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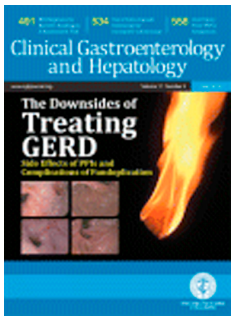

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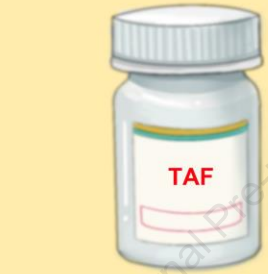
Active CHB + Pregnancy



HBV vaccine + HBIG

Healthy Baby

CHB Safely Controlled

Clinical Gastroenterology and Hepatology

Tenofovir Alafenamide for Pregnant Chinese Women with Active Chronic Hepatitis B: A Multicenter Prospective Study

Short Title: TAF for Pregnant Women with Active CHB

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Authors' contributions: Qing-Lei Zeng, Hong-Xu Zhang, Ji-Yuan Zhang, Shuo Huang, Wei-Zhe Li, and Guang-Ming Li contributed equally as joint first authors. Qing-Lei Zeng, Fu-Sheng Wang, Zu-Jiang Yu, and Yi-Hua Zhou contributed to the conception and design of this study. Qing-Lei Zeng contributed to the drafting of this manuscript. Shuo Huang and Wei-Zhe Li contributed to the data analysis. All authors contributed to the data collection, interpretation, and revision of this manuscript. All authors approved the final version of this manuscript.

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Data availability statement: All data relevant to the study are included in the article.

Abbreviations: ALT, alanine aminotransferase; anti-HBs, anti-hepatitis B surface antibody; CHB, chronic hepatitis B; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LMP, last menstrual period; MTCT, mother-to-child transmission; NUCs, nucleos(t)ide

analogs; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, target not detected; WHO, World Health Organization.

Presentation at any meeting: This study has been accepted as an Oral Presentation in the forthcoming 2021 AASLD Annual Meeting (Publication number: 19, Session of Advances with Approved HBV Therapies; November 13, 2021, 10:00 AM) and has been selected for inclusion in the "Best of The Liver Meeting's summary slide deck in the Hepatitis B category".

Main text (inclusive of main text, tables/figure legends, and references): 3936 words; **References**: 21; **Figure**: 1; **Tables**: 5; **Supplementary Tables**: 4; **Supplementary Figures**: 3.

ABSTRACT

BACKGROUND & AIMS: Data on long-term tenofovir alafenamide (TAF) therapy for pregnant women with active chronic hepatitis B (CHB, immune clearance and reactivation phases [currently and previously diagnosed]) and their infants are lacking.

METHODS: Pregnant women with active CHB treated with TAF and tenofovir disoproxil fumarate (TDF) were enrolled in this multicenter prospective study, and infants received immunoprophylaxis. The primary outcomes were rates of adverse (safety) events in pregnant women and defects in infants and fetuses. The secondary outcomes were virological responses in pregnant women, infants' safety, hepatitis B surface antigen (HBsAg) status, and growth conditions.

RESULTS: One hundred three and 104 pregnant women were enrolled, and 102 and 104 infants were born in the TAF and TDF groups, respectively. In the TAF group, the mean age, gestational age, alanine aminotransferase level, and viral loads at treatment initiation were 29.3 years, 1.3 weeks, 122.2 U/L, and 5.1 $\log_{10}$ IU/ml, respectively. TAF was well tolerated, and the most common adverse event was nausea (29.1%) during a mean of two years of treatment. Notably, 1 (1.0%) TAF-treated pregnant woman underwent induced abortion due to noncausal fetal cleft lip and palate. No infants in either group had birth defects. In the TAF group, the hepatitis B e antigen seroconversion rate was 20.7% at postpartum month 6, infants had normal growth

parameters, and no infants were positive for HBsAg at 7 months. The TDF group had comparable safety and effectiveness profiles.

CONCLUSIONS: TAF administered throughout or beginning in early pregnancy is generally safe and effective for pregnant women with active CHB and their infants.

Keywords: Chronic hepatitis B, Effectiveness, Mother-to-child transmission, Pregnancy, Safety, Tenofovir alafenamide, Tenofovir disoproxil fumarate

Introduction

In 2015, the World Health Organization (WHO) estimated that 257 million individuals were chronically infected with hepatitis B virus (HBV),[1] and HBV infection is a major cause of chronic liver disease and related complications and mortalities worldwide.[2] Annually, approximately 2 million children aged less than 5 years are newly infected with HBV,[3,4] and mother-to-child transmission (MTCT) accounts for the majority of the transmission routes.[2,5] In 2016, the WHO set goals to eliminate viral hepatitis, including HBV, as a global health threat by 2030.[6] Antiviral treatment for patients with chronic hepatitis B (CHB) and prevention of MTCT of new HBV infections are the most important strategies to achieve this goal.[6]

In clinical practice, a special population requires both the abovementioned antiviral treatment for their own liver diseases and prevention of MTCT for their newborns, namely, pregnant women with active CHB. As shown in our previous study, the first-line oral antiviral agent tenofovir alafenamide (TAF) administered during late pregnancy to inactive chronic HBV-infected pregnant women is safe and completely prevents the MTCT of HBV.[7] However, no data are available concerning the use of TAF by pregnant women with active CHB, although related data have recently become available for human immunodeficiency virus (HIV)-infected pregnant women.[8,9] Here, we report the safety and effectiveness profiles in pregnant women with active CHB and their infants when TAF is administered throughout gestation or beginning in the early phase of pregnancy.

Methods and Patients

Study Design and Participants

This multicenter prospective study was conducted in 11 public referral hospitals in China. All chronic HBV-infected pregnant women and women contemplating pregnancy were assessed for eligibility from January 1, 2019, to March 31, 2020. Pregnant women with active CHB who were treated with TAF or tenofovir disoproxil fumarate (TDF) were enrolled, and those pregnant women and their infants were followed until at least postpartum months 6 and 7, respectively. The final follow-up date was September 30, 2021.

Inclusion and Exclusion Criteria

The pregnant women or women contemplating pregnancy were enrolled in accordance with the following key eligibility criteria: female, more than 20 years old; anytime during the pregnancy (the gestational age was calculated from the first day of last menstrual period [LMP]); new diagnosis of active CHB with elevated levels of alanine aminotransferase (ALT) and detectable HBV DNA levels; previous diagnosis of active CHB and undergoing antiviral treatment with drugs other than TAF, but chose or switched to TAF or TDF for antiviral therapy, or continued TDF treatment.

Key exclusion criteria included a diagnosis of inactive chronic HBV infection with consistently normal ALT levels; concurrent disorders or conditions other than active CHB that may lead to elevated ALT levels; concurrent use of other treatments, including but not limited to immune modulators, cytotoxic drugs, or steroids;

coinfection with hepatitis A, C, D, E, or HIV; evidence of hepatocellular carcinoma or cirrhosis; systemic or other organ disorders; and evidence of fetal deformity.

Grouping Strategy

All mothers with active CHB were orally administered a dose of 25 mg of TAF (Vemlidy®, Gilead Sciences) or 300 mg of TDF (Viread®, Gilead Sciences) daily and were therefore divided into two groups, i.e., the TAF group and the TDF group. The TAF and TDF selections were based on the pregnant women's personal or their family's preferences (Supplementary Methods and Patients section).

Outcome Measurements

The primary outcomes were the rates of adverse (safety) events in pregnant women and defects in infants and fetuses. Maternal adverse events included any side effects during treatment. Maternal safety events included any pregnancy complications (such as induced abortion, threatened abortion, preterm labor, premature rupture of membrane, and postpartum hemorrhage) and any unfavorable fluctuations in routine or biochemical parameters during treatment (such as hemoglobin levels, creatine levels, and estimated glomerular filtration rate [eGFR]). Physical (structural) defects were observed in clinical examinations using equipment or testing (such as routine ultrasonography examinations) suggested by obstetricians during each visit, and further examinations or other detailed tests were performed if indicated.

The secondary outcomes were infants' safety conditions and growth parameters from birth to at least 7 months of age, the percentages of virological responses in pregnant women during treatment, and hepatitis B surface antigen (HBsAg) positivity in infants at 7 months of age. Infant safety conditions included Apgar scores at 1 minute after birth and any abnormal postnatal conditions. The anthropometric indices of infants in each group were compared with the other group and Chinese national and WHO standards.[10,11] Virological responses in pregnant women included the percentages of undetectable HBV DNA, hepatitis B virological breakthrough, ALT normalization, hepatitis e antigen (HBeAg) seroconversion, and HBsAg loss. Additionally, the status of anti-hepatitis B surface antibody (anti-HBs) in 7-month-old infants was also evaluated.

Ethical Evaluations

Informed consent was obtained from all patients for the observational process prior to inclusion in the study. The study was approved by the Ethics Committees of The First Affiliated Hospital of Zhengzhou University (2019-KY-204) and other involved centers.

Clinical Procedures, Infant Growth Analysis, Sample Size Estimation, and ***Statistical Analysis*** are included in the **Supplementary Methods and Patients section.**

Results

Participants

A total of 2688 pregnant women or women contemplating pregnancy with chronic HBV infection were assessed for eligibility, and 103 and 104 pregnant women with active CHB were enrolled for treatment with TAF and TDF, respectively (Figure 1). Notably, participants in each group were further divided into two subgroups at TAF initiation (Table 1), i.e., the treatment-naïve subgroup and the treatment-experiencing subgroup (switched to or continued TAF or TDF monotherapy). The mean time points of treatment initiation were 1.3 (± 14.6) and 1.0 (± 12.3) weeks referring to the first day of pregnancy (LMP), and 53 (51.5%) and 50 (48.1%) of these patients in the TAF and TDF groups started treatment before pregnancy, respectively. At treatment baseline, 74 (71.8%) and 71 (68.3%) pregnant women had detectable HBV DNA levels, 82 (79.6%) and 88 (84.6%) pregnant women were HBeAg-positive, and 72 (69.9%) and 67 (64.4%) pregnant women had elevated ALT levels in the TAF and TDF groups, respectively (Table 1). In total, 102 and 103 live newborns were born to women in the TAF and TDF groups, respectively (Table 2). Based on the pregnant women's personal preferences, 71 (69.6%) and 74 (71.2%) infants received breast milk in the TAF and TDF groups, respectively.

***Safety of** Pregnant Women*

The mean TAF treatment durations were 96.1 (± 24.4) and 98.7 (± 21.9) weeks in the TAF and TDF groups. TAF and TDF were both well tolerated in the pregnant women, and no pregnant woman discontinued therapy because of adverse events (Table 3). The

most common adverse events and complications were nausea (29.1% [TAF] vs. 31.7% [TDF]) and premature rupture of membranes (12.6% [TAF] vs. 13.5% [TDF]) in both groups, and no significant differences were observed in the occurrences of adverse events and complications between the two groups. Notably, 1 (1.0%) pregnant woman exposed to agricultural chemicals during early pregnancy who initiated TAF from 12 weeks plus 2 days of gestation underwent induced abortion at 23 weeks plus 4 days of pregnancy due to the diagnosis of cleft lip and palate for the fetus at 22 weeks of gestation.

In terms of laboratory abnormalities (Table 4), the most common was anemia in both groups, ranging from 10.7% to 52.9% of pregnant women during pregnancy, and 1.9% to 20.2% of them were diagnosed with moderate anemia, which was defined as a hemoglobin concentration ranging from 70 to 99 g/L.[12] However, the hemoglobin levels recovered to normal in almost all pregnant women after delivery. Additionally, the levels of platelets, total bilirubin, creatinine, β2-microglobulin, and eGFR were consistently normal, and no significant fluctuations were observed between the two groups (Table 4 and Supplementary Tables 1 and 2).

Safety of Infants or Fetuses

The prenatal TAF exposure duration for the fetuses was 32.1 (± 9.4) and 33.8 (± 8.3) weeks in the TAF and TDF groups, respectively (Table 2). No infant had an Apgar score of less than 8 at 1 minute of birth. No congenital defects or malformations were observed at birth, with the exception of the one fetus described above that underwent

induced abortion due to cleft lip and palate (Supplementary Table 3). The most common abnormal condition was prolonged (neonatal) jaundice, which was defined as neonatal jaundice lasting more than 2 weeks in term infants and more than 3 weeks in preterm infants,[13] and it occurred in 13 (12.7%) and 14 (13.4%) infants in the TAF and TDF groups, respectively. Prolonged jaundice either spontaneously resolved or was cured by phototherapy alone in these infants before 2 months of age.

Other abnormal conditions that occurred in one or more infants included fever (13/102 [12.7%] vs. 13/104 [12.5%]), cough (10/102 [9.8%] vs. 9/104 [8.7%]), vomiting (9/102 [8.8%] vs. 9/104 [8.7%]), skin rash (6/102 [5.9%] vs. 5/104 [4.8%]), diarrhea (4/102 [3.9%] vs. 5/104 [4.8%]), hearing impairment (1/102 [1.0%]) vs. 0/104 [0%], and cutaneous hemangioma (1/102 [1.0%] vs. 0/104 [0%]; on the left arm, size: 15 × 25 mm) in TAF and TDF groups, respectively. The infant diagnosed with hearing impairment at 1 week was then identified as having a conductive hearing impairment due to secretory otitis media at 3 months, but the condition eventually recovered spontaneously at 6 months; additionally, the other infant who was reported with cutaneous hemangioma at 4 weeks of age had been cured at 1 year (Supplementary Table 3). Notably, the infants' physical development at birth, 7 months, 12 months, and 18 months were comparable to the China national and WHO standards for children's growth (Table 5); at some time points, the growth parameters may be even better due to the possibly better nutrition for the infants currently. However, no significant differences in infants' growth parameters were observed between the TAF and TDF groups (Table 5).

On-time Rate of Immunoprophylaxis

Among the 206 newborns, the on-time conditions and the first doses of immunoprophylaxis are presented in Table 2. Regarding the administration of the second and third doses of HBV vaccine, 86 (84.3%) and 89 (85.6%) infants were injected on time, and the remaining 16 (15.7%) and 15 (14.4%) infants were delayed within 1-3 weeks because of prolonged neonatal jaundice, pregnant women's personal preferences, vaccination station reasons, or traffic influenced by coronavirus disease 2019 described in our previous studies.[7,14]

Effectiveness in Pregnant Women

The mean serum HBV DNA levels gradually decreased to 1.2 (± 1.7) and 0.9 (± 1.4) $\log_{10}$ IU/ml at delivery and 0.2 (± 0.2) and 0 (± 0.2) $\log_{10}$ IU/ml at postpartum month 6 in the TAF and TDF groups, respectively (Table 4 and Supplementary Tables 1 and 2). The percentages of women with undetectable HBV DNA, ALT normalization, and HBeAg seroconversion gradually increased with the continuation of treatment (Supplementary Figures 1, 2, and 3); however, no significant differences were observed between the TAF and TDF groups (all $P > 0.05$). Additionally, no pregnant woman in either group exhibited HBsAg loss during treatment. Notably, virological breakthrough occurred in 2 (2.0%) TAF-treated pregnant women after approximately 6 months of switchover from previous entecavir or entecavir/TDF regimens to TAF therapy, and Supplementary Table 4 presents the details.

Effectiveness in Infants

At the 7-month visit for infants, no infant was positive for HBsAg, i.e., the MTCT rate was 0%. Additionally, 101 (99.0%) and 104 (100%) infants were positive for anti-HBs, with mean levels of 404.9 (± 285.3) and 411.0 (± 253.8) mIU/ml in the TAF and TDF groups, respectively. Notably, the abovementioned anti-HBs levels may be underestimated because 7 and 6 infants' anti-HBs levels were reported as "> 1000 mIU/ml" in the TAF and TDF groups, respectively, and were calculated as 1000 mIU/ml.

Discussion

Although infants born to pregnant women with chronic HBV infection share the same immunization prophylaxis procedures, pregnant women who had active CHB require longer or even indefinite durations of antiviral treatment, and pregnant women with inactive chronic HBV infection only need definite short-term antiviral prophylaxis. Therefore, safety is the priority for pregnant women with active CHB who require long-term therapy. As shown in the present study, a mean of two years of TAF treatment is well tolerated with no major safety concerns and presents favorable effectiveness for pregnant women with active CHB who initiated TAF before or beginning in the early phase of pregnancy. Additionally, no congenital defects or malformations were observed in live infants at birth after approximately full gestational TAF exposure. Unsurprisingly, the MTCT rate was 0% in combination with standard HBV immunoprophylaxis for infants.

As an updated version of TDF with more potentially favorable safety profiles, TAF has been licensed for the treatment of CHB in China since December 2018 and has been recommended as a first-line antiviral agent by the main CHB guidelines.[5,15,16] Recently, TAF costs approximately 80 US dollars per bottle (30 tablets) before 50-90% reimbursement and has increasingly been used as the "first-line of three first-line drugs" for CHB in real-life clinical practice in China. Additionally, the drug label of TAF clearly indicates its usage during pregnancy in China.[17]

In July 2020, the WHO Guidelines for the Prevention of HBV MTCT suggested the "Evaluation of TAF" in the Research Gap.[1] To date, three recent studies have documented the favorable safety and effectiveness profiles of short-term TAF treatment for inactive chronic HBV-infected pregnant women.[7,17,18] However, long-term safety and effectiveness data of TAF administration during early or even before pregnancy for pregnant women with active CHB are lacking worldwide. To the best of our knowledge, this study is the first to assess TAF use for therapeutic purposes in pregnant women with active CHB, which differs from our and three other previous studies investigating TAF use for prophylactic purposes to mainly prevent HBV MTCT.[7,17,18] Notably, the present study not only included treatment-naïve pregnant women with active CHB but also included another common type of pregnant women, i.e., women who were previously diagnosed with active CHB and treated with nonclass B antiviral drugs defined by the US Food and Drug Administration before 2015 (such as entecavir) and intended for pregnancy, which increases the representativeness of the study.

Regarding safety concerns in this study, TAF-treated pregnant women experienced nonspecific adverse events and complications similar to the TDF groups, with the exception of a pregnant woman who suffered induced abortion due to fetal cleft lip and palate. Cleft lip and palate arise in approximately 1.7 per 1000 liveborn babies, and environmental risk factors might be important for their development.[19,20] Maternal exposure to smoke during pregnancy has been consistently associated with an increased risk of both cleft lip with or without cleft palate and isolated cleft palate, with a population-attributable risk as high as 20%.[19] Additionally, maternal exposure to agricultural chemicals has been associated with cleft lip and palate.[19] Notably, this pregnant woman was exposed to smoke passively for years and to agricultural chemicals during the first month of gestation. Most importantly, the developmental processes of the lip and palate are completed by 6-10 weeks of embryogenesis,[19,20] and this pregnant woman initiated TAF after 12 weeks of gestation. Therefore, we strongly doubt and almost certainly excluded a role for TAF in the development of cleft lip and palate in this fetus. Additionally, we also excluded a role for TAF in the development of hearing impairment because of the subsequent diagnosis of secretory otitis media and eventual spontaneous recovery. Unfortunately, we were unable to determine the role of TAF in infantile hemangioma, which may be induced by intrinsic factors (such as angiogenic and vasculogenic factors) and extrinsic factors (including tissue hypoxia and developmental field disturbances),[21] and future large-scale studies may resolve this confusion. Finally, although more than two-thirds of infants were breastfed during continuous TAF treatment of their mothers, the infants' growth parameters were normal

at 7 months, 12 months, and 18 months, indicating that even potential TAF exposure through breastfeeding may not increase the risk of abnormal infant growth.

Regarding the effectiveness concerns in this study, unexpectedly, two pregnant women with virological breakthrough both had excellent TAF compliance (Supplementary Table 4). Based on the extensive discussion by our team, we decided to continue TAF monotherapy for the pregnant woman with an "entecavir switch to TAF". Fortunately and even confusingly, her HBV DNA decreased to undetectable levels approximately 4 months later and thereafter. Additionally, we deliberatively decided to add lamivudine to TAF because the pregnant women who switched from the entecavir and TDF combination to TAF due to her previously poor response to either entecavir or TDF monotherapy. Fortunately, and even expectedly, her HBV DNA level decreased to undetectable levels approximately 3 months later and thereafter. These management strategies may be used in a similar situation in the future. Although we did not determine the cause of virological breakthroughs, detection errors for HBV DNA levels cannot be completely excluded in the entecavir-treated pregnant woman, and previous poor response experiences and switchover to TAF monotherapy may be the cause in another pregnant woman.

A limitation exists in this study, i.e., adverse events with a frequency of less than 5% might not be captured. However, the longer duration (a mean of approximately two years) of TAF treatment in the current study may provide a greater probability of observing more adverse events than TAF therapy of only approximately 3 months in our previous study.[7] Despite this limitation, our findings are important in understanding

and filling the gap in the long-term safety and effectiveness profiles of almost full gestational and fetal exposures to TAF for pregnant women with active CHB and their infants.

In conclusion, the current study indicates that TAF administered throughout or beginning in early pregnancy to pregnant women with active CHB was generally safe and effective for both pregnant women and infants, which provides relevant evidence to support the use of TAF in pregnant women with active CHB as an alternative option. Notably, in combination with the previous three studies involving short-term TAF treatment of pregnant women with inactive chronic HBV infection,[7,17,18] this prospective study can be viewed as another key piece of the puzzle for "TAF use in HBV-infected pregnant women" suggested by the WHO.[1] Nevertheless, future larger-scale studies are needed to validate this conclusion.

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Figure 1. Enrollment of participants.

Table 1. Baseline characteristics of pregnant women with newly or previously diagnosed active CHB at TAF or TDF initiation, switchover, or continuation

Characteristics	TAF group (n = 103)		TDF group (n = 104)		*P1* value	*P2* value
	Treat-naïve (n = 69)	Switchover (n = 34)	Treat-naïve (n = 63)	Switchover or continuation (n = 41)	0.337	0.337
Age, years	28.8 ± 4.5	30.5 ± 5.0	29.1 ± 4.1	29.8 ± 4.9	0.855	0.677
Primiparous	50 (72.5)	26 (76.5)	44 (69.8)	30 (73.2)	0.740	0.744
Previous regimens	-	34 (100)	-	41 (100)	-	0.337
Entecavir	-	29 (85.3)	-	30 (73.2)	-	-
TDF	-	2 (5.9)	-	11 (26.8)	-	-
Lamivudine + Adefovir	-	2 (5.9)	-	-	-	-
Entecavir + TDF	-	1 (2.9)	-	-	-	-
Years of treatment with previous regimens	-	3.4 ± 3.0	-	2.3 ± 1.4	-	0.072
Entecavir	-	3.0 ± 1.7	-	2.4 ± 1.5	-	-
TDF	-	2, 3	-	1.8 ± 1.1	-	-
Lamivudine + Adefovir	-	14, 13	-	-	-	-
Entecavir + TDF	-	1.6	-	-	-	-
Gestational age (from D1-LMP)†	7.8 ± 13.0	-11.6 ± 6.9	6.1 ± 12.6	-6.7 ± 6.0	0.440	0.002
Before D1-LMP	20 (29.0)	33 (97.1)	21 (33.3)	29 (70.7)	0.590	0.003
At D1-LMP‡	0 (0)	0 (0)	0 (0)	11 (26.8)‡	-	0.003
After D1-LMP	49 (71.0)	1 (2.9)	42 (66.7)	1 (2.4)	0.590	1.000
HBsAg levels, log_{10} IU/ml	4.2 ± 0.4	3.7 ± 0.5	4.2 ± 0.3	3.8 ± 0.5	0.281	0.400
< 3.0	2 (2.9)	3 (8.8)	0 (0)	3 (7.3)	0.517	1.000
3.0-3.9	12 (17.4)	19 (55.9)	14 (22.2)	20 (48.8)	0.486	0.596
4.0-4.9	55 (79.7)	12 (35.3)	49 (77.8)	18 (43.9)	0.786	0.126
HBeAg positivity	59 (85.5)	23 (67.6)	57 (90.5)	31 (75.6)	0.382	0.445

HBV DNA, log_{10} IU/ml	7.3 ± 1.0	0.5 ± 1.2	7.2 ± 0.8	0.6 ± 1.3	0.137	0.567
TND	0 (0)	29 (85.3)	0 (0)	33 (80.5)	-	0.584
1.0-3.9	1 (1.4)	4 (11.8)	0 (0)	6 (14.6)	1.000	0.982
4.0-4.9	1 (1.4)	0 (0)	0 (0)	2 (4.9)	0.925	0.558
5.0-5.9	3 (4.3)	1 (2.9)	6 (9.5)	0 (0)	0.679	0.925
6.0-6.9	20 (29.0)	0 (0)	16 (25.4)	0 (0)	0.644	-
7.0-7.9	28 (40.6)	0 (0)	32 (50.8)	0 (0)	0.239	-
> 8.0	16 (23.2)	0 (0)	9 (14.3)	0 (0)	0.192	-
ALT, U/L	171.6 ± 81.3	22 ± 17.5	141.3 ± 66.2	22.8 ± 16.3	0.009	0.445
≤ 40	0 (0)	31 (91.2)	0 (0)	37 (90.2)	-	0.563
41-80	3 (4.3)	2 (5.9)	1 (1.6)	3 (7.3)	0.678	1.000
81-200	48 (69.6)	1 (2.9)	53 (84.1)	1 (2.4)	0.049	1.000
> 200	18 (26.1)	0 (0)	9 (14.3)	0 (0)	0.093	-
Total bilirubin, μmol/L	8.5 ± 3.5	7.1 ± 2.7	8.1 ± 2.6	7.9 ± 3.6	0.635	0.526
> 17.1	1 (1.4)	0 (0)	0 (0)	0 (0)	1.000	-
Hemoglobin, g/L	122.2 ± 11.0	127.7 ± 11.5	119.9 ± 11.2	123.4 ± 8.3	0.175	0.082
< 110	10 (14.5)	1 (2.9)	9 (14.3)	2 (4.9)	0.973	1.000
100-109	9 (13.0)	0 (0)	5 (7.9)	1 (2.4)	0.341	1.000
90-99	1 (1.4)	1 (2.9)	4 (6.3)	1 (2.4)	0.309	1.000
Platelets, × 10^9/L	234.2 ± 52.1	236.1 ± 65.0	231.6 ± 51.8	221.0 ± 45.1	0.806	0.459
< 100	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Creatinine, μmol/L	51.1 ± 7.8	50.0 ± 7.8	50.5 ± 9.3	50.7 ± 10.0	0.758	0.807
> 115	0/67 (0)	0/33 (0)	0/61 (0)	0/39 (0)	-	-
β2-microglobulin, mg/L	1.5 ± 0.5	1.4 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	0.246	0.042
> 3	1/66 (1.5)	0/32 (0)	1/62 (1.6)	0/40 (0)	1.000	-
eGFR, ml/min/1.73 m^2	121.1 ± 7.4	120.1 ± 6.2	120.2 ± 9.8	120.8 ± 8.7	0.489	0.903
< 100	0/64 (0)	0/33 (0)	0/61 (0)	0/40 (0)	-	-
Splenomegaly	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Smoking	0 (0)	0 (0)	0 (0)	0 (0)	-	-

Hypertension	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Diabetes	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Renal diseases	0 (0)	0 (0)	0 (0)	0 (0)	-	-
Bone diseases[¶]	0 (0)	0 (0)	0 (0)	0 (0)	-	-

P1: TAF treatment-naïve subgroup vs. TDF treatment-naïve subgroup; *P2*: TAF switchover subgroup vs. TDF switchover or continuation subgroup. [†]Gestational age was calculated from the first day of the last menstrual period (D1-LMP). [‡]Eleven patients started TDF treatment due to the previously diagnosed active CHB at a mean of 1.8 years before pregnancy. They chose to continue TDF treatment for pregnancy. According to the clinical procedures, their TDF-initiated weeks referred to the first day of pregnancy (D1-LMP) were counted as 0 weeks, although it may result in the illusion or "coincidence" of starting TDF treatment and becoming pregnant "simultaneously". [¶]Bone diseases indicate bone pain and fractures reported by pregnant women.

Table 2. Characteristics of the infants (fetus) at birth

Characteristics	TAF group (n = 103)[†]	TDF group (n = 104)	*P* value
Male	51 (50)	50 (48.1)	0.783
TAF or TDF exposed duration before birth, weeks	32.1 ± 9.4	33.8 ± 8.3	0.250
Gestational age, weeks	39.3 ± 1.1	39.3 ± 1.2	0.982
< 37	3 (2.9)	4 (3.8)	1.000
≥ 41	8 (7.8)	8 (7.7)	0.968
Delivery by cesarean section	35 (34.3)	39 (37.5)	0.634
Weight, kg	3.4 ± 0.3	3.4 ± 0.3	0.283
Height, cm	49.9 ± 1.4	49.7 ± 1.4	0.409
Head circumference, cm	34.5 ± 1.0	34.5 ± 0.9	0.700
Apgar score at 1 minute	9.7 ± 0.5	9.5 ± 0.5	0.031
< 8	0 (0)	0 (0)	-
Congenital defects or malformations	1 (1.0)[†]	0 (0)	-
Immunoprophylaxis administration	102 (100)	104 (100)	-
Time from birth to administration of the first doses of immunoprophylaxis, hours	2.9 ± 2.7	3.0 ± 2.9	0.957
≤ 1	22 (21.6)	23 (22.1)	0.924
1-6	73 (71.6)	73 (70.2)	0.828
7-11	5 (4.9)	4 (3.8)	0.976
13-16	2 (2.0)	4 (3.8)	0.696
Breastfeeding	71 (69.6)	74 (71.2)	0.808

Data are presented as the means ± standard deviations or n (%). [†]One fetus diagnosed with cleft lip and palate by ultrasound underwent induced abortion at 23 weeks plus 4 days of gestational age, and this fetus was regarded as a congenital defect but did not have other parameters to be included in this table.

Table 3. Adverse events and complications experienced by the pregnant women during treatment

Parameters	TAF group (n = 103)	TDF group (n = 104)	*P* value
Maternal adverse events			
Nausea	30 (29.1)	33 (31.7)	0.684
Anorexia	23 (22.3)	21 (20.2)	0.707
Fatigue	19 (18.4)	20 (19.2)	0.885
Vomiting	11 (10.7)	11 (10.6)	0.981
Headache	8 (7.8)	7 (6.7)	0.774
Insomnia	5 (4.9)	5 (4.8)	1.000
Dizziness	5 (4.9)	4 (3.8)	0.988
Gastric acid regurgitation	4 (3.9)	5 (4.8)	1.000
Abdominal pain	3 (2.9)	2 (1.9)	0.991
Fever	2 (1.9)	5 (4.8)	0.450
Diarrhea	2 (1.9)	3 (2.9)	1.000
Cough	2 (1.9)	3 (2.9)	1.000
Constipation	2 (1.9)	2 (1.9)	1.000
Rash	1 (1.0)	2 (1.9)	1.000
Palpitation	1 (1.0)	0 (0)	0.996
Maternal complications			
Premature rupture of membranes	13 (12.6)	14 (13.5)	0.858
Preterm labor	3 (2.9)	4 (3.8)	1.000
Gestational hypertension	3 (2.9)	4 (3.8)	1.000
Pneumonia	1 (1.0)	4 (3.8)	0.371
Gestational diabetes mellitus	1 (1.0)	0 (0)	0.996
Placenta previa	1 (1.0)	2 (1.9)	1.000
Induced abortion	1 (1.0)[†]	0 (0)	0.996
Threatened abortion	1 (1.0)	1 (1.0)	1.000
Postpartum hemorrhage	1 (1.0)	2 (1.9)	1.000
Renal diseases	0 (0)	0 (0)	-

Bone diseases‡	0 (0)	0 (0)	-

Data are presented as n (%). †The details are presented in the main text and supplementary materials.

‡Bone diseases indicate bone pain and fractures reported by pregnant women.

Table 4. Maternal laboratory parameters at TAF initiation, delivery, and postpartum months (PPMs) 6 and 12

Parameters	Treatment initiation			Delivery			PPM 6			PPM 12		
	TAF group (n = 103)	TDF group (n = 104)	*P* value	TAF group (n = 102)	TDF group (n = 104)	*P* value	TAF group (n = 102)	TDF group (n = 104)	*P* value	TAF group (n = 70)	TDF group (n = 74)	*P* value
HBV DNA, log_{10} IU/ml	5.1 ± 3.4	4.6 ± 3.4	0.138	1.2 ± 1.7	0.9 ± 1.4	0.382	0.2 ± 0.2	0 ± 0.2	0.984	0 ± 0	0 ± 0	1.000
ALT, U/L	122.2 ± 97.5	94.6 ± 78.3	0.051	34.4 ± 35.5	33.5 ± 23.4	0.039	20.5 ± 12.1	23.8 ± 11.6	0.002	18.3 ± 6.3	22.5 ± 8.8	0.001
TBIL, μmol/L	8.0 ± 3.3	8.0 ± 3.0	0.922	6.6 ± 2.9	7.4 ± 3.0	0.143	6.1 ± 2.1	5.7 ± 1.9	0.339	6.5 ± 3.6	7.2 ± 1.3	< 0.001
Hemoglobin, g/L	124.0 ± 11.4	121.3 ± 10.2	0.067	110.3 ± 10.8	109.8 ± 11.0	0.728	126.6 ± 8.9	124.2 ± 7.8	0.004	128.4 ± 6.0	128.3 ± 6.4	0.797
Platelets, × 10^9/L	234.8 ± 56.4	227.4 ± 49.3	0.472	226.4 ± 54.4	217.6 ± 45.6	0.313	230.6 ± 48.6	227.8 ± 45.5	0.831	226.9 ± 44.6	231.0 ± 42.7	0.438
Creatinine, μmol/L	50.7 ± 7.7	50.6 ± 9.5	0.857	42.3 ± 7.1	43.8 ± 8.7	0.210	49.9 ± 8.8	50.8 ± 8.2	0.313	50.8 ± 6.6	51.4 ± 6.1	0.721
β2-microglobulin, mg/L	1.5 ± 0.5	1.6 ± 0.5	0.037	1.6 ± 0.5	1.7 ± 0.5	0.063	1.6 ± 0.5	1.6 ± 0.5	0.561	1.8 ± 0.5	1.9 ± 0.4	0.277
eGFR, ml/min/1.73 m^2	120.8 ± 7.0	120.4 ± 9.3	0.572	133.5 ± 10.5	131.8 ± 8.7	0.234	120.2 ± 9.4	120.3 ± 9.2	0.648	121.0 ± 6.3	120.7 ± 8.8	0.789

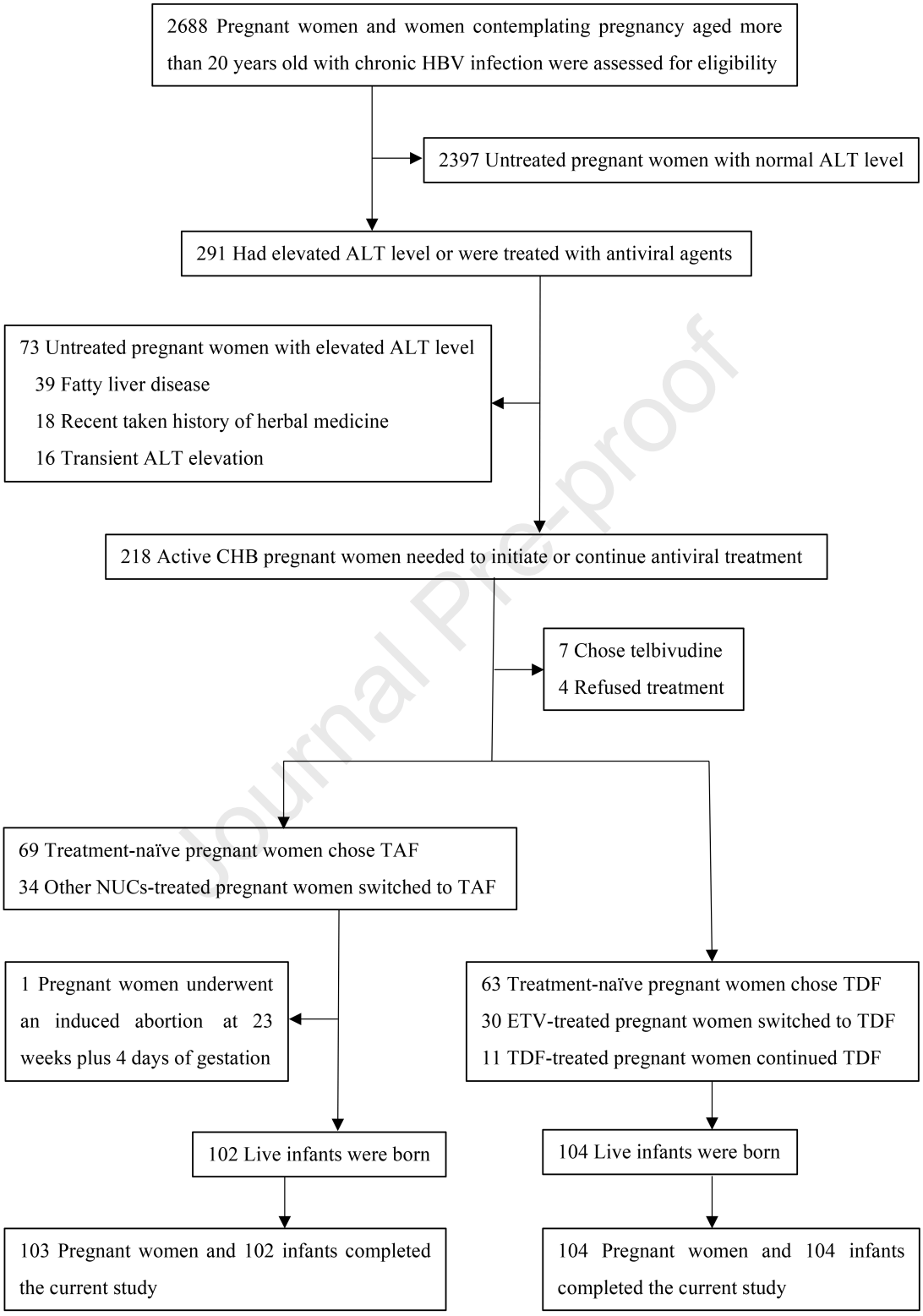
Data are presented as the means ± standard deviations. At treatment initiation, creatinine, β2-microglobulin, and eGFR data were available for 100, 98, and 97 pregnant women in the TAF group and were available for 100, 102, and 101 pregnant women in the TDF group. At delivery, creatinine, β2-microglobulin, and eGFR data were available for 100, 98, and 99 pregnant women in the TAF group and for 102, 102, and 100 pregnant women in the TDF group. At PPM 6, creatinine, β2-microglobulin, and eGFR data were available for 100, 98, and 97 pregnant women in the TAF group and 103, 103, and 102 pregnant women in the TDF group. At PPM 12, eGFR data were available for 69 pregnant women in the TAF group.

Table 5. Anthropometric indices of infants at birth, 7 months, 12 months, and 18 months

Parameters	**TAF group (n = 102)**		**TDF group (n = 104)**		**National standards**	***P1* value** *(TAF* vs. *TDF)*	***P2* value** (TAF vs. National)	***P3* value** (TDF vs. National)
	Growth indices	**WHO z scores**	**Growth indices**	**WHO z scores**				
At birth								
Boys' weight, kg	3.49 ± 0.29	0.33 ± 0.57	3.46 ± 0.31	0.27 ± 0.64	3.38 ± 0.40	0.617	0.010	0.079
Boys' height, cm	50.45 ± 1.49	0.58 ± 0.79	50.26 ± 1.53	0.48 ± 0.81	50.40 ± 1.60	0.529	0.825	0.540
Boys' head circumference, cm	34.86 ± 0.96	0.24 ± 0.76	34.83 ± 0.79	0.21 ± 0.63	34.0 ± 1.40	0.864	< 0.001	< 0.001
Girls' weight, kg	3.28 ± 0.26	0.16 ± 0.55	3.34 ± 0.37	0.26 ± 0.79	3.26 ± 0.40	0.337	0.595	0.146
Girls' height, cm	49.33 ± 1.16	0.39 ± 0.62	49.17 ± 1.14	0.30 ± 0.61	49.80 ± 1.60	0.478	0.006	< 0.001
Girls' head circumference, cm	34.11 ± 0.92	0.11 ± 0.78	34.20 ± 0.80	0.19 ± 0.68	33.70 ± 1.30	0.593	0.003	< 0.001
At 7 months								
Boys' weight, kg	8.54 ± 0.40	0.25 ± 0.42	8.65 ± 0.38	0.37 ± 0.40	8.68 ± 0.94	0.160	0.023	0.606
Boys' height, cm	69.35 ± 1.57	0.41 ± 0.72	69.24 ± 1.65	0.35 ± 0.75	69.50 ± 2.30	0.732	0.510	0.282
Boys' head circumference, cm	44.27 ± 0.76	0.24 ± 0.62	44.40 ± 0.91	0.34 ± 0.74	43.80 ± 1.30	0.437	< 0.001	< 0.001
Girls' weight, kg	7.99 ± 0.31	0.31 ± 0.30	7.98 ± 0.30	0.35 ± 0.30	8.03 ± 0.90	0.870	0.408	0.278
Girls' height, cm	67.47 ± 1.62	0.38 ± 0.72	67.57 ± 1.28	0.43 ± 0.55	67.90 ± 2.30	0.727	0.070	0.075

Girls' head circumference, cm	43.06 ± 0.61	0.17 ± 0.47	43.10 ± 0.97	0.21 ± 0.74	42.60 ± 1.20	0.800	< 0.001	< 0.001
At 12 months[†]								
Boys' weight, kg	10.04 ± 0.53	0.34 ± 0.46	9.95 ± 0.61	0.27 ± 0.56	9.88 ± 1.11	0.516	0.098	0.514
Boys' height, cm	75.78 ± 0.81	0.29 ± 0.34	75.69 ± 0.85	0.27 ± 0.36	75.10 ± 2.60	0.654	< 0.001	< 0.001
Boys' head circumference, cm	46.34 ± 0.52	0.21 ± 0.40	46.40 ± 0.45	0.26 ± 0.35	45.70 ± 1.40	0.610	< 0.001	< 0.001
Girls' weight, kg	9.30 ± 0.59	0.30 ± 0.51	9.24 ± 0.61	0.24 ± 0.52	9.24 ± 1.05	0.667	0.557	1.000
Girls' height, cm	73.97 ± 0.98	0.21 ± 0.37	73.85 ± 0.94	0.21 ± 0.37	73.70 ± 2.70	0.590	0.130	0.362
Girls' head circumference, cm	45.14 ± 0.62	0.20 ± 0.43	45.24 ± 0.54	0.26 ± 0.38	44.70 ± 1.30	0.458	< 0.001	< 0.001
At 18 months[‡]								
Boys' weight, kg	11.41 ± 0.48	0.37 ± 0.37	11.43 ± 0.47	0.38 ± 0.37	11.07 ± 1.19	0.919	0.026	0.030
Boys' height, cm	82.61 ± 0.42	0.39 ± 0.15	82.59 ± 0.54	0.38 ± 0.20	81.40 ± 3.0	0.920	< 0.001	< 0.001
Boys' head circumference, cm	47.96 ± 0.38	0.38 ± 0.16	47.95 ± 0.47	0.44 ± 0.35	47.0 ± 1.30	0.955	< 0.001	< 0.001
Girls' weight, kg	10.66 ± 0.42	0.33 ± 0.32	10.78 ± 0.50	0.41 ± 0.37	10.46 ± 1.16	0.435	0.073	0.009
Girls' height, cm	80.85 ± 0.58	0.29 ± 0.20	81.14 ± 1.01	0.39 ± 0.35	80.10 ± 3.0	0.275	< 0.001	< 0.001
Girls' head circumference, cm	46.65 ± 0.39	0.29 ± 0.28	46.76 ± 0.54	0.38 ± 0.39	46.10 ± 1.30	0.486	< 0.001	< 0.001

Data are presented as the means ± standard deviations. [†]Included 34 boys and 36 girls in the TAF group and 35 boys and 39 girls in the TDF group. [‡]Included 13 boys and 17 girls in the TAF group and 11 boys and 21 girls in the TDF group.



SUPPLEMENTARY MATERIALS

Methods and Patients

Clinical Procedures

Upon enrollment in this study, the guidelines did not recommend tenofovir alafenamide (TAF) as a treatment option for pregnant women.[1-4] However, in China, the drug label (instruction) of TAF (including tenofovir disoproxil fumarate [TDF]) has an indication for pregnant women, stating that "TAF (including TDF) can be used during pregnancy if necessary".[5,6] Notably, drug labels have far more legal power than guidelines in China. The drug labels of TAF and TDF both indicating use in pregnancy are the basis of equal recommendations by physicians; meanwhile, the proportions of patients using TAF and TDF at different participating hospitals are complementary. These factors may contribute to the potential balances of drug selections during enrollment of this study, although a much higher proportion of patients with chronic hepatitis B (CHB) choose TAF (Vemlidy®) rather than TDF (Viread®) currently.

The anticipated antiviral treatment durations for these mothers with active CHB were consistent with the CHB guidelines of China,[7] namely, at least 3 years of consolidation after hepatitis e antigen (HBeAg) seroconversion for patients with HBeAg-positive CHB and a continuously indefinite duration for patients with HBeAg-negative CHB. The mothers' TAF or TDF treatment durations in the current study were calculated from the time points of TAF or TDF initiation or switchover to the final follow-up date. The time of TAF or TDF initiation before the first day of pregnancy

(the first day of the last menstrual period) for women with active CHB who were contemplating pregnancy is presented a negative value (for example, a woman contemplating pregnancy was diagnosed with active CHB and initiated TAF therapy on January 1, 2019, her first day of pregnancy was January 28, 2019, and the TAF initiation week was counted as -4 weeks); for nontreatment-naïve (previously diagnosed active CHB) mothers in the TDF group who continued TDF therapy, the TDF-initiated weeks referred to the first day of pregnancy and was counted as 0 weeks. Notably, this calculation may lead to the illusion that many mothers happen to start treatment and become pregnant simultaneously or very closely, especially mothers in the TDF group.

Blood testing, including hepatitis B surface antigen (HBsAg), HBeAg, hepatitis B virus (HBV) DNA, and routine blood tests, liver and kidney function tests, and upper abdominal ultrasound examinations were suggested and performed at the time points of TAF initiation, approximately every 3 months during pregnancy, delivery, and postpartum months 3, 6, 12, and 18 for mothers. During treatment, maternal HBsAg titers were only detected for mothers who achieved HBeAg seroconversion. Other time points of testing and the methods of feeding the infants were based on the mothers' personal convenience or preferences. Additionally, the delivery mode, i.e., vaginal delivery or cesarean section, was based mainly on the obstetricians' judgment combined with the mothers' personal willingness or conditions.

The newborns had the following immunoprophylaxis schedule:[2-4,7-9] (1) 100 IU of hepatitis B immunoglobulin (Hualan Biological Engineering Inc., Henan Province,

China) and the first dosage of 10 μg of recombinant HBV vaccine (Hansenula yeast vaccine, Dalian Hissen BioPharm Inc., Liaoning Province, China) were administered within 12 hours of birth; (2) the second injection of 10 μg of HBV vaccine was administered at 1 month; and (3) the third dose of 10 μg of HBV vaccine was administered at 6 months. Therefore, the first doses of immunoprophylaxis included 100 IU of hepatitis B immunoglobulin and 10 μg of recombinant hepatitis B vaccine.

Maternal blood samples were collected from the vein at the elbow, and infants' blood samples were commonly collected from the jugular vein at 7 months, and the scalp vein or dorsalis pedis vein would be an alternative when the jugular vein was unavailable. Serum HBsAg and anti-hepatitis B surface antibody (anti-HBs) titers were tested using the Abbott ARCHITECT Alinity HBsAg and anti-HBs Reagent Kits (Abbott Ireland Diagnostics Division, Finisklin Bussiness Park, Sligo, Ireland), with a lower limit of quantification of 0.05 IU/ml for HBsAg, i.e., less than 0.05 IU/ml was a negative result, and an anti-HBs above 10 mIU/ml was defined as a positive result. Serum HBV DNA levels (lower limit of quantification was 10 IU/ml) were measured using an Abbott Real Time Assay (Abbott Molecular Inc., Des Plaines, IL, USA).

The upper limit of normal for ALT levels was set to 40 U/L according to the Asian-Pacific CHB guideline.[2] The upper limits of the normal ranges for alanine aminotransferase, total bilirubin, creatinine, and β2-microglobulin levels were 40 U/L, 17.1 μmol/L, 115 μmol/L, and 3 mg/L, respectively, and the lower limits of the normal ranges for hemoglobin levels and platelet counts were 110 g/L and 100×10^9/L, respectively.

Analysis of Infant Growth

The anthropometric indices recorded at birth, 7, 12, and 18 months of age were compared between the TAF and TDF groups, and each group was further compared with the Chinese national and World Health Organization (WHO) standards.[10,11] Anthropometric z scores for the growth of infants in the two groups were based on WHO standards (https://www.who.int/childgrowth/standards/en/), including the weight-for-age (at birth, 7, 12, and 18 months), head circumference-for-age (at birth, 7, 12, and 18 months), and length/height-for-age (at birth, 7, 12, and 18 months) z scores in the current study and were calculated using WHO Anthro Software (version 3.2.2). The national standards cited from "A national survey on physical growth and development of children under 7 years of age in nine cities of China in 2015"[11] in which a total of 2264 boys and 2147 girls were analyzed at birth, 1901 boys and 1884 girls were analyzed at 7 months, 1860 boys and 1862 girls were analyzed at 12 months, and 1847 boys and 1886 girls were analyzed at 18 months.

Sample Size Estimation

The primary endpoint was the rates of adverse (safety) events in pregnant women. Based on previous studies,[12,13] severe adverse events occurred in approximately 6% of participants, and the number of pregnant women needed to capture the adverse events that occurred in > 5% of pregnant women was calculated to be 92 with a significance level of 0.05 (one-tailed test). Considering a withdrawal rate of 10%, the total sample size was thus calculated to be at least 101 in each group. Notably, according to the

relevant law and regulations from the State Food and Drug Administration of China, the probability of observing 5% of the adverse events is greater than 99% after completing the observation of 100 patients.[14]

Statistical Analysis

Continuous variables are summarized as either the means ± standard deviations or the medians and ranges, as appropriate. The percentage of patients in each category was calculated for categorical variables. The percentages were compared between the two groups using the chi-square test. The Mann–Whitney U test was performed to compare continuous variables between the two groups. Paired-samples t tests or related-samples Wilcoxon signed rank tests were performed to compare continuous variables between various time points within one group, as appropriate. The WHO anthropometric z scores for infants were calculated using WHO Anthro Software (version 3.2.2, 2011).[10] A summary independent-samples t test was used to compare the differences between infants' growth parameters and Chinese national standards in either group. A two-sided $P < 0.05$ was considered significant. The analyses were performed using SPSS software 25.0 for Windows (SPSS Inc. Chicago, IL, USA).

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Supplementary Table 1 Maternal laboratory parameters at TAF initiation, 3 and 6 months of pregnancy (PM), delivery, and postpartum months (PPMs) 3, 6, 12, 18

Parameters	**TAF-treated mothers (n = 103[†])**							
	TAF initiation (n = 103)	PM 3 (n = 61)[‡]	PM 6 (n = 89)[‡]	Delivery (n = 102)	PPM 3 (n = 102)	PPM 6 (n = 102)	PPM 12 (n = 70[§])	PPM 18 (n = 30[§])
HBV DNA, log_{10} IU/ml	5.1 ± 3.4	2.0 ± 2.1	1.9 ± 1.9	1.2 ±1.7	0.2 ± 0.8	0.2 ± 0.2	0 ± 0	0 ± 0
TND	29 (28.2)	31 (50.8)	42 (47.2)	68 (66.7)	93 (91.2)	101 (99.0)	70 (100)	30 (100)
1.0-3.9	5 (4.9)	14 (23.0)	30 (33.7)	23 (22.5)	9 (8.8)	3 (2.9)	0 (0)	0 (0)
4.0-4.9	1 (1.0)	13 (21.3)	14 (15.7)	10 (9.8)	0 (0)	0 (0)	0 (0)	0 (0)
5.0-5.9	4 (3.9)	3 (4.9)	3 (3.4)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
6.0-6.9	20 (19.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
7.0-7.9	28 (27.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
> 8.0	16 (15.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Virological breakthrough	-	0 (0)	2 (2.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HBeAg seroconversion[¶]	-	0 (0)	1/69 (1.4)	2/82 (2.4)	5/82 (6.1)	9/82 (11.0)	2/57 (3.5)	1/24 (4.2)
ALT, U/L	122.2 ± 97.5	53.0 ± 50.4	45.2 ± 39.2	34.4 ± 35.5	26.1 ± 19.5	20.5 ± 12.1	18.3 ± 6.3	21.0 ± 6.4
≤ 40	31 (30.1)	32 (52.5)	50 (56.2)	76 (74.5)	82 (80.4)	93 (91.2)	68 (97.1)	29 (96.7)
41-80	5 (4.9)	18 (29.5)	27 (30.3)	15 (14.7)	19 (18.6)	9 (8.8)	2 (2.9)	1 (3.3)

81-200	49 (47.6)	9 (14.8)	12 (13.5)	10 (9.8)	1 (1.0)	0 (0)	0 (0)	0 (0)
> 200	18 (17.5)	2 (3.3)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
Total bilirubin, μmol/L	8.0 ± 3.3	6.2 ± 2.2	6.3 ± 2.3	6.6 ± 2.9	6.8 ± 3.5	6.1 ± 2.1	6.5 ± 3.6	5.7 ± 2.3
> 17.1	1 (1.0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Hemoglobin, g/L	124.0 ± 11.4	118.6 ± 9.3	112.1 ± 8.3	110.3 ± 10.8	125.5 ± 10.8	126.6 ± 8.9	128.4 ± 6.0	127.2 ± 8.2
< 110	11 (10.7)	9 (14.8)	33 (37.1)	54 (52.9)	8 (7.8)	7 (6.9)	1 (1.4)	2 (6.7)
100-109	9 (8.7)	8 (13.1)	28 (31.5)	39 (38.2)	4 (3.9)	4 (3.9)	1 (1.4)	2 (6.7)
80-99	2 (1.9)	1 (1.6)	5 (5.6)	15 (14.7)	4 (3.9)	3 (2.9)	0 (0)	0 (0)
Platelets, × 10^9/L	234.8 ± 56.4	235.2 ± 53.3	227.5 ± 55.6	226.4 ± 54.4	225.0 ± 52.0	230.6 ± 48.6	226.9 ± 44.6	228.5 ± 46.0
< 100	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Creatinine, μmol/L	50.7 ± 7.7	47.6 ± 5.6	44.1 ± 7.5	42.3 ± 7.1	50.7 ± 6.9	49.9 ± 8.8	50.8 ± 6.6	49.0 ± 5.8
> 115	0/100 (0)	0/60 (0)	0 (0)	0/100 (0)	0/101 (0)	0/100 (0)	0 (0)	0 (0)
β2-microglobulin, mg/L	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	1.9 ± 0.4
> 3	1/98 (1.0)	0/59 (0)	2/87 (2.3)	0/98 (0)	2/101 (2.0)	0/98 (0)	1 (1.4)	0 (0)
eGFR, ml/min/1.73 m^2	120.8 ± 7.0	122.9 ± 8.6	125.6 ± 7.7	133.5 ± 10.5	121.0 ± 10.0	120.2 ± 9.4	121.0 ± 6.3	124.0 ± 6.7
< 100	0/97 (0)	0/58 (0)	0/85 (0)	0/99 (0)	0/101 (0)	0/97 (0)	0/69 (0)	0 (0)

Data are presented as the means ± standard deviations, n (%), or n/N (%), where N is the total number of patients with available data. [†]One mother underwent an induced abortion at 23 weeks plus 4 days of gestation and was only included for analysis at TAF initiation. [‡]Data from 41 and 13 mothers are not presented at PM3 and PM6 mainly because their TAF-initiated time points were close to or after these two time points and were counted as TAF initiation characteristics. [§]A total of 32 and 72 mothers did not reach the time points of PPM12 and PPM18, respectively. [¶]The numerator represents the new occurrence at each time point, and the corresponding denominator is the available number of mothers who were HBeAg-positive at TAF initiation.

Supplementary Table 2 Maternal laboratory parameters at TDF initiation, 3 and 6 months of pregnancy (PM), delivery, and postpartum months (PPMs) 3, 6, 12, 18

Parameters	**TAF-treated mothers (n = 104)**							
	TDF initiation (n = 104)	PM 3 (n = 76)[†]	PM 6 (n = 96)[†]	Delivery (n = 104)	PPM 3 (n = 104)	PPM 6 (n = 104)	PPM 12 (n = 74[‡])	PPM 18 (n = 32[‡])
HBV DNA, log_{10} IU/ml	4.6 ± 3.4	1.9 ± 2.1	1.6 ± 1.8	0.9 ±1.4	0.2 ± 0.6	0 ± 0.2	0 ± 0	0 ± 0
TND (< 10 IU/ml)	33 (31.7)	38 (50.0)	49 (51.0)	71 (68.3)	96 (92.3)	103 (99.0)	74 (100)	32 (100)
1-4	6 (5.8)	22 (28.9)	39 (40.6)	30 (28.8)	7 (6.7)	1 (1.0)	0 (0)	0 (0)
4.1-5	2 (1.9)	10 (13.2)	7 (7.3)	3 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)
5.1-6	6 (5.8)	6 (7.9)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6.1-7	16 (15.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
7.1-8	32 (30.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
8.1-8.7	9 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Virological breakthrough	-	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HBeAg seroconversion[¶]	-	0/62 (0)	1/80 (1.3)	4/88 (4.5)	4/88 (4.5)	6/88 (6.8)	5/63 (7.9)	1/26 (3.8)
ALT, U/L	94.6 ± 78.3	52.7 ± 48.0	49.5 ± 41.5	33.5 ± 23.4	28.2 ± 17.4	23.8 ± 11.6	22.5 ± 8.8	25.5 ± 7.1
≤ 40	37 (35.6)	45 (59.2)	61 (63.5)	80 (76.9)	85 (81.7)	97 (92.3)	72 (97.3)	31 (96.9)
41-80	4 (3.8)	16 (21.1)	21 (21.9)	15 (14.4)	17 (16.3)	7 (6.7)	2 (2.7)	2 (6.2)

81-200	54 (51.9)	15 (19.7)	12 (12.5)	9 (8.7)	2 (1.9)	0 (0)	0 (0)	0 (0)
201-300	4 (3.8)	0 (0)	2 (2.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
301-400	5 (4.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total bilirubin, μmol/L	8.0 ± 3.0	6.7 ± 3.1	5.9 ± 2.2	7.4 ± 3.0	7.5 ± 3.2	5.7 ± 1.9	7.2 ± 1.3	6.0 ± 1.9
> 17.1	0 (0)	0 (0)	0 (0)	1 (1.0)	2 (1.9)	0 (0)	0 (0)	0 (0)
Hemoglobin, g/L	121.3 ± 10.2	120.8 ± 9.1	115.0 ± 10.0	109.8 ± 11.0	120.9 ± 9.4	124.2 ± 7.8	128.3 ± 6.4	128.6 ± 6.8
< 110	11 (10.6)	11 (14.5)	39 (40.6)	53 (51.0)	13 (12.5)	5 (4.8)	0 (0)	0 (0)
100-109	6 (5.8)	10 (13.2)	31 (32.3)	32 (30.8)	12 (11.5)	4 (3.8)	0 (0)	0 (0)
80-99	5 (4.8)	1 (1.3)	8 (8.3)	21 (20.2)	1 (1.0)	1 (1.0)	0 (0)	0 (0)
Platelets, × 10^9/L	227.4 ± 49.3	224.0 ± 51.4	223.9 ± 44.4	217.6 ± 45.6	228.9 ± 42.5	227.8 ± 45.5	231.0 ± 42.7	226.6 ± 45.5
< 100	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Creatinine, μmol/L	50.6 ± 9.5	49.2 ± 6.9	48.5 ± 6.4	43.8 ± 8.7	51.2 ± 7.3	50.8 ± 8.2	51.4 ± 6.1	50.3 ± 7.4
> 115	0/100 (0)	0/75 (0)	0 (0)	0/102 (0)	0 (0)	0/103 (0)	0 (0)	0 (0)
β2-microglobulin, mg/L	1.6 ± 0.5	1.8 ± 0.5	1.8 ± 0.4	1.7 ± 0.5	1.7 ± 0.4	1.6 ± 0.5	1.9 ± 0.4	1.9 ± 0.5
> 3	1/102 (1.0)	0/75 (0)	0 (0)	0/102 (0)	0/103 (0)	1/103 (1.0)	0 (0)	0 (0)
eGFR, ml/min/1.73 m^2	120.4 ± 9.3	123.0 ± 8.7	127.4 ± 8.2	131.8 ± 8.7	119.4 ± 8.9	120.3 ± 9.2	120.7 ± 8.8	123.5 ± 6.9

< 100	0/101 (0)	0/75 (0)	0 (0)	0/100 (0)	0 (0)	0/102 (0)	0 (0)	0 (0)

Data are presented as the means ± standard deviations, n (%), or n/N (%), where N is the total number of patients with available data. †Data from 28 and 8 mothers are not presented at PM3 and PM6 mainly because their TAF-initiated time points were close to or after these two time points and were counted as TAF initiation characteristics. ‡A total of 30 and 72 mothers did not reach the time points of PPM12 and PPM18, respectively. ¶The numerator indicates the new occurrence at each time point, and the corresponding denominator is the number of mothers who were HBeAg-positive at TDF initiation. Abbreviations: ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TND, target not detected.

Supplementary Table 3 Characteristics of one fetus and two infants with significant abnormalities in the TAF group

	Fetus 1	**Infant 2**	**Infant 3**
Mothers' characteristics			
Age, years	29	30	36
Primiparous	No	No	Yes
Treatment naïve	Yes	Yes	Yes
HBeAg status	Negative	Positive	Positive
TAF initiation weeks	12	8	26
HBV DNA, IU/ml	17200000	98600000	61700000
ALT, U/L	207	280	110
Gestational age, weeks	23	40	40
HBV DNA, IU/ml	150	390	1450
ALT, U/L	11	20	80
Delivery mode	Induced abortion	Natural labor	Natural labor
Newborn conditions at birth			
TAF exposure weeks	11	32	14
Gender	-	Girl	Boy
Weight, kg	-	3.1	3.7
Height, cm	-	48	52
Head circumference, cm	-	34	35
Apgar score at 1 minute	-	10	10
Breastfeeding	-	Yes	No
Infants' abnormalities	Cleft lip and palate	Hearing impairment	Cutaneous hemangioma
Location	Lip and palate	Left ear	Left arm
First reporting time (age)	Gestational week 22	1 week	4 weeks
Diagnostic techniques	Ultrasonography	AEP, AIA, DOPAE, VI	VI (15 × 25 mm)

Cause (clue)	Pesticide exposure[†]	Secretory otitis media	Unknown
Prognosis	Induced abortion	Spontaneously resolved	Cured

[†]Mother 1 had an agricultural chemical exposure history during the first month of pregnancy. She was diagnosed with CHB with HBV DNA and ALT levels of 17200000 IU/m and 207 U/L, respectively, at 12 weeks plus 2 days of pregnancy (June 12, 2019), and she initiated TAF treatment without ultrasound examination of the fetus. Then, she revisited at 15 weeks plus 5 days of gestation without any uncomfortable complaints, and her HBV DNA and ALT levels decreased to 8550 IU/ml and 108 U/L, respectively, after only 24 days of TAF treatment (July 6, 2019). Unfortunately, she underwent the first ultrasound examination of her fetus at 22 weeks plus 3 days of gestation and fetal cleft lip and palate was observed (August 22, 2019). Finally, she decided to undergo an induced abortion operation at 23 weeks plus 4 days of gestation (August 30, 2019). Abbreviations: AEP, auditory evoked potentials; AIA, acoustic impedance audiometry; DPOAE, distortion product otoacoustic emission; New-CHB, newly diagnosed active chronic hepatitis B; TAF, tenofovir alafenamide; VI, visual inspection.

Supplementary Table 4 Characteristics and management of two mothers with virological breakthroughs

	Mother 1	**Mother 2**
Age, years	31	30
Primiparous	Yes	Yes
Treatment naïve	No	No
Previous antiviral regimen	ETV	ETV and TDF
TAF initiation time	2 weeks before pregnancy	11 weeks before pregnancy
Weeks of treatment with the former regimen	40	84
HBeAg status	Positive	Positive
HBV DNA, IU/ml	Undetectable	Undetectable
ALT, U/L	21	40
Breakthrough time	24 weeks of pregnancy	25 weeks of pregnancy
HBeAg status	Positive	Positive
HBV DNA, IU/ml	3840	120
ALT, U/L	13	148
TAF compliance	Excellent	Excellent
Monitoring method chosen by doctors	Pill counts at visit	Pill counts at visit
Monitoring method chosen by mothers	Set three alarms for each pill	Set two alarms for each pill
Management strategy	Continue TAF treatment	Add LAM
Gestational age, weeks	41.5	39
HBV DNA at delivery, IU/ml	Undetectable	Undetectable
ALT at delivery, U/L	10	122
Delivery mode	Natural labor	Natural labor
Newborn conditions at birth		

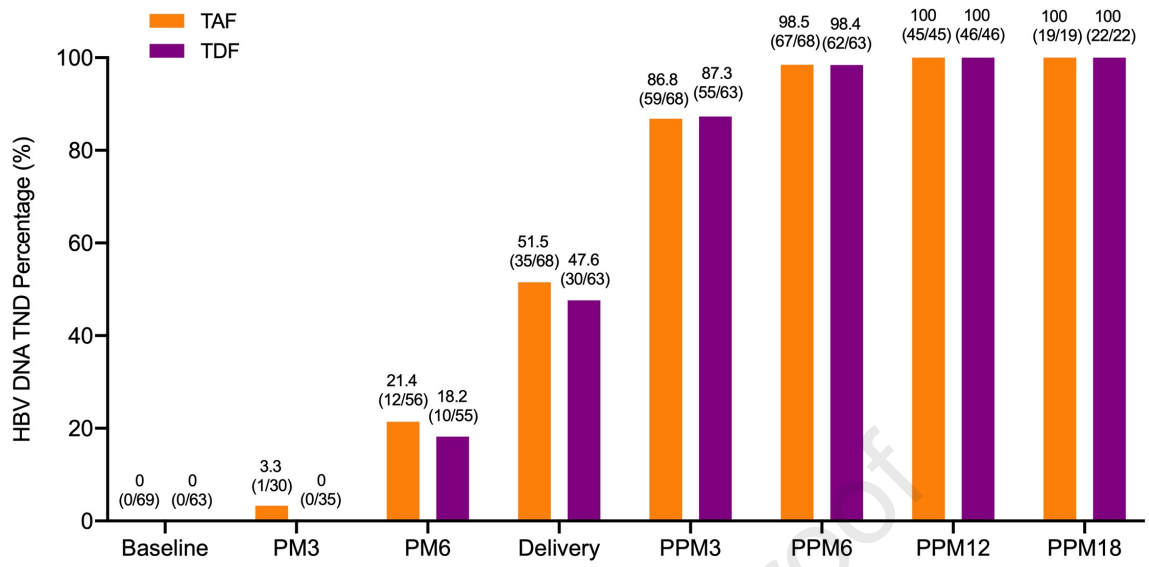
TAF exposure, weeks	41.5	39
Gender	Boy	Boy
Weight, kg	3.5	3.8
Height, cm	50	52
Head circumference, cm	35.5	35
Apgar score at 1 minute	10	10
Breastfeeding	Yes	Yes

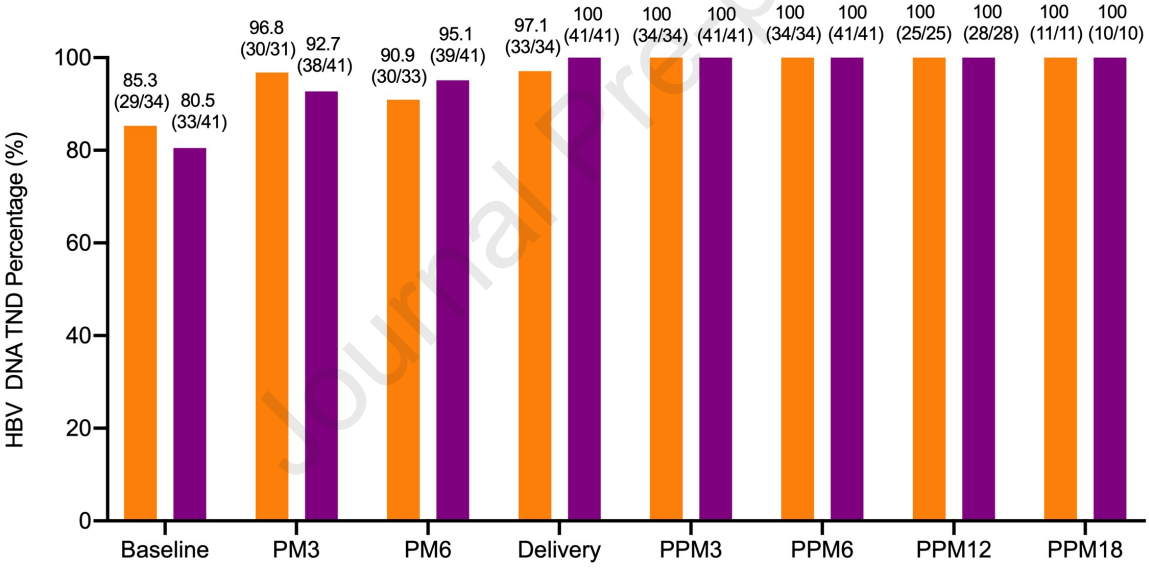
Abbreviations: ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LAM, lamivudine; TAF, tenofovir alafenamide.

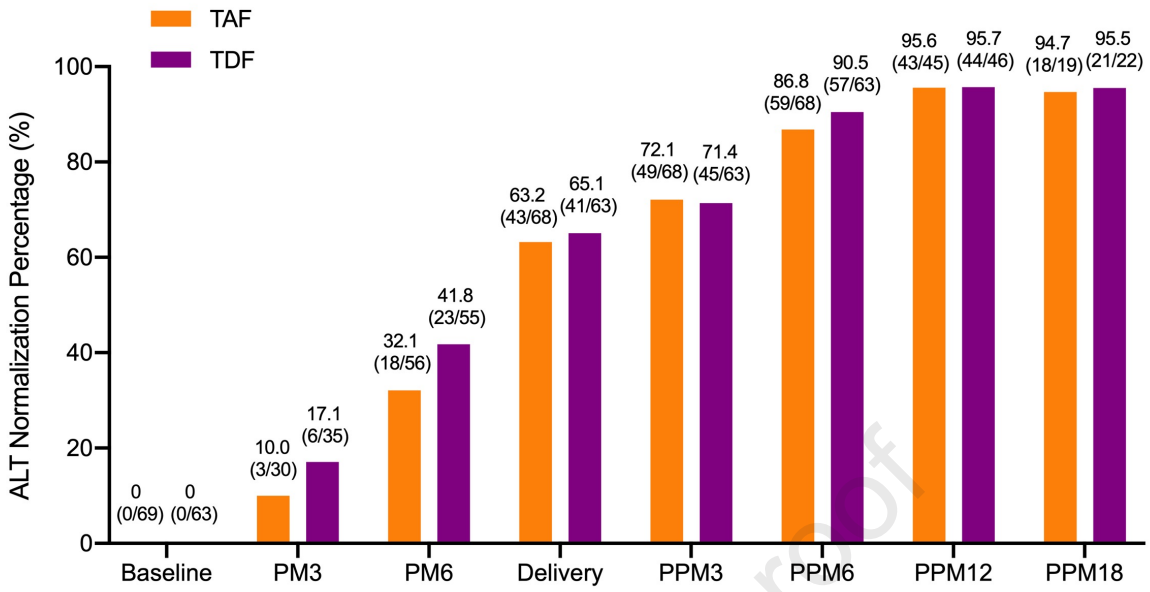
Supplementary Figure 1. The percentages of patients with undetectable HBV DNA in the treatment-naïve group (upper panel) and treatment-experienced group (switchover or continuation, lower panel).

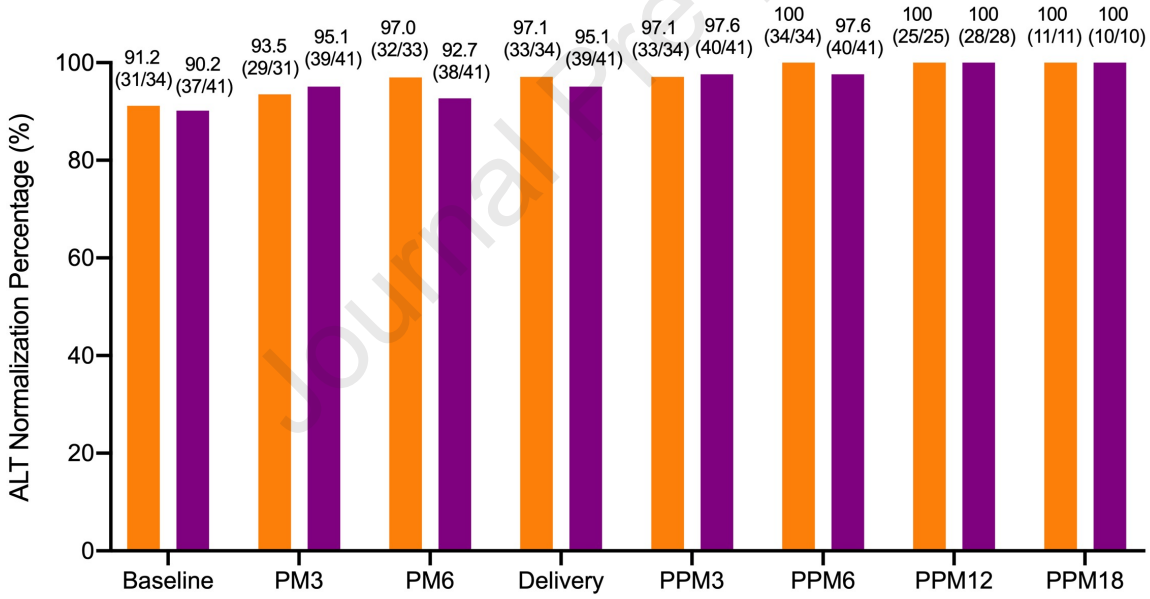
Supplementary Figure 2. The percentages of patients with ALT normalization in the treatment-naïve group (upper panel) and treatment-experienced group (switchover or continuation, lower panel).

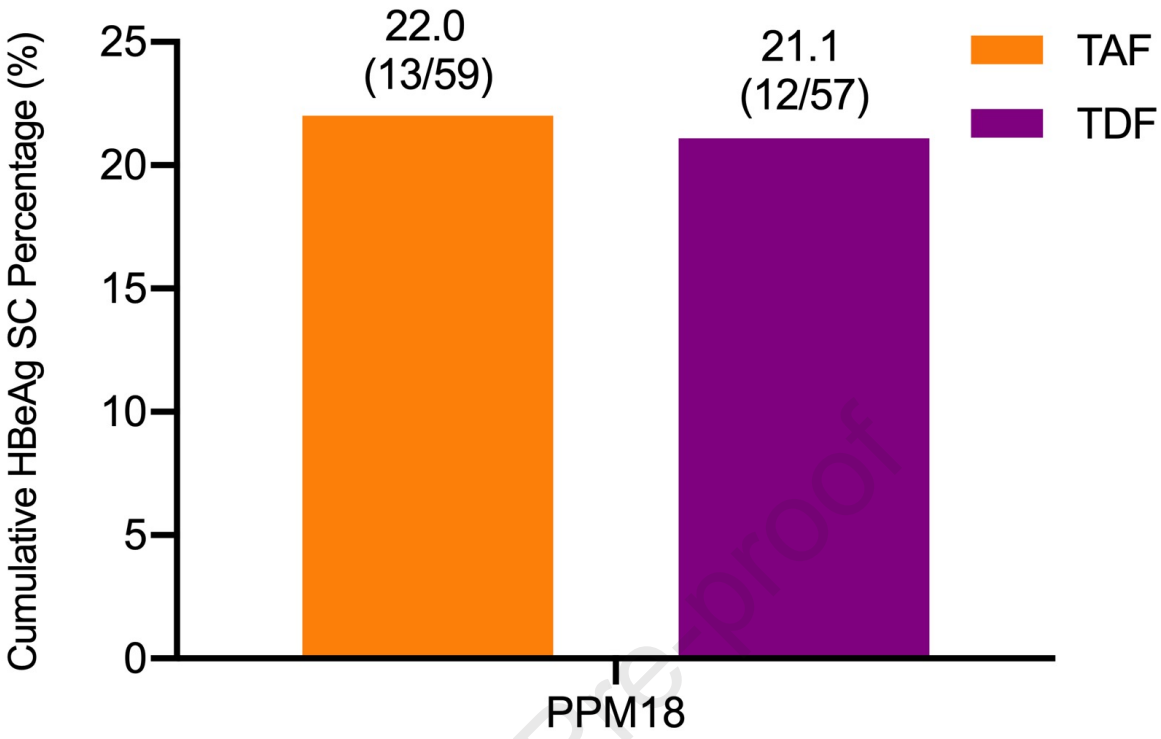
Supplementary Figure 3. The percentages of patients who achieved HBeAg seroconversion in the treatment-naïve group (upper panel) and treatment-experienced group (switchover or continuation, lower panel).

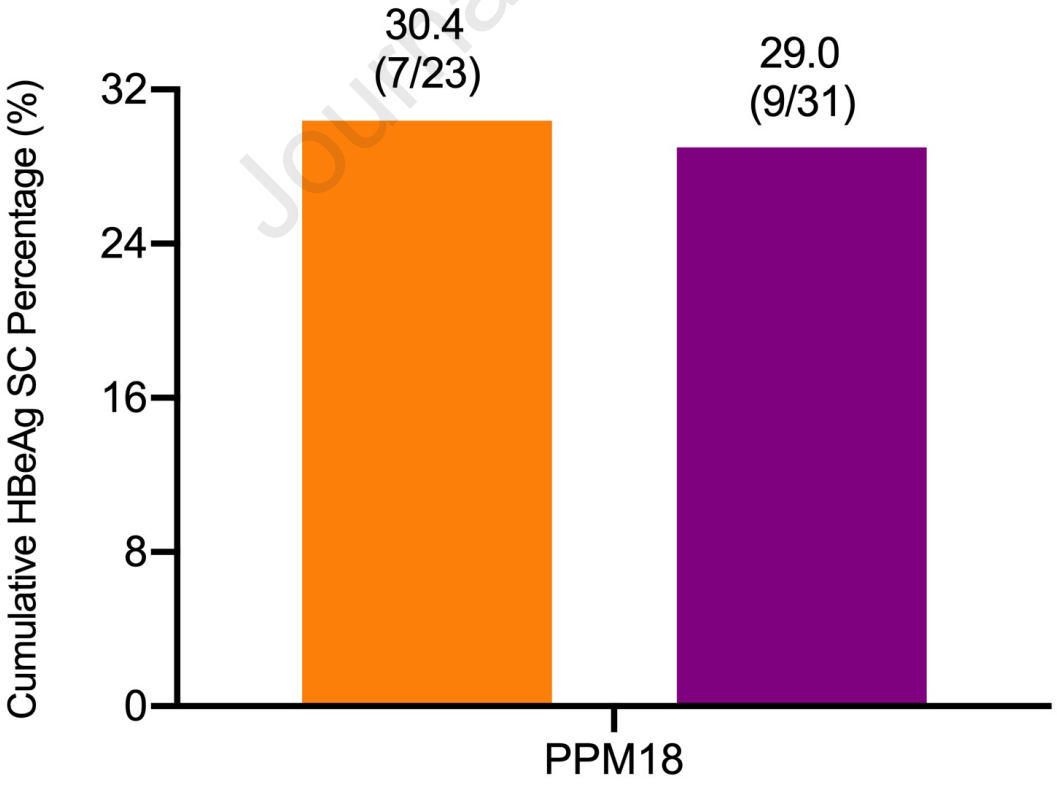












What You Need to Know

Background

Recent studies have documented the favorable safety and effectiveness profiles of short-term (mean 11-13 weeks) tenofovir alafenamide (TAF) treatment for inactive chronic hepatitis B virus (HBV)-infected pregnant women with high viral loads. No published studies have evaluated the safety and effectiveness of long-term TAF administration for pregnant women with active chronic hepatitis B (CHB).

Findings

A mean of two years of TAF treatment was safe for pregnant women with active CHB and their infants, and the infants' physical development was normal up to 18 months of age. Approximately 70% of infants received breast milk, no infants were positive for hepatitis B surface antigen at 7 months of age, and the virological responses of pregnant women were generally favorable.

Implications for patient care

This study supports the use of TAF as an alternative option to treat pregnant women with active CHB and to prevent perinatal transmission of HBV.