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Real-world study of tenofovir disoproxil fumarate to prevent hepatitis B transmission in mothers with high viral load

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Summary

Background: Data on tenofovir disoproxil fumarate (TDF) therapy for preventing vertical transmission of hepatitis B virus (HBV) in the real-world setting are limited.

Aim: To investigate TDF for preventing vertical transmission of HBV in real-world practice.

Methods: Hepatitis B e-antigen (HBeAg)-positive mothers with HBV-DNA >6 $\log_{10}$ IU/mL to receive TDF between gestational weeks 24-33 and delivery were prospectively enrolled and followed until post-partum week 28. All infants received immunoprophylaxis. Primary endpoints were safety of TDF use and mother-to-child transmission rates. Secondary outcomes were maternal HBV-DNA level suppression (<200 000 IU/mL) at delivery and HBeAg and hepatitis B surface antigen (HBsAg) serologic changes during the study.

Results: Among 147 mothers enrolled, 143 started TDF and 143/144 infants completed the study. At delivery, 93.7% (134/143) of the mothers achieved HBV-DNA<200 000 IU/L. On-treatment, alanine aminotransferase (ALT) flares were observed in 8.4% (12/143) of mothers. After TDF cessation, ALT increased in 7.7% (11/143) of the mothers and 2.8% (4/143) achieved HBeAg negativity, but none had HBsAg loss. At birth, HBsAg was detected in 13.9% (20/144) of newborns and none at post-partum week 28. Vertical transmission rates among infants were 0.7% (1/144, intention-to-treat) and 0% (per-protocol). No infants had birth defects. No serious adverse effects were reported in either mothers or infants. Breastfeeding did not increase the HBV infection rate among infants although mothers had viral rebound after TDF cessation.

Conclusions: TDF for highly viraemic mothers was well tolerated and reduced vertical transmission of HBV in a real-world setting. There were no safety concerns during the postpartum 28-week follow-up.

Registry number: Chinese Clinical Trial Registration No. ChiCTR-OIC-17010869

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1 | INTRODUCTION

Chronic hepatitis B (CHB) virus infection is an epidemic associated with cirrhosis and liver cancer.[1–3] Management of CHB during pregnancy remains a challenge. Previous studies indicate that mothers with CHB pose a high risk of vertical transmission of hepatitis B virus (HBV) to infants.[4–7] Without intervention, 80%-90% of infants born to hepatitis B e antigen (HBeAg)-positive mothers may develop CHB infection.[5,8] The administration of HBV vaccine and hepatitis B immunoglobulin G (HBIg) within 12 h of birth, followed by two additional HBV vaccination inoculations within 6 months, reduces mother-to-child transmission (MTCT) rate from 90% to 5%-10%.[9,10] However, immunoprophylaxis fails in about 10% of infants born to mothers positive for HBeAg and with a high level of HBV deoxyribonucleic acid (HBV DNA; >200 000 IU/mL).[10–13] Previous studies indicated that inhibiting HBV replication with lamivudine, telbivudine, or tenofovir disoproxil fumarate (TDF) during late pregnancy in highly viraemic mothers may reduce the risk of MTCT.[3,11,12,14–17]

A recent randomised controlled trial (RCT) by Pan et al enrolled HBeAg-positive mothers with an HBV DNA level >200 000 IU/mL and compared those who received TDF during the third trimester with those who were under usual care without anti-viral therapy.[11] MTCT rates were significantly lower in the TDF-treated group than in the control group, both in the intention-to-treat (5% [5/97] vs 18% [18/100], $P = 0.007$) and per-protocol analyses (0% vs 7% [6/88], $P = 0.01$). Maternal and infant safety profiles were similar in the two groups, including birth defect rates (2% [2/95] and 1% [1/88], respectively; $P = 1.00$). After TDF cessation, elevated alanine aminotransferase (ALT) levels above the normal range were more frequent in mothers in the TDF group than in those in the control group. The maternal HBV serologic outcomes did not differ significantly between the groups. However, in another RCT conducted by Jourdain et al including 168 mothers who were treated with TDF and 163 with placebo, the MTCT rate did not differ between the groups (0% [0/147] vs 2%[3/147]; $P = 0.12$).[18] The rates of adverse events (AEs) were similar between the groups. The results of several non-randomised cohort studies were consistent with findings from Pan's RCT. Chen et al in Taiwan enrolled 62 mothers on TDF during the third trimester and 56 untreated mothers. The MTCT rates were significantly reduced in the treatment group (1.6% [1/65] vs 11% [6/56]).[19] Another cohort study was conducted in Australia on high viraemic pregnant women with 58 mothers treated with TDF, 52 with lamivudine, and 20 with no treatment. Perinatal transmission reduced significantly to 2% and 0% in TDF and lamivudine cohorts, respectively, compared with 20% in untreated mothers.[20]

Because the aforementioned RCTs showed different results comparing the TDF-treated and control groups, a more complete picture of real-world clinical outcomes is needed to enhance the body of knowledge and capture uncommon adverse events.[21] Furthermore, a real-world study of the prevention of HBV vertical prevention will also provide opportunities to initiate treatment earlier based on the patient-physician mutual decision and collect data for mothers who were willing to breastfeed their infants.[22] Therefore, we conducted a prospective uncontrolled study of 143 patients to verify the safety and efficacy of TDF based on the patient-physician decision of initiating treatment during either the second (gestational weeks 24-27) or third trimester (gestational weeks 28-32), as recommended by the national guidelines, in a real-world setting.

2 | METHODS

2.1 | Patient selection and study setting

This was a prospective, open-label, single-arm study. Patients were recruited from Beijing Youan Hospital in China, between 1 February 2016 and 30 September 2017. Beijing Youan Hospital is the appointed hospital by the department of health in Beijing to evaluate mothers with hepatitis B. Patients were referred by community hospitals city wide, and there are clinics covering different residential areas in the city. The trial was approved by the institutional ethics review committee (approval number: Jing-you-ke-lun-zi [2016]15) and has been registered with Chinese Clinical Trial Registration (no. ChiCTR-OIC-17010869). The study was conducted according to International Conference Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. Information reported in this manuscript is based on records readily available for verification. Pregnant mothers were screened for the following criteria of eligibility: age between 20 and 45 years, gestational age 24-32 weeks (as recommended by the national guidelines in China for the timing of initiating anti-viral therapy on preventing MTCT, HBsAg and HBeAg positivity, and HBV DNA levels above 6 $\log_{10}$ IU/mL). Key exclusion criteria included ALT ≥80 U/L upper limit of normal (ULN) = 40 U/L, as patient often received treatment with herbal medications to reduce ALT levels as per local practice; co-infection with hepatitis C, D, E, or HIV; evidence of hepatocellular carcinoma or cirrhosis; concurrent treatment with immune modulators, cytotoxic drugs, or steroids; and evidence of foetal deformity by ultrasound examination.

2.2 | Study procedures and data collections

Pregnant women fulfilling these enrolment criteria were offered participation in the study. Investigators explained the key information to patients and their family members before the mother made a decision and consented to the study. The study consents were obtained prior to enrolment. All mothers who agreed to participate in the study were instructed to take an oral dose of 300 mg of TDF (Viread; Gilead Sciences) daily, starting during the window period between 22 and 33 weeks of gestation until delivery. Patients were followed at 4-week intervals before the due date with routine blood testing including HBV serologic markers, ALT, and HBV DNA. Their paired infants had the following prophylaxis schedule: 200 IU of HBIg (Chengdu Institute of Biological Products, China; or Hualan Biological Engineering Inc., China), and the first dose of 10 μg of recombinant HBV vaccine (Hansenula yeast vaccine; Dalian Hissen

BioPharm Inc., China) were administered within 6 h of birth. The second injection of the same dose of HBIg and HBV vaccine was administered at week 4 as per local standard of care in Beijing, China. Finally, the third dose of HBV vaccine was given at 24 weeks after birth. Infants' HBV serologic markers and HBV DNA were tested at birth prior to receiving immunisation and again at week 28.

Mothers were instructed to discontinue TDF if hepatitis B remained inactive after delivery, and all mothers were evaluated at post-partum weeks 4, 8, 12, 24, and 28. Mothers voluntarily selected their ways of feeding the infants. During TDF, resistance surveillance was performed using direct HBV genome sequencing when patients had a virologic breakthrough (defined as any increase in serum HBV DNA by >1 $\log_{10}$ from nadir or redetection of serum HBV DNA at levels 10-fold the lower limit of detection of the HBV DNA assay after having an undetectable result) or viraemic patients who prematurely discontinued TDF between baseline and delivery. Patients who discontinued TDF with ALT levels above the ULN (40 U/L) were monitored every 4 weeks for 12 weeks or until the ALT level normalised, whichever was longer. As per local standard of care, TDF was resumed in patients who had signs of hepatic decompensation or elevated ALT levels>400 U/L or ALT levels more than five times above baseline.

2.3 | Outcome measurements and endpoints

Primary outcomes were safety of TDF and MTCT rates. Data of mothers and infants who dropped out of the study (lost to follow-up) were included in the safety analysis. ALT flares (>5 times baseline level or >10 times ULN) were considered severe adverse events. Perinatal and partum complications (eg, hypertensive disorders in pregnancy, gestational diabetes mellitus, foetal growth restriction, pre-term labour, pre-mature rupture of membrane, and post-partum haemorrhage), and caesarean section rates were included in the safety analysis.[23,24] Cases of a structural defect or other safety reports in newborns or infants were tabulated using data acquired from infants during the pre-natal or post-natal period up to age 28 weeks, which included ultrasonography examination, reports of birth defects and APGAR scores, measurements from growth charts, and development milestones. MTCT rates were the percentage of infants who had HBsAg positivity or detectable HBV DNA levels (≥20 IU/mL) at age 28 weeks. The secondary efficacy outcomes were the percentage of mothers who had an HBV DNA level of less than 200 000 IU/mL at delivery and the percentage of HBeAg-negative or HBsAg loss mothers at post-partum week 28.

2.4 | Statistical analysis

Based on the RCT by Pan et al, we estimated that 45% of mothers with ALT elevations during the study period and severe adverse events occurred in about 6% of mothers, and the number of patients needed to capture the adverse events occurred in >5% of patients was calculated to be 92 with a significance level of 0.05 (one-tailed). Considering a 10% dropout rate in the aforementioned RCT, a sample size of more than 140 was a reasonable estimation for the current study. For endpoint measurements, we performed intention-to-treat analysis of the MTCT rates, and we included all enrolled infants. Infants who were lost to follow-up were counted as having treatment failure. Baseline characteristics and laboratory results were summarised for the three groups by descriptive statistics, including percentage, means ± standard deviation (SD), and 95% confidence interval. For the quantitative variable, Student's *t* test was used to compare group differences. For categorical variables, the chi-squared test was used for group comparisons. Significance level was set at $P < 0.05$; all data were analysed by SPSS 17.0 (SPSS, Inc, Chicago, IL).

3 | RESULTS

3.1 | Study population

Among 329 mothers screened, 147 were enrolled in the study. However, four patients withdrew consent prior to the baseline visit, resulting in 143 mothers who took at least one dose of TDF and were included in the safety and efficacy analysis data set of our study. From baseline to the last visit at post-partum week 28, no mothers or infants dropped out or withdrew from our study, except one infant who was relocated to another city and did not complete the 28-week follow-up (his mother completed the study without him). The disposition of our study patients is shown in Figure 1. Total live-birth from 143 study subjects were 144 infants including one pair of twins. Thus, 100% of mothers (143/143) and 99.3% of infants (143/144) completed the study. The characteristics of mothers at baseline and infants at birth are presented in Table 1. The mothers' mean (±SD) gestational age at enrolment was 27.3 (±2.2) weeks, and they all initiated the TDF within the window of gestational weeks 24-33. Mothers were treated with TDF orally (300 mg) for a mean (±SD) duration of 12.0 (±2.6) weeks before delivery.

3.2 | Safety of mothers and infants

TDF was generally well tolerated by pregnant women without discontinuation due to adverse events, although one mother was reported non-adherent after the first 4 weeks of therapy. Twenty-two itemised adverse events were recorded based on maternal complaints, physical findings, and laboratory abnormalities. Adverse events were mainly headache, diarrhoea, nausea, arthralgia, dizziness, dyspepsia, abdominal pain, insomnia, and ALT elevation (Table 2). However, all adverse events reported were grades I-II, and there were no severe adverse events in the mothers. No mothers received amniocentesis during pregnancy.[25] In terms of laboratory abnormalities, 0.7% (1/143) and 7.7% (11/143) of patients had ALT elevations during TDF and after TDF cessation, respectively (Table 3). Mothers who had on-treatment ALT flares had a peak level of 187.8 U/L. Although mothers with post-partum ALT flares had peak levels at postpartum weeks 4-8, all elevations returned to normal by post-partum week 12. Their mean (SD) ALT peak levels were 63.6 (±19.5) U/

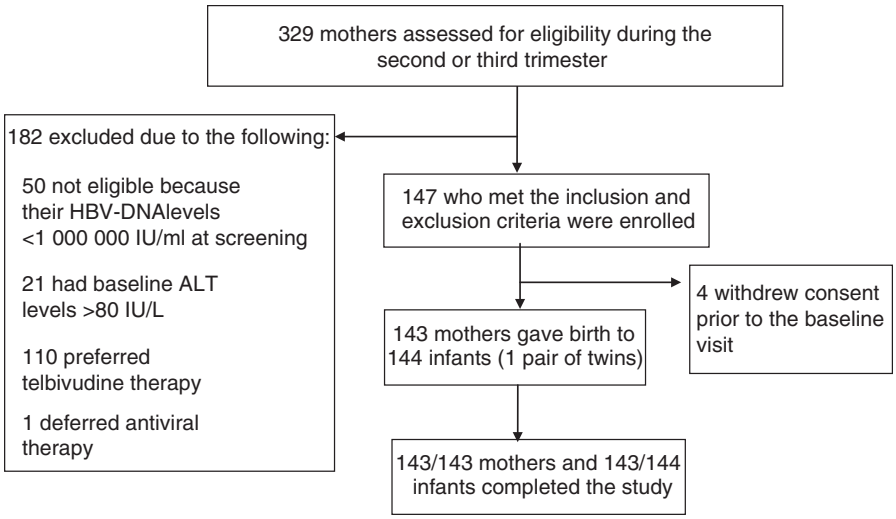

FIGURE 1 Disposition of mothers and infants. ALT, alanine aminotransferase; HBV-DNA, hepatitis B virus deoxyribonucleic acid

L for post-partum flares. No severe hepatitis flare (ALT >10 times of ULN or five times of baseline) was noted in this cohort. Thus, ALT flares during the study were considered grade I adverse events except one case that met grade II criteria because the ALT elevations were four times above the ULN (187.8 U/L) during TDF therapy.

In terms of infant safety, the mean (SD) gestational age of infants was 39.3 (±1.4) weeks, and the rate of caesarean section was 37.5% (54/144). The majority of mothers who had caesarean section had the following top three indications: caesarean section performed on previous delivery, failure to progress from the first to the second stage of labour, and foetal distress during labour. There were no birth defects or congenital malformations in the entire cohort (Table 1). Breastfeeding was based on mothers' personal preferences; 21.7% (31/143) of infants received breast milk. None of these infants was infected with HBV at the end of the study. No severe adverse events were observed among infants (Table 2). Common adverse events (>5%) were cough and fever, which were considered unrelated to foetal exposure to TDF. Their physical and neurological development were within the normal range based on the national children's growth reference standards.[26] Data comparisons between physical parameters of infants collected at birth or at age 28 weeks and the national standards for infants' growth are presented in Table 4.

TABLE 1 Maternal and infant baseline values

	TDF treated
Mothers (mean ± SD, or specified)	(n = 143)
Age (y)	29.7 ± 4.2
Primipara (%)	76.2 (109/143)
HBV DNA-$\log_{10}$ (IU/mL)	7.6 ± 0.59
ALT U/L (normal ≤40)	20.2 ± 8.6
Serum creatinine (μmol/L)	41.9 ± 5.9
HBeAg (COI/mL)	1556.0 ± 678.7
Infants' data at birth (mean ± SD, or specified) (n = 144)	
Gestational age (wks)	39.3 ± 1.4
Delivery with caesarean section (%)	37.5 (54/144)
Infant height (cm)	49.8 ± 1.9
Infant weight (kg)	3.3 ± 0.41
Head circumference (cm)	33.6 ± 1.4
APGAR score (1 min)	8.9 ± 0.39
HBsAg+at birth (%)	3.9 (20/144)
HBeAg+at birth (%)	90.3 (130/144)
Detectable HBV-DNA, n (%)	0 (0)
Congenital defects or malformations, n (%)	0 (0)

HBsAg positive means HBsAg>1 IU/mL.
HBeAg positive means HBsAg>1 COI.
ALT, alanine transferase; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid.

3.3 | Efficacy assessment

All mothers tolerated treatment well without treatment cessation due to adverse events. Between baseline and delivery, the mean (±SD) serum HBV DNA decline of mothers on treatment was 4.08 (±0.95) $\log_{10}$ IU/mL, resulting in a mean (±SD) level of HBV DNA of 3.6 (±1.08) $\log_{10}$ IU/mL at delivery. Upon delivery, 93.7% (134/143) of mothers achieved HBV DNA levels below 200 000 IU/mL, although only one mother reported non-adherence to TDF during pregnancy. Her HBV DNA level at delivery was 5.09×10^6 IU/mL, and the infant was not infected with HBV at age 28 weeks.

Additional analysis on viral suppression showed that 7.0% (10/143) of mothers achieved HBV DNA <100 IU/mL at delivery. Among mothers who discontinued TDF after delivery, 92.5% (124/134) had detectable HBV DNA levels (>100 IU/mL) at post-partum week 4. Four mothers had HBeAg loss and two of them achieved HBeAg seroconversion. However, there was no HBsAg loss/seroconversion in the cohort. All infants received HBIg with the first dose of HBV vaccine within 6 h of birth and completed the additional two vaccinations, except for one infant who was moved to another city and was lost to follow-up. At birth, 13.9% of infants were HBsAg-

TABLE 2 Maternal and infant adverse events reported in the study

	TDF treated
Maternal adverse events (n = 143)	
Nausea	24 (16.8)
Vomiting	4 (2.8)
Fatigue	11 (7.7)
Headache	3 (2.1)
Anorexia	28 (19.6)
Gastric acid regurgitation	3 (2.1)
Dizziness	13 (9.1)
Pyrexia	2 (1.4)
Back pain	3 (2.1)
Insomnia	6 (4.2)
Abdominal distension	4 (2.8)
ALT elevation	12 (8.4)
Maternal complications (n = 143)	
Gestational hypertension	5 (3.5)
Gestational diabetes mellitus	4 (2.8)
Premature rupture of membranes	26 (18.2)
Intrahepatic cholestasis of pregnancy	1 (0.7)
Foetal growth restriction	3 (2.1)
Preterm labour	8 (5.6)
Placenta praevia	3 (2.1)
Placental abruption	1 (0.7)
Postpartum haemorrhage	0 (0)
Infants with fatal TDF exposure[a] (n = 144)	
Fever	8 (5.6)
Skin rash	5 (3.5)
Cough	20 (13.9)
Diarrhoea	2 (1.4)
Vomiting	5 (3.5)
Jaundice	6 (4.2)
Pneumonia	1 (0.69)

Values are expressed as n (%).
ALT, alanine transferase; TDF, tenofovir disoproxil fumarate.
[a]All were reported by investigators as non-study related drug adverse events.

TABLE 3 Alanine transferase flares in TDF-treated mothers

ALT flares, n (%)	All treated (n = 143)	Peak ALT value, (mean ± SD)
On treatment (baseline-delivery)	1 (0.7)	187.8 U/L
Postpartum periods	11 (7.7)	63.6 ± 19.5
Any time during the study period	12 (8.4)	73.2 ± 38.1

ALT, alanine transferase; SD, standard deviation; TDF, tenofovir disoproxil fumarate.

positive. At post-partum week 28, the MTCT rate was 0.69% (1/144) in the intention-to-treat analysis (one infant was lost to follow-up) and 0% in the per-protocol analysis.

4 | DISCUSSION

In this study, we report our prospective data on TDF therapy for preventing MTCT under real-world conditions. To our knowledge, this is the first and largest real-life study involving 143 subjects in this special population. Our results indicated that TDF for mothers with HBV DNA levels >1 000 000 IU/mL in the second or third trimester appears to be safe for both mothers and foetus/infant during the 28-week follow-up period. In combination with standard infant HBV immunoprophylaxis, TDF use during pregnancy yielded a 100% success rate in preventing MTCT in the per-protocol analysis in a real-life setting. Our study also showed that 94% of mothers achieved target levels of HBV DNA below 200 000 IU/mL at delivery by initiating TDF at any time from gestational age 24-32 weeks. None of the breastfed infants was infected with HBV although 93% of the mothers remained viraemic post-partum after TDF cessation at delivery.

Other anti-virals have also been studied for preventing immunoprophylaxis failure in infants who were born to highly viraemic mothers. In a double-blind RCT, lamivudine was found to prevent MTCT in highly viraemic mothers in the intention-to-treat analysis.[14] In a cohort study, telbivudine started in the second and third trimester of pregnancy was shown to reduce MTCT to 2.2% compared to 7.6% in the control group on intention-to-treat analysis.[12] Telbivudine was also safe in pre-clinical trials and does not have mutagenic, teratogenic, or carcinogenic potential. Recently, Pan et al reported data on highly viraemic mothers who were treated with TDF (n = 92 for endpoint analysis) during pregnancy.[15] This RCT demonstrated the effectiveness of TDF use during the late trimester for preventing MTCT in highly viraemic mothers. However, a second RCT conducted by Jourdain et al on TDF (n = 147 for endpoint analyses) did not produce similar results in terms of effectiveness, partially because the sample size was underestimated. Both studies demonstrated the safety profile of TDF use during late pregnancy.

Our current study enrolled 143 mothers, and all were included in the endpoint analyses. The sample size is comparable with the largest RCT for TDF but provided data in a real-world setting. Most subjects in our study started TDF earlier than mothers who were enrolled in the aforementioned two RCTs. We observed 94% of mothers achieving HBV DNA levels <200 000 IU/mL before delivery, which could be the reason of lower MTCT rates in our study. Our data point to the use of TDF during the late second trimester as a better strategy to achieve maternal viraemia control before delivery.[27] In our study, the MTCT rate of 0.69% (1/144) was lower than that of 18% (18/100) in the untreated group of the previous RCT from China on the intention-to-treat analysis. Our findings confirmed the efficacy of TDF on MTCT observed by Pan et al. Thus, the RCT

TABLE 4 Comparison of infants with TDF exposure and the National Reference Value of Children

Mean (±SD)	National Children's Reference value[a]	Infant's with TDF exposure	*P* value
Boys' weight—at birth (kg)	3.38 ± 0.40	3.33 ± 0.41	0.31
Boys' weight—28 wks (kg)	8.68 ± 0.94	8.74 ± 1.14	0.66
Girls' weight—at birth (kg)	3.26 ± 0.40	3.23 ± 0.43	0.55
Girls' weight—28 wks (kg)	8.03 ± 0.90	8.05 ± 1.08	0.88
Boys' height—at birth (cm)	50.4 ± 1.6	50.12 ± 1.90	0.22
Boys' height—28 wks (cm)	69.5 ± 2.3	70.78 ± 3.17	0.21
Girls' height—at birth (cm)	49.8 ± 1.6	49.45 ± 1.84	0.11
Girls' height—28 wks (cm)	67.9 ± 2.3	68.96 ± 3.43	0.52
Boys' head circumference—at birth (cm)	34.0 ± 1.4	33.72 ± 1.49	0.12
Boys' head circumference—28 wks (cm)	43.8 ± 1.3	44.85 ± 1.76	0.10
Girls' head circumference—at birth (cm)	33.7 ± 1.3	33.43 ± 1.35	0.09
Girls' head circumference—28 wks (cm)	42.6 ± 1.2	43.84 ± 1.45	0.08

TDF, tenofovir disoproxil fumarate.
[a]A national survey on physical growth and development of children under 7 years of age in nine cities of China in 2015.[26]

results were replicable in a real-world setting. Our data, together with Pan's RCT and other cohort studies from Taiwan and Australia,[19,20] further support the use of TDF during late pregnancy for preventing MTCT in HBeAg-positive CHB mothers with high levels of HBV DNA.

Antiviral therapy during pregnancy remains a challenge for clinicians because the safety of foetal exposure to anti-viral medication is a primary concern.[11–15] In terms of safety data, we identified that more than 5% of pregnant mothers experienced fatigue, nausea, anorexia, or dizziness. These observations yielded similar safety profiles with those data published in two aforementioned RCTs. Our lower frequency of post-treatment ALT flares could be due to the longer treatment period before delivery and better viral suppression, resulting in less disease activity after cessation of treatment. A recent large study by Yi et al indicated that HBV DNA level ≥5 $\log_{10}$ IU at delivery was an independent predictor for postpartum ALT flares.[28] Resistance surveillance with genotypic analysis has been emphasised by society guidelines when using telbivudine or lamivudine to treat viraemic patients for longer than 12 weeks.[29,30] Our data suggest that, in highly viraemic mothers, there was no anti-viral resistance when receiving TDF during late pregnancy. Our study had 144 infants born to TDF-treated mothers, and no safety concerns were identified in 143 infants at the 28-week follow-up. TDF treatment did not increase the rate of foetal and infant complications or birth defects. The rates of birth defects or congenital malformations in our cohort were compared to those reported by the Antiviral Pregnancy Registry Interim report.[31] The limitations of our study include its single-centre setting and lack of control group. Since anti-viral treatment for highly viraemic mothers during late pregnancy had become the standard of care at some developed areas in China by the time we proposed our study, it was not feasible or ethical to conduct a prospective study with patients at high risk for MTCT in a control arm without therapy. Although infants in our study received an additional dose of HBIg as standard of care, it is unlikely to have affected the study outcome.[11]

In conclusion, HBeAg-positive mothers with HBV DNA >6 $\log_{10}$ IU/mL who received TDF at 24-32 gestational weeks displayed a very high success rate of viral suppression at delivery and very low MTCT rates when their infants received standard immunoprophylaxis. TDF should be considered the first-line treatment for preventing MTCT in highly viraemic mothers with CHB.[4] Although there was a limited number of mothers who breast-fed, breastfeeding did not seem to increase the infection rate while maternal postpartum rebound of viral load occurred after TDF cessation. There were no safety concerns on maternal use of TDF, although on-treatment and post-treatment ALT flares were observed. Close monitoring during and after cessation of TDF should be considered.

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AUTHOR CONTRIBUTIONS

Guarantor of the article: Calvin Pan.

Author contributions: Dr Calvin Pan proposed the concept, designed the study and acts as guarantor to this paper. Drs. Pan and Zhang obtained the research funding. All authors except Drs. Pan and Tiongson contributed to the acquisition of data. Dr Zhang supervised the data collection. Drs. Pan and Wang performed the statistics. Dr Pan interpreted the data and wrote the manuscript with assistance from Dr Wang. Dr Tiongson assisted data analyses and

editorial work. All authors provided inputs for the manuscript. Dr Pan performed critical revision of the manuscript and addressed the comments from the journal. All Authors have read and agreed to this version of the manuscript.

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