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Lamivudine *versus* tenofovir for preventing mother-to-child transmission of hepatitis B virus in highly viremic pregnant women: A prospective, matched cohort study

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ABSTRACT

Objective: To evaluate the efficacy and safety of lamivudine and tenofovir in preventing mother-to-child transmission of hepatitis B virus (HBV) in pregnant women with chronic HBsAg positivity and high viral load.

Methods: A prospective, matched cohort study was conducted on pregnant women with high viral load (>10^6 copies/mL) from March 2015 to March 2018 at two hospitals in Vietnam. Infants born to these women were followed up until January 2019. Data were collected on maternal HBV DNA load, organ function test results, and adverse reactions, as well as infant HBV markers at birth and at 1, 6, and 12 months of age. Data were analyzed between February and June 2019.

Results: A total of 80 pregnant women were enrolled and divided into lamivudine group (n=39) and tenofovir group (n=41). In the tenofovir group, the median maternal HBV DNA load decreased sharply from 7.2 (6.8-7.6) $\log_{10}$ copies/mL before treatment to 4.4 (2.8-5.6) $\log_{10}$ copies/mL at delivery, which was a significantly greater reduction than that observed in the lamivudine group. The mean ALT and creatinine levels in both groups increased by no more than 2-fold compared with baseline, but remained within the normal range. The efficacy of preventing HBV mother-to-child transmission was similar between the two infant groups: 4.8% in the lamivudine group and 3.8% in the tenofovir group.

Conclusions: Tenofovir should be the preferred option for preventing mother-to-child transmission of hepatitis B virus in pregnant women with high HBV viral load. Future studies with larger sample sizes and additional control groups are warranted to strengthen the evidence and improve the quality of treatment recommendations.

KEYWORDS: Hepatitis B virus; Lamivudine; Tenofovir; Vertical transmission; Pregnancy

1. Introduction

Hepatitis B, caused by the hepatitis B virus (HBV), remains a major global public health burden due to its high prevalence, associated mortality, and substantial healthcare costs. According to the World Health Organization report in 2022, approximately 254 million people, accounting for 3.3% of the world's population, were

Summary

Question: Among pregnant women with chronic hepatitis B and high viral load, is tenofovir more effective and safer than lamivudine in preventing mother-to-child transmission of hepatitis B virus?

Findings: In this prospective matched cohort study of 80 pregnant women, tenofovir reduced maternal HBV DNA levels more markedly than lamivudine at delivery, while both drugs showed comparable safety profiles. The rates of mother-to-child transmission were low and not significantly different between the two groups.

Meaning: Tenofovir provides superior viral suppression with similar safety and should be prioritized for preventing HBV mother-to-child transmission in highly viremic pregnant women.

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chronically infected with HBV, and 1.1 million deaths and 1.23 million new cases occur each year[1]. In Vietnam, the prevalence of HBV infection in the general population is high, ranging from 10% to 15%[2], while the number of chronic hepatitis B cases was 8.7 million, and the number of deaths related to hepatitis was around 23 500 according to the report in 2019 by the Ministry of Health[3].

Studies worldwide have shown that besides the common transmission routes of HBV, such as blood and sexual transmission, vertical transmission from mother to child during the perinatal period is the main and most important transmission route, especially in high HBV prevalence areas including Vietnam. Specifically, this transmission route accounts for 40% to over 90% of all HBV infections depending on the mother's HBeAg status and HBV DNA load[1,4].

To control chronic hepatitis B and eliminate HBV transmission, many new drugs have been developed and applied in clinical practice. However, treatment can only alleviate the progression severity of hepatitis B; once chronic infection occurs, it is almost impossible to eliminate HBV[5]. Therefore, the global consensus is to prioritize preventing HBV spread, with the primary focus on mother-to-child transmission.

A safe and effective measure to reduce mother-to-child transmission of HBV is HBV vaccination for infants[3]. In fact, 10%-20% of infants born to HBsAg(+)/HBeAg(+) mothers are still infected with HBV despite being fully vaccinated against HBV (*i.e.*, HBV "vaccine escape" phenomenon)[1,6]. The main cause of this phenomenon is intrauterine HBV transmission, which is primarily due to maternal high HBV DNA loads exceeding the placenta's barrier capacity[7]. In recent years, antiviral treatment during late pregnancy for women with chronic HBV infection and high HBV DNA load has been proven safe and effective in numerous international studies, including those conducted in Vietnam[8–12]. However, to date, this antiviral treatment strategy has not been widely adopted, especially in provincial healthcare facilities in Vietnam, and relevant research conducted locally remains limited. In addition, there have been no in-depth studies exploring the efficacy of this treatment in both mothers and infants with maternal high HBV DNA load. Therefore, this study was conducted to evaluate the efficacy and safety of lamivudine and tenofovir in preventing HBV mother-to-child transmission in pregnant women with chronic HBsAg positivity and high HBV DNA load.

2. Methods

2.1. Study design

A prospective, matched cohort study was conducted from March 2015 to March 2018 at two hospitals in Hai Duong province-the northern area of Vietnam by the Strengthening the Reporting of Observational Studies in Epidemiology statement (https://www.strobe-statement.org/). Follow-up of hepatitis B infection status in children born until January 2019.

2.2. Participants

Pregnant women who attended antenatal care and were scheduled to give birth in the hospital were enrolled in the study. Pregnant women participate in the study if they meet the following criteria: 1) having chronic hepatitis B virus infection with high blood HBV DNA load (>10^6 copies/mL)-that aligns with recommendations from the EASL (2017) guidelines[13], and the HBeAg status of pregnant women was also assessed at enrollment, HBeAg-positive and HBeAg-negative mothers were both included in the study; 2) giving birth during the study period; and 3) singleton pregnancy. Women were excluded or withdrawn from the study if they: 1) co-infected with human immunodeficiency virus or hepatitis C virus; 2) clinical manifestations related to liver disease, and laboratory tests assessing liver, kidney, and hematological function, as well as pregnancy poisoning and gestational diabetes; 3) abnormal test indicators: aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ⩾2 times the normal limit, blood creatinine >150 μmol/L, haemoglobin <80 g/L; 4) being treated with antiviral drugs before; 5) having ultrasound or prenatal examination results that suggest the fetus is underdeveloped or has morphological abnormalities (congenital malformations); 6) history of complication of pregnancy. The flow diagram of the study is shown in Figure 1.

2.3. Grouping

All eligible pregnant women were counseled in detail by the investigator about the treatment [purpose of treatment, previously published treatment efficacy of lamivudine (LAM) or tenofovir disoproxil fumarate (TDF) drugs, treatment duration, type of treatment, side effects, dosage and timing of medication, other issues to be noted during and after treatment]. For subjects who agreed and signed a voluntary participation form, they were divided into LAM or TDF groups depend on medicine prescription. The minimum sample size was calculated to be 39 participants per group. Eligible pregnant women were consecutively enrolled during the study period until the required sample size was reached.

To ensure comparability between groups in this prospective matched cohort design, each woman initiated on TDF was matched with a woman receiving LAM based on key baseline characteristics, including maternal age (±2 years), gestational age at treatment initiation (⩾28 weeks), baseline HBV DNA level (same viral load

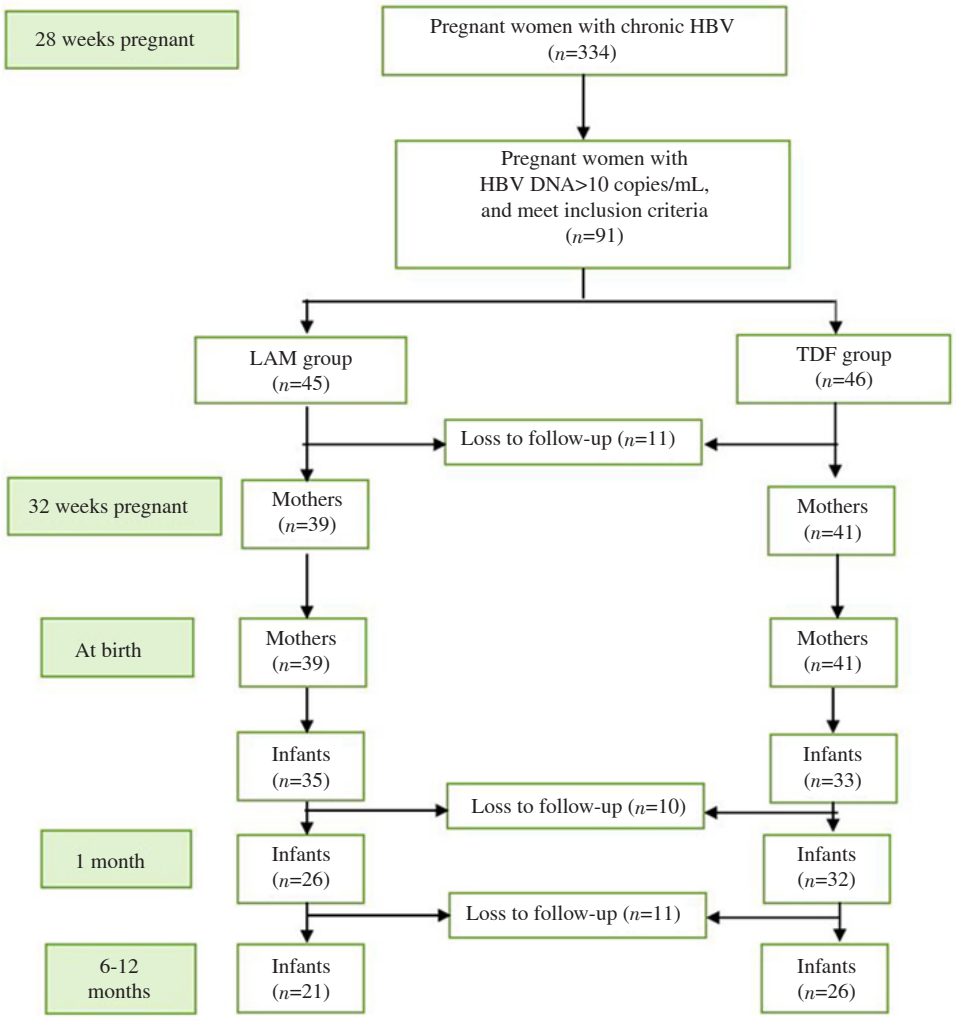

Figure 1. The subject selection flow chart.

category: 10^6-10^7 or >10^7 copies/mL), and HBeAg status. Matching was performed sequentially during enrollment until each group had a minimum of 39 participants.

Treatment begins from the 28th week of pregnancy and continues for 3 months after birth. Patients in the LAM group were orally administered lamivudine at a daily dose of 100 mg, taking 1 tablet/day, while patients in the TDF group were orally administered tenofovir disoproxil fumarate at a daily dose of 300 mg, taking 1 tablet/day.

2.4. Neonatal immunization

All newborns were injected with the hepatitis B vaccine (according to the Expanded Program on Immunization in Vietnam approved by the Ministry of Health) at 0, 2, 3, and 4 months after birth. The infant was also injected with HBIG (Immuno-HBs 180 IU/mL, Kedrion, Italy) at the anterior thigh site of the infant and on the opposite side of the newborn hepatitis B vaccine injection, at a dose of 180 IU, injected as soon as possible within the first 24 hours after birth.

2.5. Observation index

For mothers: The evaluation of the effect of LAM and TDF was determined by the blood HBV DNA load test, while the safety of both drugs was assessed by functions of organs (liver, kidney, blood) test (including AST, ALT, urea, creatinine, and hemoglobin indices) at the time before treatment and delivery and side effects in mothers during treatment appearing immediately after taking the drug and in the following days.

For infant: HBV infection status of 2 groups having mothers treated with LAM or TDF, determined by comparing the test results of markers HBsAg, HBV DNA, anti-HBsAg at the time points immediately after birth, 1 month, and 6-12 months. The conclusion on vertical transmission of hepatitis B virus from mother to child assessing at 6-12 months was if there have HBsAg (+) and/or HBV DNA (+). At the same time, the test results confirm chronic infection with HBcAb total (+)/HBcAb IgM (-).

2.6. Laboratory examinations

Serum HBV DNA level was determined by Realtime PCR gene amplification molecular biology technique to quantify HBV virus concentration, maternal venous blood at 28 weeks of pregnancy, at birth, umbilical cord blood, and fetal venous blood at 1, 6, and 12 months of age. Using the Realplex 4 machine of Eppendorf (Federal Republic of Germany), and the chemical kit for real-time PCR reaction, iVAHBV qPCR Mix of Viet A Technology Joint Stock Company with a detection threshold of 3×10^2 copies/mL. Serum hepatitis B markers were detected by immunochromatographic techniques (HBsAg and HBeAg qualitative), and anti-HBsAg antibody concentrations were quantified by chemiluminescent immunoassay. Liver and renal functions were detected with a fully automatic biochemistry analyzer while total peripheral blood cell analysis was performed by LASER.

2.7. Statistical analysis

Data were statistically analyzed between February and June 2019 using IBM SPSS Statistics (version 20; IBM Corporation, United States), with a significance level of 0.05. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean±standard deviation and were compared using the independent-sample *t*-test for comparisons between two groups and the paired-sample *t*-test for comparisons before and after treatment within the same group. Non-normally distributed continuous variables are presented as median (Q1-Q3) and were compared using the Mann-Whitney *U* test for between-group comparisons and the Wilcoxon signed-rank test for paired comparisons. Categorical variables are presented as frequencies and percentages and were compared using the *Chi*-square test or Fisher's exact test when the expected frequency in any cell was less than 5. To reduce the risk of Type I error due to multiple statistical testing, Bonferroni correction was applied for sets of related comparisons. All statistical tests were two-tailed, and a *P*-value <0.05 after correction was considered statistically significant.

2.8. Ethical statements

The study was approved by Department of Science and Technology of Hai Duong province and Hai Phong University of Medicine and Pharmacy with Decision No. YD.14. HKTYT.15 dated on January 6, 2015. All participants were provided a detailed explaination about purpose of the study and all agreed to voluntarily participate. This study does not involve any form of inducement or coercion. Pregnant women participating in the study received free treatment and testing according to the implementation budget.

3. Results

During the period from March 2015 to March 2018, a total of 91 pregnant women were eligible to participate in the study. Finally, 80 pregnant women completed the treatment, including 41 patients in the TDF group and 39 patients in the LAM group. There were no significant differences in age, parity, HBV DNA load, HBeAg levels, and other indicators between the two groups before treatment (Table 1).

3.1. Comparison of the efficacy of tenofovir versus lamivudine in antiviral therapy for hepatitis B–infected women with high HBV DNA load during pregnancy

The distribution of HBV DNA load of pregnant women at delivery in Table 2 showed that the proportion of participants in LAM group with high HBV DNA load $>10^6$ copies/mL and from 10^4-10^6 copies/mL was high, with 10.3% (4/39) and 71.8% (28/39), respectively, it was significantly higher in the group of TDF treatment with the corresponding rates of 4.9% (2/41) and 19.5% (8/41), respectively. The difference in both groups was statistically significant ($P<0.001$).

The median HBV DNA load of pregnant women after LAM treatment was 2.3 (1.9-3.8) $\log_{10}$ copies/mL, higher than after TDF treatment 4.4 (2.8-5.6) $\log_{10}$ copies/mL ($P<0.001$). In the LAM group, the proportion of patients with HBV DNA $\leqslant$2.4 $\log_{10}$copies/mL was significantly higher (64.1% *vs.* 22.0%, $P<0.01$), whereas in the TDF group, higher HBV DNA levels ($\geqslant$3.5 $\log_{10}$ copies/mL) were more frequently observed ($P<0.01$) (Table 2).

3.2. Comparison of the safety of tenofovir versus lamivudine in antiviral therapy for women with hepatitis B infection and high HBV DNA load during pregnancy

Table 3 showed that among pregnant women treated with LAM, the mean levels of urea, creatinine, and hemoglobin after treatment were significantly higher than at baseline and remained within normal limits ($P<0.001$). There was no statistically significant change in AST and ALT levels after treatment in the LAM group ($P>0.05$). In the LAM group, only one case showed a marked increase in ALT level, with an increase of 5.4 times compared to baseline, reaching a maximum value of 115.5 U/L.

In the TDF group, the levels of AST, ALT, creatinine, and hemoglobin significantly increased after treatment compared

Table 1. Participants' characteristics.

Contents	Drug treatment group		*P*-value
	LAM (*n*=39)	TDF (*n*=41)	
Age, years, mean±SD	24.7±3.4	26.2±4.5	0.06[a]
Occupation			0.73[b]
Workers	15 (38.5)	23 (56.1)	
Office staff	11 (28.2)	7 (17.1)	
Freelance work	9 (23.1)	7 (17.1)	
Teacher	2 (5.1)	2 (4.9)	
Medical staff	1 (2.6)	1 (2.4)	
Farmer	1 (2.6)	1 (2.4)	
Number of births			0.73[b]
1	26 (66.7)	24 (58.5)	
2	11 (28.2)	13 (31.7)	
3	2 (5.1)	4 (9.8)	
Number of family members with hepatitis			0.14[c]
1	34 (87.2)	29 (70.7)	
2	5 (12.8)	10 (24.4)	
>2	0 (0)	2 (4.9)	
HBV DNA load at baseline, $\times 10^6$ copies/mL, median (Q1, Q3)	5.2 (1.1-22.8)	12.6 (2.3-65.4)	0.12[d]
HBV DNA load at baseline, $\log_{10}$ copies/mL, median (Q1, Q3)	7.0 (6.7-7.3)	7.2 (6.8-7.6)	0.19[d]
Mean of treated time, days, mean±SD	74.1±12.1	73.6±14.3	0.86[a]
HBeAg (+) at baseline	36 (94.7)	39 (97.5)	0.61[c]
Infant birth weight, g, mean±SD	3 169.0±464.6	3 071.0±422.6	0.32[a]
<2 500	3 (7.7)	5 (12.2)	0.71[c]
≥2 500	36 (92.3)	36 (87.8)	
Gestational age, weeks, mean±SD	38.6±1.7	38.5±2.0	0.86[a]
<37	4 (10.3)	7 (17.1)	0.52[c]
≥37	35 (89.7)	34 (82.9)	
Breastfeeding	38 (97.4)	41 (100.0)	0.49[c]

Data are expressed as *n* (%) unless indicated. LAM: Lamivudine; TDF: Tenofovir. [a]Independent sample *t*-test. [b]*Chi*-square test. [c]Fisher's exact test. [d]Mann-Whitney *U* test.

Table 2. Effects of lamivudine and tenofovir treatment on pregnant women at delivery [*n* (%)].

Contents	Drug treatment group		*P*-value
	LAM (*n*=39)	TDF (*n*=41)	
HBV DNA load after treatment			<0.001[a]
HBV DNA ≤10^4 copies/mL	7 (17.9)	31 (75.6)	
10^4 < HBV DNA ≤10^6 copies/mL	28 (71.8)	8 (19.5)	
HBV DNA >10^6 copies/mL	4 (10.3)	2 (4.9)	
HBV DNA load after treatment, $\log_{10}$ copies/mL, median (Q1, Q3)	2.3 (1.9-3.8)	4.4 (2.8-5.6)	<0.001[b]
≤2.4 $\log_{10}$	25 (64.1)	9 (22.0)	<0.01[a]
2.5-3.4 $\log_{10}$	8 (20.5)	3 (7.3)	0.13[a]
3.5-4.4 $\log_{10}$	3 (7.7)	14 (34.1)	<0.01[a]
≥4.5 $\log_{10}$	3 (7.7)	15 (36.6)	<0.01[a]

Data are expressed as *n* (%). LAM: Lamivudine; TDF: Tenofovir. [a]Fisher's exact test. [b]Mann-Whitney *U* test.

with baseline and remained within normal limits (P<0.01), while no significant difference was observed in urea levels (P=0.14). Similarly, only one case in the TDF group showed a notable increase in ALT level, with an increase of 3.9 times compared to baseline, and the highest recorded value was 115 U/L.

Side effects were more frequently observed in TDF group (9.8%) compared with those in the LAM group (2.6%), although the overall incidence was low. All side effects occurred within the first week of treatment, were mild in severity, and did not require additional medical intervention.

3.3. Comparison of the efficacy of tenofovir versus lamivudine in preventing mother-to-child transmission of hepatitis B virus

At birth, 68 children were tested for umbilical cord blood, of which 7/68 children (10.3%) had HBsAg(+). Specifically, in the group of children whose mothers were treated with LAM, 4 children were infected with HBV (11.4%), and this number was 3 for the TDF group (9.1%). At the time of 6-12 months of age-the conclusion time on hepatitis B infection status, only 47/80 children were evaluated,

Table 3. Effects of lamivudine and tenofovir treatment on organ functions of women.

Contents	LAM (n=39)			TDF (n=41)		
	Before treatment	After treatment	P-value	Before treatment	After treatment	P-value
Liver function test						
AST, U/L	22.4±7.8	25.8±11.7	0.06[a]	24.6±6.1	31.0±12.1	<0.01[a]
ALT, U/L, median (Q1-Q3)	23 (18-30)	24 (18-34)	0.36[b]	22 (17-28)	30 (22-45)	<0.01[b]
Renal function test						
Urea, mmol/L	2.7±0.6	3.2±1.0	<0.01[a]	3.1±0.7	3.3±0.9	0.14[a]
Creatinine, mmol/L	51.0±6.4	58.7±10.3	<0.001[a]	53.3±6.2	65.5±11.3	<0.001[a]
Haemoglobin, g/L	110.8±9.3	123.1±10.8	<0.001[a]	112.2±7.8	123.2±12.9	<0.001[a]
Side effects, n (%)		1 (2.6)			4 (9.8)	

Data are presented as mean±SD unless indicated. LAM: Lamivudine; TDF: Tenofovir. [a]Paired sample t-test. [b]Wilcoxon signed-rank test.

Table 4. Serum HBsAg at birth, 1 months and 6-12 months of age in infants born to mothers treated by tenofovir *versus* lamivudine.

Duration	Drug treatment group of mothers				P-value
	LAM		TDF		
	Infected (HBsAg+)	Not infected (HBsAg-)	Infected (HBsAg+)	Not infected (HBsAg-)	
At birth n_{LAM}=35 n_{TDF}=33	4 (11.4)	31 (88.6)	3 (9.1)	30 (90.9)	>0.99
1 months n_{LAM}=26 n_{TDF}=32	0 (0.0)	26 (100.0)	0 (0.0)	32 (100.0)	>0.99
6-12 months n_{LAM}=21 n_{TDF}=26	1 (4.8)	20 (95.2)	1 (3.8)	25 (96.2)	>0.99

P-values represent comparisons of infection rates (HBsAg positive *vs.* negative) between the LAM and TDF groups at each time point, using Fisher's exact test. Data are expressed as n (%). LAM: Lamivudine; TDF: Tenofovir.

Table 5. Development of HBV markers in 3 cases of children infected with hepatitis B.

Duration	HBV markers	Drug treatment group of mothers		
		LAM		TDF
		Case 1	Case 2	Case 3
At birth	HBsAg	Neg	NC	Neg
	HBV DNA, copies/mL	Neg	NC	Neg
1 month	HBsAg	Neg	Neg	Neg
	HBV DNA	Neg	Neg	Neg
	Anti HBsAg, mIU/mL	121.6	212	304
6 months	HBsAg	Neg	NC	NC
	HBV DNA, copies/mL	Neg	NC	NC
	Anti HBsAg, mIU/mL	31.1	NC	NC
12 months	HBsAg	Neg	Pos	Pos
	HBV DNA, copies/mL	2.44×10^4	1.87×10^7	3.57×10^8
	Anti HBsAg, mIU/mL	104	Neg	Neg
	HBcAb total	Pos	Pos	Pos
	HBcAb IgM	Pos	Neg	Neg
Results		Acute hepatitis B infection	Chronic hepatitis B infection	

NC: Can not calculated; Neg.: Negative result; Pos.: Positive result. LAM: Lamivudine; TDF: Tenofovir.

of which 1 children of LAM group (4.8%), and 1 infant of TDF group (3.8%) were chronic infected with HBV, and both cases were not detected with HBV infection at 1 month of age (Table 4).

In addition, an infant case of acute HBV infection belonged to the group whose mothers were treated with LAM during pregnancy, and HBV markers were all negative at the time of birth, 1 month, and 6 months of age; while test results at 12 months of age showed coexistence of HBV DNA and antiHBs, with negative HBsAg. Both children with chronic HBV infection had very high HBV DNA levels (>10^7 copies/mL). The anti-HBsAg antibody levels of these two children at 1 month were high (>100 mIU/mL) (Table 5).

4. Discussion

Systematic evaluation of the efficacy of LAM and TDF prophylaxis in both pregnant women and their offspring is important in providing valuable evidence for the recommendation of this regimen for widespread use. In this study, we observed the treatment duration for pregnant women with high HBV DNA load from the 28th week of pregnancy with the aim of reducing HBV DNA viral load in pregnant women, thereby preventing transmission of HBV to their children. Thus, the treatment time was earlier, and the treatment threshold was lower, which was completely consistent with the general trend of the world according to guidelines of the EASL and the American Association for the Study of Liver Diseases[13,14].

Regarding the effectiveness of treatment in reducing viral load at the time of delivery, our study found that the rate of pregnant women with high HBV DNA load (>10^4 copies/mL) after LAM treatment accounted for 82.1%, significantly higher than that of pregnant women after TDF treatment at 24.4% (P<0.001). In addition, when comparing the mean reduction of HBV DNA before and after treatment, the results showed that the reduction in the TDF group was greater than that in the LAM group, with levels 7.2 (6.8-7.6) and 7.0 (6.7-7.3) before treatment down to 4.4 (2.8-5.6) and 2.3 (1.9-3.8) $\log_{10}$ copies/mL (P<0.001). Other previous studies also clearly showed that the effectiveness of reducing HBV DNA load after treatment with TDF was superior to that with LAM[12,15,16]. Specifically, the study by Jourdain *et al.* in Thailand showed that after TDF treatment, the mean HBV DNA load at the time of birth was 4 $\log_{10}$ IU/mL, significantly reduced compared to the baseline, which was 7.6 $\log_{10}$ IU/mL[15]. In Vietnam, a study by Nguyen Van Bang *et al*. noted that in the group of pregnant women treated with TDF, the HBV DNA load decreased by a concentration of 3-4 $\log_{10}$ (81.7%), whereas in the LAM group, the HBV DNA load decreased by a lower level of 1-3 $\log_{10}$ copies/mL (75.8%) (P<0.05)[12].

After treatment, the ALT liver enzyme concentration and creatinine index in both groups of pregnant women increased on average ⩽2 times compared to before treatment. Of which, 1 case in the LAM treatment group had the highest increase of 115.5 U/L, and 1 case in the TDF treatment group had the highest increase of 115 U/L. Both cases had no clinical manifestations of the disease, and the birth process proceeded normally. The hemoglobin index after LAM treatment increased more than before treatment and was within normal limits. This result is similar to other studies with an increase in liver enzymes during TDF and LAM treatment[8,12,17]. The study by Pan *et al*. showed that ALT increased from 1.1 to 5 times and creatinine increased from 1.3 to 3 times the normal value after TDF treatment for pregnant women, and there were no cases of hepatitis B outbreak during treatment[17]. Similarly, Zhang *et al*. also found that during the treatment of LAM for 53 pregnant women from gestational weeks 28-30 to 4 weeks postpartum, there was an increase in ALT from 1.3-4.5 times the normal values. At the same time, no pregnant woman had an outbreak of hepatitis B during the treatment[18].

Regarding side effects of the drug during treatment, 6.3% (5/80) of pregnant women experienced side effects, including 1 case in the LAM treatment group and 4 cases in the TDF group. The result of our study was similar to previous studies[8,12]. However, a study by Pan *et al*. recorded more side effects than our study. In addition to the manifestations in the digestive system, other events also appeared such as cough, headache, insomnia, dizziness, itching, and rash. In addition, one pregnant woman had to stop treatment due to severe vomiting[17]. The study by Zhang *et al*. recorded additional side effects after LAM treatment for pregnant women including muscle pain and joint pain[18].

The presence of HBV in umbilical cord blood indicates that HBV can be transmitted from mother to child in utero or during labor[17]. Our study found that the rate of HBV infection in umbilical cord blood was 11.4% (4/35) in infants whose mothers received LAM and 9.1% (3/33) in those whose mothers received TDF. The HBV DNA load in infected cord blood samples was generally low, with only two cases showing high viral load. These findings are consistent with previous studies. In Vietnam, Nguyen Van Bang *et al.* reported cord blood infection rates of 8.2% in the TDF group and 9.1% in the LAM group[12], while Chen *et al.* documented a low HBV DNA-positive rate of 6.15% after TDF prophylaxis[19]. Although maternal viral load at delivery was significantly lower in the TDF group, the similar cord blood positivity rates between groups suggest that viral load alone may not fully explain the risk of in utero or intrapartum transmission. Other factors may influence transmission, including maternal HBeAg status[20], placental microtransfusion, or occult infection of placental tissues[21], viral escape mutations[22], and the timing of viral suppression before delivery[17]. These observations highlight that prevention of mother-to-child transmission depends not only on reducing maternal HBV DNA levels but also on multiple maternal, viral, and placental factors, which may explain the comparable cord blood infection rates despite the greater viral load reduction achieved with TDF.

At 6-12 months of age, 2/47 children were infected with HBV with high HBV DNA load. However, none of these children were detected with HBV in their blood at birth and 1 month of age. This could be explained based on the research results of Zhang *et al*. that HBV marker positivity at birth cannot conclude HBV transmission from mother to child and *vice versa*, HBV marker negativity at birth cannot rule out HBV transmission from mother to child because it may be related to the long incubation period of hepatitis B virus[7]. To have more evidence to confirm that HBV infection in children was due to infection from the mother during the perinatal period, the research team conducted additional HBcAb total and HBcAb IgM tests in these 2 children. The results showed that there was 1 child with acute infection with HBcAb total (+)/HBcAb IgM (+) and 2 children with chronic infection with HBcAb total (+)/HBcAb IgM (-). This acute case is unusual, as the simultaneous presence of HBV DNA and anti-HBs with a negative HBsAg result suggests a possible occult HBV infection or immune-escape variant. Occult hepatitis B has been documented in infants born to HBsAg-positive mothers, where HBV DNA persists despite the presence of anti-HBs, and is often associated with mutations in the HBV *S/pre–S* gene region that alter HBsAg detection in routine assays[23,24]. Additionally, circulating immune complexes or immune-escape mutations can mask HBsAg even when viral replication continues, leading to this serological pattern[25]. According to authors Nguyen Van Bang *et al.*, if both parents in the family are infected with HBV, the child has a 45 times higher risk of infection than a child without either father or mother infected with HBV[12]. However, the acute infection case in our study was the first child, the father was not infected with HBV. In addition, this infant was vaccinated with HBV and HBIG vaccines after birth, and was breastfed continuously until 12 months of age, the mother did not have nipple damage or mastitis, colostrum, and regular milk tests were both negative for HBsAg. In addition, the hepatitis B virus marker test of this infant at 12 months of age showed the parallel existence of HBV DNA and anti-HBs, with negative HBsAg. The cause of this phenomenon may be due to the escape mutation of the hepatitis B virus, so current tests cannot detect the HBsAg antigen of the virus, or this child was infected with a different strain of hepatitis B virus, which is not neutralized by anti-HBs antibodies. Two chronically infected children had very high HBV DNA load. Thus, the rate of HBV transmission from mother to child in the perinatal period in our study was 4.25% (2/47). The results of our study showed that treatment with antiviral drugs LAM and TDF in late pregnancy was effective in preventing HBV transmission from mother to child. Although there was no control group to compare treatment efficacy, the rate of vertical transmission of HBV from mother to child after LAM and TDF treatment in our study was very low, similar to many studies in this field in the world and in Vietnam[8,10,12].

Our study has some limitations. First, this was a longitudinal study requiring long treatment time and follow-up periods, leading to many difficulties in maintaining study subjects in the groups. The dropout rate of mother-child pairs was still high, greatly affecting the final assessment results. Second, the study design with a small sample size limits the reliability of the study. Third, the study did not have a real control group, so the results could not separate the real effectiveness of drugs (LAM and TDF) treating mothers from the effectiveness of hepatitis B vaccine and HBIG vaccine injected into children. Finally, in our study, only 47 out of 80 infants were evaluated at 6-12 months, mainly because several families relocated or were unable to return for follow-up blood testing after childbirth. This loss to follow-up reflects common challenges in mother-infant studies conducted in real-world clinical settings. As a result, the final estimate of chronic HBV infection should be interpreted with caution due to the reduced sample size. In addition, although the data for this study were collected between 2015 and 2018, with follow-up until early 2019, the findings still provide meaningful evidence and practical guidance for current research and clinical management of preventing mother-to-child transmission of hepatitis B in similar healthcare settings.

Lamivudine and tenofovir are effective in preventing the transmission of HBV from mothers with high HBV DNA load to their infants in late pregnancy. Accordingly, the HBV DNA load in the maternal blood of the TDF group decreased sharply; this effect was significantly stronger than that of the LAM group. In addition, the effectiveness of preventing mother-to-child transmission of HBV at 6-12 months of age in the two groups of children whose mothers treated with lamivudine and tenofovir was equal. From the above results, the study recommends the priority choice of tenofovir in the treatment to prevent mother-to-child transmission of hepatitis B virus for pregnant women with high blood HBV DNA load from the 28th week of pregnancy, and recommends popularizing the use of drugs to prevent mother-to-child transmission of hepatitis B in primary health care facilities. Future studies need to be conducted with larger sample sizes and additional control groups to increase the value and raise the level of drug recommendations.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

NHTT contributed to the study conception and design, definition of intellectual content, literature search, data acquisition, data analysis,

statistical analysis, and manuscript preparation. DTV participated in clinical studies, manuscript editing, manuscript review, and served as a guarantor of the study. NBV was involved in clinical studies, manuscript editing, manuscript review, and served as a guarantor of the study. All authors read and approved the final manuscript.

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