Received: 16 June 2020 | First decision: 5 July 2020 | Accepted: 25 July 2020

DOI: 10.1111/apt.16043

AP&T Alimentary Pharmacology & Therapeutics WILEY

Efficacy and safety of tenofovir alafenamide fumarate for preventing mother-to-child transmission of hepatitis B virus: a national cohort study

Yang Ding[1] | Lihua Cao[2] | Liying Zhu[3] | Yan Huang[4] | Chaoshuang Lin[5] | Yuming Wang[6] | Yingxia Liu[7] | Qiuju Sheng[1] | Shouyun Wang[2] | Jian Fan[3] | Ruochan Chen[4] | Weiqiang Gan[5] | Bryan Chen[8] | Calvin Q. Pan[9,10]

[1]Shenyang, China
[2]Qinhuangdao, China
[3]Harbin, China
[4]Hunan, China
[5]Guangzhou, China
[6]Chong Qing, China
[7]Shenzhen, China
[8]Los Angeles, CA, USA
[9]Beijing, China
[10]New York, NY, USA

Correspondence
Calvin Q. Pan, MD, FAASLD, FACG, MACP, Center of Liver Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China; Tisch Hospital of NYU Langone Health, NYU School of Medicine, NY, USA; and No. 8, Jingshun East Street, Chaoyang District, Beijing, China.
Email: Panc01@NYU.edu

Funding information
Wu Jieping Medical Foundation, Grant/Award Number: 320.6750.18012; China National Science and Technology Major Project, Grant/Award Number: 2017ZX10201201

Summary

Background: Data on tenofovir alafenamide fumarate (TAF) for preventing mother-to-child transmission of hepatitis B virus (HBV) are lacking.

Aims: To investigate the efficacy and safety of TAF therapy for preventing hepatitis B mother-to-child transmission.

Methods: Mothers with chronic HBV infection, positive for hepatitis B e-antigen and with HBV DNA >200 000 IU/mL received TAF for preventing mother-to-child transmission were enrolled retrospectively from multiple centres with data collection on mother-infant dyads up to postpartum week 24-28. Primary measurements were the mother-to-child transmission rate and infants' malformation rate. Secondary assessments included maternal HBV DNA reduction at delivery, and maternal or infant adverse events during follow up.

Results: Among 71 mothers enrolled, the mean (±SD) age was 30.3 (±2.2) years. TAF was initiated during the second or third trimester and continued to delivery with a mean (±SD) duration of 12.8 (±4.0) weeks. At delivery, 85.9% (61/71) of the mothers achieved HBV DNA <200 000 IU/L. Seventy-three infants (two sets of twins) were born from mothers treated with TAF and none had congenital defects or malformations. All infants received HBV immunoglobulin and vaccine at birth with additional HBV vaccinations at one and six months. At age 24-28 weeks, all infants had negative hepatitis B surface antigen and undetectable levels of HBV DNA (<100 IU/mL). Body weight, height, and head circumferences were comparable to national standards for physical development. No severe adverse effects were reported in either mothers or infants.

Conclusions: TAF for highly viraemic mothers effectively prevented mother-to-child transmission of hepatitis B. There were no safety concerns for either mothers or infants with 24-28 weeks of follow up.

Yang Ding, Lihua Cao, and Liying Zhu are co-first authors.

The Handling Editor for this article was Professor Grace Wong, and it was accepted for publication after full peer-review.

The complete list of authors' affiliation are listed in Appendix 1.

1 | INTRODUCTION

It is estimated that 292 million persons worldwide have chronic infection with hepatitis B virus (HBV),[1] which is the leading cause for hepatocellular carcinoma worldwide.[2-4] Although long-term antiviral therapy can reduce complications of cirrhosis and hepatocellular carcinoma, eradication of the HBV has not been accomplished.[5,6] Thus, the prevention of HBV transmission is the most effective way to reduce the global burden of HBV infection and liver cancer.[7,8] Currently, preventing perinatal transmission relies upon testing all pregnant women for hepatitis B surface antigen (HBsAg) and administering timely prophylaxis with HBV vaccine and hepatitis B immune globulin to infants born to infected mothers.[8] In addition, mothers with HBV DNA levels >200 000 IU/mL should receive antiviral treatment during late pregnancy to control viraemia because the level of viraemia is an independent predictor for the infants' immunoprophylaxis failure.[5,9]

Use of antiviral agents such as lamivudine, telbivudine, and TDF in several studies have been shown to reduce rates of mother to child transmission in highly viraemic mothers with chronic hepatitis B.[10] Considering the risk of developing antiviral drug resistance during lamivudine or telbivudine therapy, TDF is recommended as the first-line therapy for mothers by the major association guidelines due to the lack of resistance potential among patients on TDF treatment.[5,11] In addition, data from the Antiretroviral Pregnancy Registry also support the use of TDF during pregnancy with a favourable safety profile in a short-term follow-up.[12] However, several recent studies have indicated that infants with foetal exposure to TDF had experienced negative effects on bone mineral density and neutropenia at the early age.[13,14] The long-term safety data for TDF use in pregnancy are thus lacking.

Recent advances in antiviral treatment have been made with better options in terms of drug safety profiles. Tenofovir alafenamide (TAF) is an orally bioavailable prodrug of tenofovir, a nucleotide analogue that inhibits reverse transcription of HIV and HBV. TAF was designed to have greater plasma stability than TDF, thus allowing more efficient delivery of the active metabolite, tenofovir diphosphate, to hepatocytes than TDF. A lower systemic exposure of tenofovir diphosphate can therefore be achieved with TAF therapy.[15,16] TAF was shown in pivotal studies to be statistically non-inferior to TDF in antiviral efficacy, as measured by rates of suppression of HBV DNA to <29 IU/mL. Moreover subjects receiving TAF in both trials for e-antigen positive and negative patients had significantly smaller decreases in bone mineral density in the lumbar spine and hip, smaller increases in serum creatinine and smaller decreases in estimated creatinine clearance than those receiving TDF. TAF is therefore recommended by the international association guidelines as the first-line treatment for chronic hepatitis B patients (CHB), except in the treatment for pregnant mothers, because the efficacy and safety profile in this special population has not been established. With that in mind, we designed a retrospective multicentre study to investigate the efficacy and safety of TAF in highly viraemic mothers for the prevention of mother to child transmission of hepatitis B. Our data could potentially provide preliminary evidence to support TAF therapy as one of the treatment options for pregnant women and contribute to the knowledge of selecting antiviral therapy with better safety outcomes.

2 | METHODS

2.1 | Patient selection and study setting

This is a retrospective, multicentre, single-arm national cohort study. Patients were recruited from seven university medical centres representing east (Qin Huang Dao city), south (Guangzhou and Shenzhen cities), west (Chong Qing city), north (Harbin and Shen Yang cities) and central China (Chang Sha city), between 4 December 2018 and 18 May 2020. Patients were referred by the local community hospitals city wide, and participating study sites have clinics covering different residential areas in the city. The trial was approved by the institutional ethics review committee in each study site and the need for informed consent was waived by the institutional review board because the study posed minimal risk to enrolees. TAF has been licensed for the treatment of chronic hepatitis B in China since December 2018 and the drug label has the indication for pregnant mothers, stating "TAF can be used during pregnancy if necessary." In the study sites, prenatal drug safety consultation with the attending physicians was routinely given to mothers who wanted to take TAF during pregnancy and alternative options were discussed. Consents were obtained from all patients prior to starting on TAF. Blood tests were performed in the central laboratories of participating sites. The hepatitis B serological markers were measured by the following equipment: chemiluminescent micro-particle immunoassay (Architect i2000 analyser; Abbott Diagnostics, or IS 1200 automatic analyser, Maccura Biotechnology Co., Ltd.), or chemiluminescence immunoassays (Cobas e 801 module; Roche Diagnostics GmbH). Quality control was conducted every 24 hours at least, during which the kit would be replaced. We collected patient data from medical records, and all data were de-identified before analysis. Information reported in this manuscript is based on records readily available for verification.

Pregnant mothers with chronic hepatitis B were screened for the following criteria of eligibility: age above 20 years, hepatitis B e-antigen (HBeAg) positivity with HBV DNA levels above 200 000 IU/mL during pregnancy, received TAF therapy during pregnancy for the prevention of mother to child transmission, and had data available from prenatal care and postpartum follow up longer than 24 weeks. Key exclusion criteria included the use of other HBV antiviral treatment as monotherapy or in combination of TAF during pregnancy; participation in other clinical trials and use of investigational regimens; co-infection with HIV, pallidin, toxoplasma gondii or hepatitis C; 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 | Data collection

Medical records of pregnant women with hepatitis B at each study site during the study period were reviewed. When patients who had fulfilled the aforementioned enrolment criteria were selected, pertinent data were extracted from their medical records into the pre-specified data collection forms by the research coordinators. The site investigators then verified the information before submitting the de-identified data to the correspondent author for data analyses.

Data were itemized in the collecting forms as follows: the pertinent maternal data included the general demographic data, HBV status prior to the pregnancy to determine the chronicity of hepatitis B infection and treatment regimens, singleton status, gestational age when initiating TAF therapy, duration of TAF treatment and adverse events during the therapy, perinatal complications, gestational age at delivery, delivery mode, serum alanine transaminase (ALT) levels and HBV serologic markers including hepatitis B surface antibody (HBsAb), HBsAg, hepatitis B core antibody (HBcAb), HBeAg and hepatitis B e-antibody (HBeAb) during pregnancy and postpartum up to week 24-28. Maternal HBV DNA test results were collected at the time points of prior to initiating TAF treatment, at delivery and at postpartum week 24-28. The following infants' data were collected: birth weight, birth length, Apgar score at birth, breast feeding status, the details of immunoprophylaxis administration for HBV and HBV virological testing at birth and after completion of the three hepatitis B vaccination doses (age of 24-28 weeks). In addition, the data on infants' adverse events and physical growth measurements were collected from birth to the age of 24-28 weeks.

2.3 | Outcome measurements

Primary outcomes were infants' physical (structural) malformation or congenital defect and mother to child transmission rates. The infants who had HBsAg positivity or detectable levels of HBV DNA at the age of 24-28 weeks were counted as the infected cases with chronic hepatitis B. The mother to child transmission rates were the percentage of infants with chronic hepatitis B among all live births in the current cohort.

Secondary assessments included the following: (a) secondary efficacy outcomes including 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-negative mothers at postpartum week 24-28; (b) the frequency of ALT flares, which was defined as an ALT level >5 times the baseline level or >10 times the upper limits of normal (ULN) during the TAF therapy or after the cessation of TAF treatment; (c) other maternal adverse events and perinatal complications (eg hypertensive disorders in pregnancy, gestational diabetes mellitus, foetal growth restriction, preterm labour, premature rupture of membrane and postpartum haemorrhage). In addition, caesarean section rates were included in the safety analysis[17,18]; (d) physical development of new-borns and infants, which their physical growth parameters were compared with the Chinese national standard; (e) safety outcome assessments for the infants, which included all adverse events from birth to the age of 24-28 weeks.

2.4 | Statistical analysis considerations

Based on the randomised control trial by Pan et al,[19] it was estimated that 5% mother to child transmission rate and severe adverse events occurred in about 6% of mothers who received TDF therapy. Thus, the number of patients needed to capture the transmission and adverse events occurring in >6% of patients was calculated to be 70 with a significance level of 0.05 (one-tailed). The target enrolment number for the current study was planned as 70-80 mother-infant dyads from seven study sites and each site enrolled about 10-12 consecutive patients. All patients enrolled in the study were analysed. We compiled data regarding demographic and clinical variables for each patient. Categorical variables are presented as proportions or frequencies. Continuous variables are presented as mean with standard deviations or medians with ranges. For infants' physical development, parameters were compared with the Chinese national children's growth reference standards (as the reference group). For the quantitative variable, Student's *t* test was used to compare group differences. For categorical variables, the chi-square test or Fisher's exact test as appropriate, was used for group comparisons. All statistical analyses were performed using SPSS version 24.0 (IBM Corp.). All tests were two-tailed, and $P < 0.05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Study patients and treatment duration

Among 91 mother infant dyads screened, 71 mothers were eligible and enrolled in the study. The majority of non-eligible mothers were those who were lost to follow up due to relocation to another city or had missing HBV virological test results (Figure 1). The mean (±SD) maternal age was 30.3 (±2.2) years with median [interquartile range, IQR] gestational age of 27 [24, 30] weeks at the time of initiating TAF treatment. Prior to initiating TAF therapy, hepatitis D virus specific total antibodies were tested in 52% (37/71) of mothers, and the results were all negative. All mothers were treated with oral TAF (brand name-Vemlidy, Gilead Science, Inc) at the dose of 25 mg daily (patients were instructed to take it every 24 hours at any time of each day) for a mean (±SD) duration of 12.8 (±4.0) weeks before the delivery. All mothers were compliant with the treatment during pregnancy except for 22.5% (16/71) of mothers that had skipped

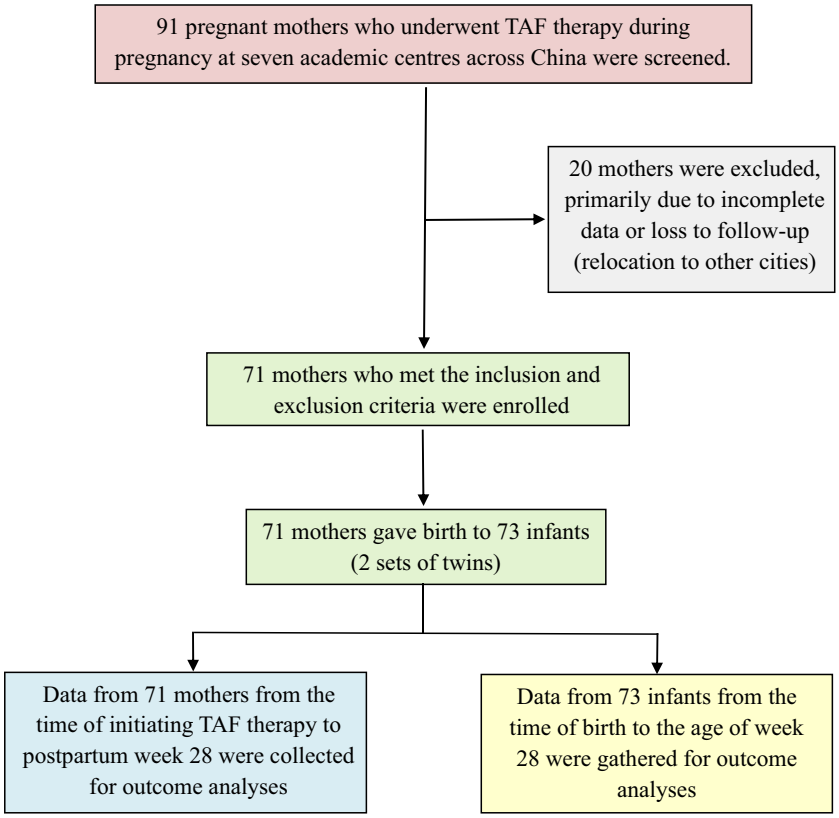

FIGURE 1 The *enrollment of study patients and data analyses*

TAF denotes tenofovir alafenamide fumarate

one or more doses of TAF medication (self-reported) ranging from 1 to 7 days during pregnancy. No mothers received amniocentesis during pregnancy.[20] Immediately after delivery, 78.9% (56/71) mothers discontinued the treatment. Between delivery and the last study follow up at postpartum week 24-28, 14.1% (10/71) mothers discontinued TAF treatment, with a median (range) of 30 (1-92) days on TAF after delivery. At postpartum week 24-28, a total of 93.0 % (66/71) mothers had discontinued treatment, while 7.0% (5/71) continued taking TAF through to the end of the study period. All pregnancies were singleton except for two sets of twins. Thus, the total number of live-births from 71 mothers was 73 infants. The characteristics of mothers at baseline and infants at birth are presented in Table 1.

3.2 | Assessments of vertical transmission and congenital defects

The primary efficacy assessment in the study was the mother to child transmission rates among infants who were born to highly viraemic mothers treated with TAF during pregnancy. The median (range) time between the infant's birth and their receiving of the hepatitis B immune globulin (100 IU) along with the first dose of recombinant HBV vaccine (10 μg) intramuscularly was 5.5 (2-24) hours. Forty-five percent (33/73) and 40% (29/72) of infants received the immunoprophylaxis within 2 hours and within 3-6 hours at birth respectively. The HBV vaccine was supplied by the following manufacturers in China: Dalian Hissen Bio-Pharmaceutical Co., Ltd, Dalian; Shenzhen Kangtai Biological Products Co., Ltd, Shenzhen; Hualan Biological Engineering Co., Ltd, Henan; and Beijing Tiantan Biological Products Co., Ltd, Beijing. All infants completed the additional two vaccinations at their age of 1 and 6 months. Among 73 infants, 52 were tested at birth with venous blood specimens for HBV marker and HBV DNA; all were HBsAg negative with non-detectable levels of serum HBV DNA (<100 IU/mL). At the age of 24-28 weeks, all infants were tested HBsAg negative. In addition, all infants had serum HBV DNA tested at the age of 24-28 weeks, which were all below the level of detection (<100 IU/mL). Thus, there was no mother to child transmission of HBV in our study patients. In addition, all infants (73/73) developed HBsAb levels above 10 IU/mL at the age of 24-28 weeks, which was considered a completed response to HBV vaccination. There were no congenital malformations nor defects reported in the entire cohort at birth and at the age of 24-28 weeks.

3.3 | TAF effects on maternal virological parameters

Regarding viral suppression during pregnancy, the adherence rate to TAF therapy before delivery was 77.5% (taking TAF daily). At delivery, 85.9% (61/71) of mothers achieved serum HBV DNA levels below 200 000 IU/mL. The reduction in the mean (±SD) level of

TABLE 1 Maternal and infant baseline values

Mothers (mean ± SD, or specified)	TAF treated (n = 71)
Age (y)	30.3 ± 2.2
Primipara, n (%)	51/71 (71.8)
HBV DNA-Log_{10} (IU/mL)	7.78 ± 0.72
ALT, U/L (normal ≤40)	32.64 ± 68.86
AST, U/L (normal ≤40)	30.15 ± 48.91
Serum creatinine, μmol/L (normal ≤170)	52.88 ± 9.49
Serum phosphate, mg/dL (normal: 2.3-4.3)[a]	3.59 ± 0.56
HBeAg positivity, n (%)	71/71 (100)
HBsAg titre (S/CO)	28 937.74 ± 23 413.77
Infants data at birth (mean ± SD, or specified)	(n = 73)
Gestational age (wks)	38.22 ± 2.94
Male gender, n (%)	30/73 (41.1)
Delivery with caesarean section, n (%)	26/73 (35.62)
Infant height (cm)	50.55 ± 2.03
Infant weight (kg)	3.32 ± 0.41
Head circumference (cm)	33.55 ± 1.03
APGAR score at 1 min	9.70 ± 1.11
APGAR score at 5 min	9.85 ± 0.12
HBsAg+ at birth, n (%)[b]	0/52 (0)
HBeAg+ at birth, n (%)[b]	40/52 (76.92)
Detectable HBV DNA at birth, n (%)[b]	0/52 (0)
Congenital defects or malformations, n (%)	0/73 (0)

Abbreviations: ALT, alanine transferase; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid.

[a]Of the mothers, 98.5% (70/71) patients had reported serum phosphate levels (mg/dL) from all time points.

[b]In this cohort, HBV virological testing were not performed in 21 infants at birth due to the local hospital standard of practice. HBV tests were only performed after the completion of all HBV vaccinations.

maternal serum HBV DNA from the time points of initiating treatment to delivery was 3.7 (±1.1) log_{10} IU/mL during the TAF treatment, resulting in a mean (±SD) level of HBV DNA of 4.1 (±1.1) log_{10} IU/mL at the time of delivery. Additional analysis on viral suppression showed that 14.1% (10/71) of mothers achieved HBV DNA <100 IU/mL at delivery. Among 66 mothers who discontinued TAF therapy after delivery, 92.4% (61/66) of them had detectable HBV DNA levels (>100 IU/mL) at postpartum week 24-28. Although the mean level of maternal HBsAg decreased significantly at delivery after TAF treatment when compared to that of baseline, the mean maternal HBsAg level at postpartum week 24-28 was similar to that at baseline. Data on TAF treatment effects and maternal HBV DNA viral breakthrough during pregnancy or postpartum were presented on Table 2. One mother (1.4%) had HBeAg loss during TAF therapy prior to the delivery, but none of them had HBsAg seroconversion during the study.

3.4 | Maternal adverse events and complications

During the treatment of TAF, all mothers tolerated TAF therapy well and there was no treatment discontinuation among mothers due to adverse events. Ten itemised adverse events or complications were presented in the current study based on medical record reviewed. The adverse events with frequency >2% were vomiting, upset stomach, nausea, gestational diabetes mellitus, and postpartum ALT flares (Table 3). All symptoms were reported on the severity of grades I-II and there were no maternal severe adverse events observed in the entire cohort. In terms of laboratory abnormalities, none of the mothers had ALT flares on TAF treatment during pregnancy (n = 0/71). However, 15.5% (11/71) of them had postpartum ALT flares, with a mean (±SD) ALT peak level of 140.2 (±81.3) U/mL, without the consequences of elevation of total bilirubin levels, decrease in albumin levels, or coagulopathy. The ALT flares may be due to TAF therapy cessation, as 81.8% (9/11) had stopped taking TAF after delivery. Data on ALT flares and changes in HBV DNA levels in mothers who discontinued the treatment vs those who continued on TAF is presented on Table 4. In the two patients (n = 2/11) who were on postpartum TAF treatment and developed ALT flares, their peak ALT levels during flares were 149 and 159 U/mL. No hepatic decompensation was observed among patients with ALT flares on TAF therapy.

Although there was no decline on the mean estimated glomerular filtration rates (calculated with CKD-EPI equations) during TAF treatment before delivery, a statistically significant increase in the mean (±SD) serum creatinine level from baseline (52.9 ± 9.5 μmol/L) to delivery (56.3 ± 9.7 μmol/L, $P = 0.04$) was observed (Table 2). However, there were no significant changes on the mean (±SD) serum phosphorous levels between the baseline (3.6 ± 0.6 mg/dL) and at the time of delivery (3.7 ± 0.5 mg/dL, $P = 0.58$).

3.5 | Infant's adverse events, breastfeeding and physical growth

There were no negative events for any foetus in the cohort. The mean (±SD) gestational age of infants was 38.2 (±2.9) weeks, and the rate of caesarean section was 35.6% (26/73). Although there was no severe adverse events observed in infants (Table 2), common adverse events (>5%) were diarrhoea, vomiting, constipation and eczema. Breastfeeding status was assessed for all infants: 57.5% (42/73) fed with breastmilk only, 34.2% (25/73) fed with formula feeding and 8.2% (6/73) fed their infants with both. None of them were infected with HBV at the age of 24-28 weeks.

The physical development of infants with foetal exposure to TAF were within the normal range,[21] except that the mean (±SD) head circumference among girls at birth was significantly smaller than that of the national standard (33.2 ± 1.02 cm vs 33.7 ± 1.3 cm; $P = 0.001$) However, the aforementioned parameter had exceeded the national standards when girls grew up to the age of 24-28 weeks (43.4 ± 2.6 cm vs 42.6 ± 1.2 cm; $P = 0.01$). All other physical growth

TABLE 2 Maternal treatment effects with tenofovir alafenamide fumarate

Variables, mean (±SD) or specified	Baseline	Follow-up assessments	*P* values
Effects from baseline to delivery			
HBV DNA changes (Log $_{10}$ IU/mL)	7.78 ± 0.72	4.09 ± 1.12	<0.001
HBsAg titre changes	28 937.74 ± 23 413.77	19 266.89 ± 15 876.36	0.005
HBeAg positivity, n (%)	71/71 (100)	70/71 (98.59)	-
HBsAg positivity, n (%)	71/71 (100)	71/71 (100)	-
ALT changes (U/L)	32.64 ± 68.86	22.77 ± 10.84	0.24
AST changes (U/L)	30.15 ± 48.91	24.29 ± 9.75	0.33
Creatinine changes (umol/L)	52.88 ± 9.49	56.25 ± 9.72	0.04
Serum phosphate changes (mg/dL)[a]	3.59 ± 0.56	3.65 ± 0.46	0.58
eGFR changes (mL/min/1.73 m^2)[b]	122.04 ± 10.56	118.58 ± 11.60	0.07
Virological Breakthrough, n (%)	-	1/71 (1.41%)	-
Effects from baseline to postpartum week 28			
HBV DNA changes (Log $_{10}$ IU/mL)	7.78 ± 0.72	6.16 ± 2.19	<0.001
HBsAg titre changes	28 937.74 ± 23 413.77	27 101.17 ± 26 167.90	0.66
HBeAg positivity, n (%)	71/71 (100)	70/71 (98.59)	-
HBsAg positivity, n (%)	71/71 (100)	71/71 (100)	-
ALT changes (U/L)	32.64 ± 68.86	42.4 ± 48.66	0.33
AST changes (U/L)	30.15 ± 48.91	34.17 ± 37.74	0.59
Creatinine changes (umol/L)	52.88 ± 9.49	57.48 ± 8.54	0.003
Serum phosphate changes (mg/dL)[a]	3.59 ± 0.56	3.68 ± 0.50	0.42
eGFR changes (mL/min/1.73 m^2)[b]	122.04 ± 10.56	117.37 ± 10.67	0.01
Virological breakthrough any time during the study, n (%)	-	37/71 (52.11)	-

[a]Of the mothers, 98.5% (70/71) patients had reported serum phosphate levels (mg/dL) from all time points.

[b]eGFR, estimated glomerular filtration rate (calculated with CKD-EPI equations).

parameters for infants with foetal exposure to TAF were comparable to or exceeded the national children's growth reference standard at birth or the age of 24-28 weeks.[21] Stratified by sex gender, data comparisons between physical growth parameters of infants with foetal exposure to TAF and the national standards for infants' growth are presented in Table 5.

4 | DISCUSSION

In this study, we report data from a retrospective national cohort on TAF therapy for the prevention of mother to child transmission under real-world conditions. To the best of our knowledge, this is the first study involving a significant number of infants with foetal exposure to TAF for the evaluation of efficacy and safety of TAF in highly viraemic chronic hepatitis B mothers. We observed that TAF initiated at the second or early third trimester appears to be safe for both mothers and infants during the 24-28 week follow-up period. There was no congenital defects nor malformations found among infants after the exposure. With the use of maternal TAF treatment during pregnancy in combination with standard infant HBV immunoprophylaxis, there was a 100% success rate in preventing mother to child transmission in the current study. In addition, the treatment was well tolerated and there were no major safety concerns for both mothers and infants during a short-term follow-up. Our investigation provides very important evidence to support the use of TAF

TABLE 3 Maternal and infant adverse events reported in the study

Adverse events or complications, n (%)	TAF treated
Maternal adverse events	n = 71
Nausea	2/71 (2.82)
Vomiting	2/71 (2.82)
Upset stomach	2/71 (2.82)
Palpitations	1/71 (1.41)
Pyrexia	1/71 (1.41)
Constipation	1/71 (1.41)
Maternal fall	1/71 (1.41)
Birth canal hematoma	1/71 (1.41)
On treatment (baseline-delivery) ALT flares	0/71 (0)
Postpartum ALT flares[a]	11/71 (15.49)
Maternal complications	n = 71
Gestational diabetes mellitus	2/71 (2.82)
Premature rupture of membranes	1/71 (1.41)
Preterm labour	1/71 (1.41)
Infants adverse events[b]	n = 73
Skin rash	1/73 (1.37)
Diarrhoea	5/73 (6.85)
Vomiting	4/73 (5.48)
Constipation	4/73 (5.48)
Eczema	6/73 (8.22)

Abbreviations: ALT, alanine transferase; TAF, tenofovir alafenamide.

[a]During postpartum follow-up, 78.9% (56/71) of mothers discontinued TAF therapy. The median [interquartile range, IQR] peak ALT level was 138 [89, 154] U/mL in patients who had ALT flares (ALT level >5 times baseline level or >10 times ULN).

[b]All were reported without any indication as TAF-related drug adverse events.

during pregnancy in highly viraemic mothers as an alternative option to TDF therapy.

The effects of TAF for HBV DNA reduction were similar to TDF in pivotal trials.[22,23] In the current study with TAF therapy for a mean (±SD) of 12.8 (±4.0) weeks, maternal mean (±SD) level of HBV DNA was suppressed to 4.1 ± 1.1 $\log_{10}$ IU/mL with 85.9% (61/71) of patients achieved the target level of below 200 000 IU/mL at delivery. When compared with the real world study of TDF by Wang et al,[24] 93.7% of mothers in their study achieved the HBV DNA level of <200 000 IU/mL at delivery. These differences could be due to the higher maternal HBV DNA levels prior to initiating TAF treatment in our study. However, the HBV DNA reduction rate before delivery in our study was similar to that of mothers treated with TDF in the randomized control trial performed by Jourdain et al (88% achieved the target level).[25]

None of the mothers had changes in their HBsAg and HBeAg status during the study period except one who had HBeAg loss, which is expected because of the short TAF therapy duration and the relatively low efficacy of oral antiviral agents for HBV seroconversion, especially in the genotype B and C dominant Asian patient population.[6] Because of the maternal HBeAg positive status at delivery, 77% of infants had positive HBeAg at birth but became negative at the age of week 24-28. The transient HBeAg positivity could be from the passage of maternal HBeAg protein through the placentas.[7]

Postpartum ALT flares have been a major concern for both clinicians and patients when taking antiviral therapy during pregnancy and most patients may discontinue the treatment during postpartum period due to lack of medical indication for long term therapy. Current international guidelines recommend that the cessation of antiviral treatment in these patients should be planned for anytime between delivery and postpartum week

TABLE 4 Alanine transferase flares and hepatitis B viraemia after delivery among mothers with or without TAF treatment

Variables, mean (±SD) or specified	Mothers who discontinued TAF (N = 66)[a]	Mothers who continued on TAF (N = 5)	*P-values*
ALT at delivery (U/L)	23.03 (±11.13)	19.30 (±4.92)	0.16
ALT at postpartum week 28 (U/L)	43.75 (±50.22)	24.62 (±5.22)	0.005
HBV DNA at delivery, $\log_{10}$ (IU/mL)	4.39 (±4.73)	5.06 (±5.36)	0.02
HBV DNA at postpartum week 28, $\log_{10}$ (IU/mL)	7.85 (±8.09)	1.90 (±1.65)	<0.001
ALT Flare, n (%)	9/66 (13.60)	2/5 (40)	0.12
Peak ALT Flare (U/L)	137.1 (±90.10)	154.0 (±7.10)	0.59
Virological rebound, n (%)	53/66 (80.30)	0/5 (0)	<0.001
Peak HBV DNA level of virological rebound, $\log_{10}$ (IU/mL)	7.95 (±8.11)	0	-

Note: ALT denotes alanine aminotransferase.

[a]78.9% (56/71) mothers discontinued TAF treatment immediately after delivery. Between delivery and the last study follow up at postpartum week 24-28, 14.1% (10/71) mothers discontinued TAF treatment. At postpartum week 24-28, a total of 93.0 % (66/71) mothers had discontinued treatment.

TABLE 5 Comparison of infants with TAF exposure and the national reference value of children

Growth parameters, mean (±SD)	National children's reference values[a] (N = 3811)	Infant's with TAF exposure (N = 73)	*P*-values
Boys' weight—at birth (kg)	3.38 ± 0.40	3.40 ± 0.34	0.62
Boys' weight—28 wks (kg)	8.68 ± 0.94	8.86 ± 1.34	0.26
Girls' weight—at birth (kg)	3.26 ± 0.40	3.26 ± 0.44	1.00
Girls' weight—28 wks (kg)	8.03 ± 0.90	8.63 ± 1.34	<0.001
Boys' height—at birth (cm)	50.4 ± 1.6	50.91 ± 2.10	0.04
Boys' height—28 wks (cm)	69.5 ± 2.3	69.94 ± 3.55	0.30
Girls' height—at birth (cm)	49.8 ± 1.6	50.30 ± 1.98	0.04
Girls' height—28 wks (cm)	67.9 ± 2.3	68.96 ± 4.26	0.04
Boys' head circumference—at birth (cm)	34.0 ± 1.4	33.95 ± 0.93	0.66
Boys' head circumference—28 wks (cm)	43.8 ± 1.3	44.17 ± 2.09	0.14
Girls' head circumference—at birth (cm)	33.7 ± 1.3	33.27 ± 1.02	0.001
Girls' head circumference—28 wks (cm)	42.6 ± 1.2	43.37 ± 2.56	0.01

Abbreviations: ALT, alanine transferase; HBeAg, hepatitis B e antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; TAF, tenofovir alafenamide fumarate.

[a]A national survey on physical growth and development of children under seven years of age in nine cities of China in 2015.[21]

12.[5,11] However, the optimal timing has not been determined yet. For the convenience of breast-milk feeding and concern over uncertainty of TAF concentration in the breast-milk, most patients in the current study stopped the therapy after delivery. ALT flares occurred in 15.5% (11/71) of patients without hepatic decompensation. Because of the heterogeneity in the definition of "ALT flare" among studies, it is difficult to compare the frequency of ALT flares in our study with that of other studies. The current postpartum ALT flare rate after the cessation of TAF appears to be high. Further studies with randomized designs on stopping TAF may provide better data on understanding the post-treatment ALT flares in mothers after delivery. Our study observed that TAF could be discontinued right after delivery. The increase of creatinine levels when mothers received TAF therapy in our study suggests that the monitoring of renal functions are needed during pregnancy. Although data for breast-milk feeding were limited in our study, there was no transmission of HBV observed in the cohort. Further studies should be conducted for the safety assessment of breast-milk feeding when mothers are taking TAF.

Recent advances have been made in establishing the safety and efficacy of TDF therapy during pregnancy in high viraemic mothers for preventing mother to child transmission of HBV.[10,19,24] This is a critical step for achieving the World Health Organization (WHO) goal for global elimination of HBV infection in 2030 since there is no cure therapy available at the present time. In addition, the prevention of HBV infection in children is the most effective way by far for the reduction of global burden of hepatocellular carcinoma from HBV. Data from our study on the role of TAF therapy in HBV prevention would potentially provide opportunities for future studies on this option to fill the knowledge gap and provide evidence for the enhancement of perinatal care in chronic hepatitis B mothers.

Several limitations exist in our study. Obviously, the study inherited the shortcomings of the retrospective study design, which includes possible missing data on potential confounding factors with unknown effects on the study outcomes. Another major limitation is the lack of a control group in our study because finding matching cases without antiviral therapy in highly viraemic mothers is not feasible under the current standard of care. The follow up duration in the current study was within 28 weeks. Therefore, the long term consequences of foetal exposure to TAF have not been investigated yet. In addition, adverse events with a frequency of less than 5% might not be detected in the current sample size. Despite these limitations, our findings are important in understanding the role of TAF on the prevention of mother to child transmission for CHB mothers with high viral load. The safety data in the current study collectively contribute to the database of antiviral therapy during pregnancy. Considering the recent goals set by the World Health Organization for the elimination of HBV, our findings provide timely evidence for selecting TAF therapy as a viable option for the target population to achieve these goals. In addition, the study data was generated from multiple centres in a real-world setting with clear clinical implications, which may help enhance this study's generalizability.

In conclusion, our study indicated that TAF treatment at the second or early third trimester for pregnant women with chronic hepatitis B and high levels of viraemia displayed a 85.9% rate of viral

suppression to the target level (serum HBV DNA <200 000 IU/mL) at delivery and a 100% success rate in preventing mother to child transmission when their infants received standard immunoprophylaxis. TAF therapy also has favourable safety profiles for both mothers and infants when used during the second or third trimester during pregnancy for chronic hepatitis B mothers. In the short term outcome assessments, there were no safety concerns on maternal use of and foetal exposure to TAF, except that maternal renal function should be monitored. Further studies with prospective design and long-term follow-up are needed to verify the findings above. Our preliminary data suggests that TAF should be considered as one of the first-line treatments for preventing mother to child transmission in this special population.

ACKNOWLEDGEMENTS

This study is supported by the research grants from China National Science and Technology Major Project (grant number: 2017ZX10201201), and from the Wu Jieping Medical Foundation (grant number: 320.6750.18012).

Declaration of personal interest: Dr Calvin Q. Pan has received research grants from Gilead. He also serves as a speakers' bureau for Gilead. Other authors have no conflict of interest to be disclosed.

AUTHORSHIP

Guarantor of the article: Dr Calvin Q. Pan.

Author contributions: Dr Calvin Q. Pan proposed the concept, designed the study protocol and database. All authors except Calvin Pan and Bryan Chen contributed to the acquisition of data. Dr Calvin Q. Pan supervised the data collection with assistance from Bryan Chen. Dr Pan also performed the statistical analyses with assistance from Drs Ding, Cao, Zhu and Bryan Chen. Dr Pan interpreted the data and wrote the manuscript. Bryan Chen proofread the manuscript and assisted the editorial work. Dr Pan performed critical revision of the manuscript and addressed the comments from the journal. All authors reviewed and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

ORCID

Yang Ding https://orcid.org/0000-0002-7066-2865
Calvin Q. Pan https://orcid.org/0000-0002-3723-6688

REFERENCES

1. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol*. 2018;3:383-403.
2. Ringelhan M, McKeating JA, Protzer U. Viral hepatitis and liver cancer. *Philos Trans R Soc Lond B Biol Sci*. 2017;372:20160274.
3. Pan CQ, Zhang JX. Natural history and clinical consequences of hepatitis B virus infection. *Int J Med Sci*. 2005;2:36-40.
4. Pan CQ, Chiang B. Revisiting the natural history of chronic hepatitis B in Asian Americans. *N Am J Med Sci*. 2009;2:111-119.
5. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67:370-398.
6. Tong MJ, Pan CQ, Han SB, et al. An expert consensus for the management of chronic hepatitis B in Asian Americans. *Aliment Pharmacol Ther*. 2018;47:1181-1200.
7. Pan CQ, Duan Z, Bhamidimarri KR, et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. *Clin Gastroenterol Hepatol*. 2012;10:452-459.
8. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67:1-31.
9. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. *J Viral Hepat*. 2012;19:e18-e25.
10. Brown RS, McMahon BJ, Lok ASF, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. *Hepatology (Baltimore, MD)*. 2016;63:319-333.
11. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Clin Liver Dis*. 2018;12:33-34.
12. APR. Antiviral Pregnancy Registry Interim report - January 1989 through July 2019; Issued in December 2019. http://wwwapregistrycom. Accessed June 8, 2020
13. Seidel V, Weizsäcker K, Henrich W, et al. Safety of tenofovir during pregnancy: early growth outcomes and hematologic side effects in HIV-exposed uninfected infants. *Eur J Pediatr*. 2020;179:99-109.
14. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis*. 2015;61:996-1003.
15. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. *Mol Pharm*. 2013;10:459-466.
16. Murakami E, Wang T, Park Y, et al. Implications of efficient hepatic delivery by tenofovir alafenamide (GS-7340) for hepatitisBvirustherapy.*AntimicrobAgentsChemother*.2015;59:3563-3569.
17. Pan CQ, Zou H-B, Chen YU, et al. Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis B surface antigen-positive women to their infants. *Clin Gastroenterol Hepatol*. 2013;11:1349-1355.
18. Pan C, Perumalswami PV. Pregnancy-related liver diseases. *Clin Liver Dis*. 2011;15:199-208.
19. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med*. 2016;374:2324-2334.
20. Yi W, Pan CQ, Hao J, et al. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. *J Hepatol*. 2014;60:523-529.
21. Capital Institute of Pediatrics, The Coordinating Study Group of Nine Cities on the Physical Growth and Development of Children. A national survey on physical growth and development of children under seven years of age in nine cities of China in 2015. *Zhonghua Er Ke Za Zhi*. 2018;56:192-199.
22. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:196-206.

23. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1:185-195.
24. Wang M, Bian Q, Zhu Y, et al. Real-world study of tenofovir disoproxil fumarate to prevent hepatitis B transmission in mothers with high viral load. *Aliment Pharmacol Ther*. 2019;49:211-217.
25. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med*. 2018;378:911-923.

How to cite this article: Ding Y, Cao L, Zhu L, et al. Efficacy and safety of tenofovir alafenamide fumarate for preventing mother-to-child transmission of hepatitis B virus: a national cohort study. *Aliment Pharmacol Ther*. 2020;52:1377–1386. https://doi.org/10.1111/apt.16043

APPENDIX 1

THE AUTHORS' COMPLETE AFFILIATION LIST

Yang Ding and Qiuju Sheng: Shengjing Hospital of China Medical University, Shenyang, China; Lihua Cao and ShouyunWang: Qinhuangdao Third Hospital, Qinhuangdao, China; Liying Zhu: The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China; Jian Fan: The Fourth Affiliated Hospital of Harbin Medical University, Harbin, China; Yan Huang and Ruochan Chen: Xiangya Hospital, Central South University, Hunan, China; Chaoshuang Lin and Weiqiang Gan: The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; Yuming Wang: Chong Qing Public Health Medical Center, Chong Qing, China; Yingxia Liu: Shenzhen Third People's Hospital, Shenzhen, China; Bryan Chen: University of California in Los Angeles, Los Angeles, CA, USA; Calvin Q. Pan: Beijing Ditan Hospital, Capital Medical University, Beijing, China and Tisch Hospital of NYU Langone Health, NYU School of Medicine, Flushing, NY, USA.