had off-treatment ALT elevations (range, 1.38-2.57 × ULN) at postpartum week 8, but all patients normalized by postpartum week 16. Although a significant portion of mothers on antiviral treatment had on- or post-treatment ALT flares, compared to untreated mothers (Supporting Table 1), there was no severe hepatitis flare (ALT >10 × ULN or 5 times of baseline) were noted. All mothers followed the instructions of no breastfeeding during LdT or LAM treatment. Thus, no safety data for breastfeeding on LdT/LAM are available in this study. Incidence and nature of AEs in infants of both groups were similar, and no significant differences were found in terms of infants' weights, heights, or Apgar scores (Tables 1 and 3). Congenital deformities was reported in 0.32% (95% CI: −0.31-0.95) of infants in the treatment group (only 1 infant with unilateral cleft palate in the LdT-

Table 2. Maternal AEs Reported in the Study

N (%)	LdT Treated (n = 263)	Lam Treated (n = 55)	All Treated (n = 318)	Nontreated (n = 374)	*P* Value (All Treated vs. Nontreated)
Fatigue	13 (4.9)	2 (3.6)	15 (4.7)	9 (2.4)	0.098
Headache	16 (6.1)	3 (5.5)	19 (6.0)	1 (0.3)	<0.001
Cough	2 (0.8)	1 (1.8)	3 (0.9)	2(0.5)	0.855
Diarrhea	9 (3.4)	1 (1.8)	10 (3.1)	1 (0.3)	0.007
Epigastric pain	3 (1.1)	1 (1.8)	4 (1.3)	1 (0.3)	0.279
Nausea	23 (8.7)	3 (5.5)	26 (8.2)	1 (0.3)	<0.001
Pharyngeal/laryngeal pain	3 (1.1)	1 (1.8)	4 (1.3)	1 (0.3)	0.279
Arthralgia	22 (8.4)	2 (3.6)	24 (7.5)	13 (3.5)	0.018
Pyrexia	2 (0.8)	1 (1.8)	3 (0.9)	2 (0.5)	0.855
Rash	7 (2.7)	1 (1.8)	8 (2.5)	2 (0.5)	0.063
Back pain	0 (0)	0 (0)	0 (0)	1 (0.3)	1.000
Dizziness	12 (4.6)	1 (1.8)	13 (4.1)	1 (0.3)	0.001
Lower abdominal pain	13 (4.9)	2 (3.6)	15 (4.7)	2 (0.5)	0.001
Myalgia	1 (0.4)	1 (1.8)	2 (0.6)	1 (0.3)	0.888
Dyspepsia	15 (5.7)	3 (5.5)	18 (5.7)	2 (0.5)	<0.001
Insomnia	17 (6.5)	4 (7.2)	21 (6.6)	6 (1.6)	0.001
Abdominal distension	5 (1.9)	1 (1.8)	6 (1.9)	2 (0.5)	0.193
Pruritus	11 (4.2)	2 (3.6)	13 (4.1)	17 (4.5)	0.768
ALT elevation	41 (15.6)	2 (3.6)	43 (13.5)	10 (2.7)	<0.001
Creatine kinase elevation	4 (1.5)	0	4 (1.3)	0	0.124

Table 3. AEs Occurring in Infants*

N (%)	LdT Treated (n = 262)	LAM Treated (n = 54)	All Treated (n = 316)	Nontreated (n = 370)	*P* Value†
Fever	52 (19.9)	11 (20.4)	63 (19.9)	67 (18.1)	0.542
Skin rash	79 (30.2)	13 (24.1)	92 (29.1)	105 (28.4)	0.832
Cough	42 (16.0)	7 (13.0)	49 (15.5)	57 (15.4)	0.971
Diarrhea	92 (35.1)	16 (29.6)	108 (34.1)	119 (19.9)	0.576
Vomiting	25 (9.5)	3 (5.6)	28 (8.9)	26 (32.2)	0.374
Jaundice	10 (3.8)	1 (1.9)	11 (3.5)	14 (3.8)	0.833
Pneumonia	35 (13.4)	3 (5.6)	38 (12.0)	41 (11.1)	0.699
Bronchitis	51 (19.5)	7 (13.0)	58 (18.4)	62 (16.8)	0.583

*All were reported by investigators as non-study-drug-related AEs.
†*P* value: all treated versus nontreated.

treated group), which did not significantly differ from the rate of 0.54% (95% CI: −0.22-1.31) among infants in the untreated group ($P > 0.05$). Two infants with congenital deformities were reported in the untreated group (1 infant had six digits and another had talipes equinovarus).

Efficacy Assessment: Mothers. Before delivery, LdT-treated mothers had a mean serum HBV DNA decline >4 $\log_{10}$ copies/mL, resulting in a mean (SD) HBV DNA of 3.16 (1.59) $\log_{10}$ copies/mL, compared to no significant change in HBV DNA levels for the untreated group ($P < 0.001$). Similarly, LAM-treated mothers had a mean serum HBV DNA decline >3 log10 copies/mL, resulting in a mean (SD) HBV DNA of 3.78 (1.32) $\log_{10}$ copies/mL, compared to no change in HBV DNA levels for the untreated group ($P < 0.001$). According to ITT analysis at postpartum week 4, 36% (95% CI: 30.13-41.87) of mothers in the LdT-treated group achieved HBV DNA <500 copies/mL, compared to 0% of those in the untreated group ($P < 0.001$); 29% (95% CI: 16.78-41.22) of mothers in the LAM-treated group achieved HBV DNA <500 copies/mL, compared to 0% of those in the untreated group ($P < 0$ .001). In total, 35% (95% CI: 29.69-40.30) of mothers in the treated cohort achieved HBV DNA <500 copies/mL, compared to 0% of those in the untreated group ($P < 0.001$). During the study period, 2 mothers had HBeAg loss (2 of 257) and 1 displayed HBeAg seroconversion (1 of 257) in the LdT-treatment group, but none in the LAM or untreated group did. HBsAg loss did not occur in any of the groups in this study. In the treatment arms, 1.61% of mothers (n = 5 of 310) were nonadherent to antiviral treatment in the treatment group (all were in the LAM-treated group with HBV DNA levels <2 $\log_{10}$ copies/mL), resulting in viral breakthrough. There was no genotypic resistance mutant detected in the above-described 5 subjects during the course of antiviral treatment.

Efficacy Assessment: Infants. All infants in the study received HBIg with HBV vaccine within 6 hours of birth and completed all vaccinations according to the protocol, except for 25 infants (treated/untreated; n = 7 vs. 18) who were lost to follow-up when their age was 4 weeks or older. At birth, 19.62% (95% CI: 15.22-23.98) of infants in the treatment group and 24.32% (95% CI: 19.93-28.67) of infants in the untreated group were $HBsAg^+$ ($P = 0.95$). However, a significantly lower portion of infants in the treated group had an HBsAg titer >5 cut-off index (normal value: <1], compared to those in the untreated group (16.7% [95% CI: 12.61-20.79] vs. 43.4% [95% CI: 38.22-48.58]; $P < 0.05$). Among the 661 infants who completed the 52-week follow-up (96% retention rate), 309 and 352 infants were in the treated (LdT/LAM; n = 257 vs. 52) and untreated group, respectively, and their MTCT rates are shown in Fig. 2. At an infant age of week 52, compared to the untreated group, HBV transmission was significantly reduced in the treatment group both by on-treatment analysis (0% vs. 2.84% [95% CI: 1.1-4.6]; $P = 0.002$) and ITT analysis (2.2% [95% CI: 0.6-3.8] vs. 7.6% [95% CI: 4.9-10.3]; $P = 0.001$). However, there was no significant difference in HBV infection rate among infants in the LdT-treated group (n = 5 of 262) versus those in the LAM-treated group (n = 2 of 54) by ITT analysis (1.9% [95% CI: 0.2-3.6] vs. 3.7% [95% CI: −1.3-8.7]; $P = 0.758$) or according to on-treatment analysis (no infant was infected in both arms; 0% in LdT vs. 0% in LAM; $P > 0.05$). All infants who were $HBsAg^+$ at 52 weeks were from the group of infants who were $HBsAg^+$ at birth. None of the infants who were $HBsAg^-$ at birth developed CHB at week 52. Clinical features of infants with CHB and those without infection were compared and are shown on Table 4. Compared to noninfected infants, maternal HBV DNA levels were significantly higher among infants who were infected with CHB because their paired mothers did not receive antiviral treatment. The maternal complications of each group are shown in Supporting Table 2. All infants who were $HBsAg^+$ at week 52 were born to mothers with HBV DNA levels above 6 $\log_{10}$ copies/

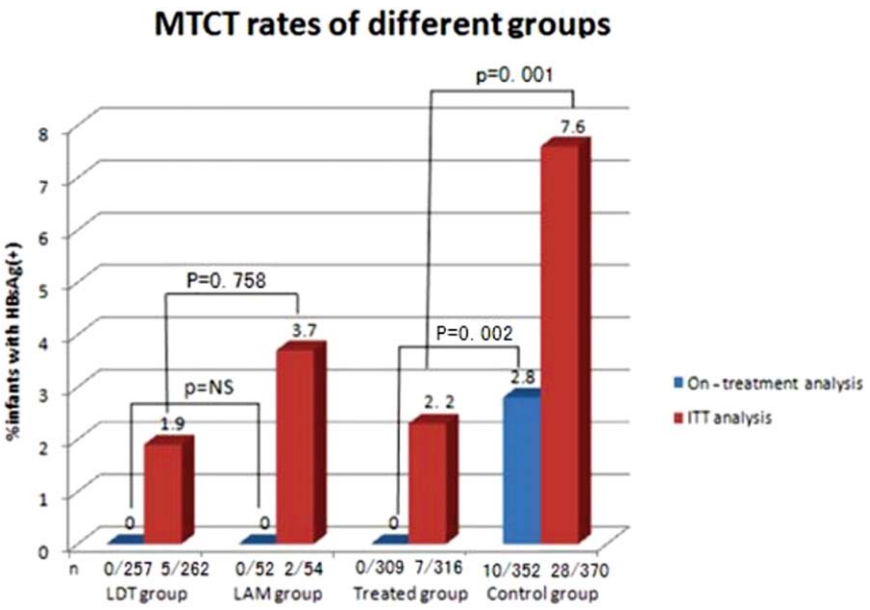

Fig. 2. MTCT rates among infants born to mothers who received antiviral or no treatment. ITT = Intention-to-treat, analysis performed in all enrolled patients. Patients lost to follow-up during the study were counted as treatment failures (infected cases). On-treatment analysis was defined as analysis performed in patients who completed the 52-week follow-up. Patients who were lost to follow-up or who discontinued the study were excluded.

mL. They were $HBsAg^+$ at birth with high HBsAg titers. In addition, there were no changes in infants' HBsAg status and HBV DNA levels when comparing tests performed at the age of 28 weeks versus those performed at the age of 52 weeks in all infants who completed the 52 week follow-up (Table 4).

Discussion

In this study, we report on prospective data of LdT and LAM therapy for prevention of MTCT. To our knowledge, this is the largest real-life study with 700 subjects enrolled to evaluate the effects and safety of antiviral treatment in this special population. Our results indicate that treatment with LdT or LAM for highly viremic mothers in the third trimester appears to be safe for both mothers and the fetus/infant after 1 year of follow-up. In combination with standard infant HBV immunoprophylaxis, a significant reduction in MTCT rates was observed for mothers treated with LdT or LAM, compared to those untreated.

Antiviral therapy during pregnancy remains a challenge for clinicians because the safety of fetal exposure to antiviral medication is a primary concern.[14-16] Recently, Han et al. examined 136 mothers treated with LdT during pregnancy with follow-up to 28 weeks postpartum.[10] Although the trial design included monitoring all AEs and biochemical tests, the study only reported on maternal and fetus and infant complications without details on patient symptoms and laboratory abnormalities. Our

Table 4. Clinical Features of Infants With or Without HBV Infection

	Infants With CHB (n = 10)	Infants Without CHB (n = 676)	*P* Value
Maternal features			
Mother's age, years (means ± SD)	28.3 ± 1.45	27.9 ± 0.53	0.85
Duration of pregnancy, weeks (means ± SD)	38.5 ± 0.43	39.1±0.35	0.51
HBV DNA at delivery, log_{10} c/mL (means ± SD)	8.67 ± 0.38	7.24 ± 0.30	0.03
Maternal complications, %	30.0	18.3	0.718
Infants at birth			
Sex, male/female	6/4	345/331	0.94
Birth weight, g (means ± SD)	3,450 ± 457	3,501 ± 716	0.58
HBsAg titers, IU/mL (means ± SD)	4,023 ± 256	2.31 ± 0.58	<0.01
HBV DNA, log_{10} c/mL (means ± SD)	4.2 ± 0.52	0	<0.01
Infants at 28 weeks			
HBsAg titers, IU/mL (means ± SD)	3,052 ± 562	0	<0.01
HBV DNA, log_{10} c/mL (means ± SD)	3.1 ± 0.62	0	<0.01
Infants at 52 weeks			
HBsAg titers, IU/mL (means ± SD)	3,126 ± 326	0	<0.01
HBV DNA, log_{10} c/mL (means ± SD)	3.5 ± 0.28	0	<0.01

All infants were vaccinated with genetically engineered HBV vaccine (10 μg) according to a standard vaccination regimen (i.e., within 6 hours of birth, at week 4, and at week 24) and 200-IU doses of HBIg immediately (within 2 hours) after birth and at day 15. c/mL refers to copies/mL.

study, with a much larger sample size (n = 252 on LdT), identified that more than 10% of pregnant mothers experienced the following AEs: fatigue; headache; nausea; arthralgia; pruritus; abdominal pain; insomnia; and dyspepsia. On-treatment ALT flares are considered to be either from disease activity or secondary to medication. In our study, there were mothers with ALT >19 U/L, and they could have potentially been in the early stage of immune clearance. It is noteworthy that 16.0% of mothers had ALT elevation with LdT treatment, which was significantly higher than the percentage in the control group (2.8%; $P < 0.001$). Onset of ALT elevation could be as early as 4 weeks into LdT treatment. Mothers treated with LdT in our cohort had a higher frequency of on-treatment ALT flare than patients in the LdT registration trial (GLOBE study; ALT flare: 3.2%). In addition, frequent ALT flares were observed among LdT-treated mothers in our trial, compared with previous studies of pregnant mothers. Close monitoring of ALT flare and careful assessment of its severity in mothers receiving LdT treatment is highly recommended. Post-treatment follow-up of ALT flare should be mandated. There were 1.6% of subjects who had mild CK elevation during LdT treatment in our study, but none in the LAM-treated group displayed CK elevation. However, they were all asymptomatic without EKG abnormality and considered by investigators as not clinically significant. The lower rate of CK elevation observed in our study may be the result of the short duration of LdT exposure. Although ALT flares at postpartum after cessation of LdT or LAM treatment were also common, none of the cases displayed severe flares in this large cohort.

Resistance surveillance with genotypic analysis has been emphasized by society guidelines when using LdT or LAM to treat viremic patients over 12 weeks.[18,19] Our data suggest that in treatment-naïve mothers, antiviral resistance was uncommon when receiving antiviral treatment during late pregnancy to prevent MTCT because the treatment cessation generally occurs within 12-16 weeks after receiving the first dose. There were 5 cases of viral breakthrough among patients on antivirals in this cohort, but all were the result of nonadherence to medication. In our study, there were no genotypic mutants detected among patients with viral breakthrough on LAM or LdT therapy. It is possible that our laboratory did not detect emergent mutants at a low level of replication because of the sensitivity of the test in this study.[19] However, with cessation of antiviral treatment at postpartum, wild-type HBV is likely to repopulate and suppress mutants with resistance to the antiviral medication. Although drug-resistant mutants can be selected for,[20] the long-term consequence of low levels of antiviral-resistant mutant replication remains unknown. However, we found that testing the HBV DNA level monthly before delivery was beneficial because monitoring treatment adherence was an important aspect of achieving HBV DNA levels below 6 $\log_{10}$ copies/mL.

Several recent publications indicate that there are no differences in fetus and infant complication rates or birth defect rates when using LdT or LAM to treat pregnant women versus no antiviral treatment.[7,9,10,21,22] Brown et al. analyzed neonatal safety data after maternal exposure to LAM or TDF in the Antiretroviral Pregnancy Registry database and compared their findings to population-based controls.[22] They concluded that the major birth defect rates in the two groups were comparable (2.8% [95% CI: 2.6-3.1] vs. 2.72% [95% CI: 2.68-2.76]; $P = 0.8$, respectively). However, there were not sufficient data on maternal LdT exposure for review (<200 cases), and conclusions concerning the birth-defect rate from LAM exposure were based on self-reported results at birth. Recently, Liu et al. reported on 86 mothers treated with LdT either before or in early pregnancy.[21] They reported that 6.7% of mothers suffered early embryonic death or spontaneous abortion and that 1.1% of mothers suffered ectopic pregnancy after LdT exposure. Among 52 live newborns with maternal LdT exposure, the rate of congenital abnormality was 3.8%. However, there was no control group in this study. We believe that our data significantly contribute to the above-described data gap because we had a larger sample size and longer observation. Our study had 262 and 52 infants born to LdT- and LAM-treated mothers without safety concerns identified at 52 weeks of follow-up, respectively. We demonstrated that treatment with LdT or LAM did not increase fetus and infant complications or birth defects, compared to infants in the untreated group. Thus, this study supports the safe use of LdT and LAM in a real-life setting in highly viremic mothers.

Although the efficacy of LdT in reducing MTCT has been reported on in several studies,[9,10] use of LAM on highly viremic mothers for prevention of MTCT remains controversial. Xu et al. reported that 18% of infants born to mothers receiving LAM in late pregnancy were infected with CHB. There was no significant difference in MTCT rates between infants in the LAM treated versus untreated group, according to sensitivity analysis.[7] By both ITT and on-treatment analysis, our study indicated that use of LAM in highly viremic mothers significantly reduced MTCT, compared to no treatment. Subjects in our study started on LAM approximately 2-4 weeks earlier than those mothers in Xu et al.'s study, resulting in predelivery maternal HBV DNA <5 $\log_{10}$ copies/mL. In contrast, subjects in

Xu et al.'s study received LAM between 32 and 34 weeks of gestation and had significant viremia at delivery, resulting in a high MTCT rate. It appears that our early use of LAM may have a better chance to achieve maternal HBV DNA reduction to levels below the transmission threshold of 6 $\log_{10}$ copies/mL.

A number of features are worth noting in the current study. Our trial provides the largest cohort examining the safety and efficacy of LdT and LAM treatment in late pregnancy. The study design simulated the decision-making process for antiviral therapy for pregnant women in a real-life setting and allowed patient selection of antiviral therapy versus no treatment at late pregnancy. Our study also indicates that using LdT or LAM may be equally effective in reducing MTCT in this population. However, there are inevitable limitations of our study. It was a nonrandomized study and did not include treatment-experienced patients because tenofovir is not currently available in China for CHB. Thus, our results may not be generalizable to patients with LdT or LAM resistance.

In conclusion, our results indicate that $HBsAg^+$ mothers with HBV DNA >6 $\log_{10}$ copies/mL who received LdT or LAM treatment at gestation weeks 28-30 displayed a significant reduction in MTCT rate with comparable safety and efficacy. However, on-treatment ALT flares are common and should be monitored. Infants' HBsAg statuses at the age of 28 weeks were consistent with those at 52 weeks. Thus, MTCT rate may be determined at the infant age of 28 weeks. Our data support the use of LdT or LAM during late pregnancy in highly viremic mothers for the purpose of reducing MTCT of CHB.

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Supporting Information

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