Tenofovir Alafenamide to Prevent Perinatal Hepatitis B Transmission: A Multicenter, Prospective, Observational Study

Qing-Lei Zeng,[1,a,*] Zu-Jiang Yu,[1,a,*] Fanpu Ji,[2,a] Guang-Ming Li,[3] Guo-Fan Zhang,[4] Jiang-Hai Xu,[5] Zhi-Min Chen,[6] Guang-Lin Cui,[7] Wei Li,[8] Da-Wei Zhang,[9] Juan Li,[1] Jun Lv,[1] Zhi-Qin Li,[1] Hong-Xia Liang,[1] Chang-Yu Sun,[1] Ya-Jie Pan,[1] Yan-Min Liu,[1] and Fu-Sheng Wang[9,*]

[1]*Department of Infectious Diseases and Hepatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China,* [2]*Department of Infectious Diseases, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China,* [3]*Department of Hepatology, The Sixth People's Hospital of Zhengzhou City, Zhengzhou, Henan, China,* [4]*Department of Infectious Diseases, The First Affiliated Hospital of Nanyang Medical College, Nanyang, Henan, China,* [5]*Department of Hepatology, The Fifth People's Hospital of Anyang City, Anyang, Henan, China,* [6]*Department of Obstetrics, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China,* [7]*Department of Clinical Laboratory, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China,* [8]*Department of Infectious Diseases, Henan Provincial People's Hospital, Zhengzhou, Henan, China, and* [9]*Treatment and Research Center for Infectious Diseases, The Fifth Medical Center of Chinese PLA General Hospital, National Clinical Research Center for Infectious Diseases, Beijing, China*

[a]These authors contributed equally as joint first authors.

[*]These authors contributed equally as joint senior authors.

*Correspondence: Prof. Qing-Lei Zeng, Department of Infectious Diseases and Hepatology, The First Affiliated Hospital of Zhengzhou University, No. 1, Eastern Jianshe Road, Zhengzhou 450052, Henan Province, China (zengqinglei2009@163.com);

Summary: Rare clinical data are available regarding TAF treatment during pregnancy. This multicenter, prospective, TDF-controlled, observational study demonstrated that TAF was safe for highly viremic pregnant women and their infants and reduced the mother-to-child transmission rate of HBV to 0%.

ABSTRACT

Background. Few safety and effectiveness results have been published regarding the administration of tenofovir alafenamide fumarate (TAF) during pregnancy for the prevention of mother-to-child transmission (MTCT) of hepatitis B virus (HBV).

Methods. In this multicenter prospective observational study, pregnant women with HBV DNA levels higher than 200,000 IU/ml who received TAF or tenofovir disoproxil fumarate (TDF) from gestational weeks 24-35 to delivery were 1:1 enrolled and followed until postpartum month 6. Infants received immunoprophylaxis. The primary endpoint was the safety of mothers and infants. The secondary endpoint was the hepatitis B surface antigen (HBsAg)-positive rate at 7 months for infants.

Results. In total, 116 and 116 mothers were enrolled, and 117 and 116 infants were born, in the TAF and TDF groups, respectively. TAF was well tolerated during a mean treatment duration of 11.0 weeks. The most common maternal adverse event was nausea (19.0%). One (0.9%), 3 (2.6%), and 9 (7.8%) mothers had abnormal alanine aminotransferase levels at delivery and at postpartum months 3 and 6, respectively. The TDF group had safety profiles that were comparable to those of the TAF group. No infants had birth defects in either group. The infants' physical and neurological development at birth and at 7 months in the TAF group were comparable with those in the TDF group. The HBsAg positive rate was 0% at 7 months in all 233 infants.

Conclusion. Antiviral prophylaxis with TAF was determined to be generally safe for both mothers and infants and reduced the MTCT rate to 0%.

Keywords: Effectiveness; Hepatitis B Virus; Immunoprophylaxis; Mother-to-Child Transmission; Perinatal transmission; Prevention; Safety; Tenofovir Alafenamide

Presentation at meeting.

This study was accepted as an Oral Presentation (publication number: 0160) by the 2020 AASLD Annual Meeting (Monday, November 16, 2020, 10:30 AM, Boston, USA) and has been selected for inclusion in the Best of The Liver Meeting summary slide deck in the Hepatitis B category and awarded the AASLD International Early Career Investigator Award (to Dr. Qing-Lei Zeng).

INTRODUCTION

It is estimated that more than 240 million people worldwide are chronically infected with hepatitis B virus (HBV), which is the major cause of cirrhosis and hepatocellular carcinoma [1-3]. The mother-to-child transmission (MTCT) route accounts for the majority of HBV transmission in China, and more than 90% of infants born to mothers with hepatitis B e antigen (HBeAg) develop chronic HBV infection (CHB) [3, 4]. Immunoprophylaxis with hepatitis B immunoglobin (HBIG) and HBV vaccine reduces the rate of MTCT from 90% to 10-20% [5-7]. Previous studies indicated that the addition of antiviral agents, such as lamivudine, telbivudine, or tenofovir disoproxil fumarate (TDF), in highly viremic mothers during the second or third trimester of pregnancy further decreased the rate of MTCT to 0-5% [5-8].

Tenofovir alafenamide (TAF) is a nucleotide analog that was first approved for antiretroviral treatment of human immunodeficiency virus (HIV) in March 2016 [9]. Currently, TAF is recommended as one of the first-line oral antiviral agents in the latest HBV guidelines [10-12]. However, to date, insufficient data concerning safety and effectiveness are available on the use of TAF during pregnancy [11]. In China, TAF was licensed for the treatment of CHB in December 2018; the drug label indicates, “TAF can be used during pregnancy if necessary”, but it discourages breastfeeding when taking TAF. In real-world clinical practice, an increasing number of highly viremic pregnant Chinese women take TAF as antiviral prophylaxis for the prevention of MTCT of HBV. In this report, we describe the safety and effectiveness of TAF to prevent MTCT of HBV in a real-world setting.

METHODS

Study Design and Participants

This multicenter prospective observational study was conducted in four public referral hospitals in Henan Province, China. All mothers who were evaluated and initiated antiviral treatment from January 1 to July 31, 2019 were enrolled, and they and their infants were followed up until postpartum month 6 and 7, respectively. The final follow-up date was July 31, 2020. The inclusion and exclusion criteria, grouping strategy, and clinical procedures are presented in the Supplementary Materials.

Safety Assessment

The primary endpoint was the safety of prophylactic therapy assessed for mothers and infants. Maternal safety assessment mainly included perinatal adverse events and complications and alanine aminotransferase (ALT) flare and creatinine elevations at delivery and at postpartum months 3 and 6. The ALT flare was defined as a level greater than 5 or 10 times the upper limit of normal (ULN) [7].

Infant safety profiles mainly included structural defects at birth, Apgar scores at 1 minute, abnormal conditions from birth to month 7, and anthropometric indexes at birth and month 7. The infants' growth parameters of the TAF group were compared with those of the TDF group, the China national standards, and World Health Organization (WHO) standards at birth and at 7 months [13].

Effectiveness Evaluation

The secondary endpoints concerning effectiveness were the rates of maternal HBV DNA < 200,000 IU/ml, HBeAg and hepatitis B surface antigen (HBsAg) clearances at delivery, and the HBsAg positive rate for infants at 7 months. The positive rate and levels of anti-HBsAg antibody (anti-HBs) and the positive rate of anti-hepatitis B core antigen (anti-HBc) for infants at 7 months were evaluated.

Sample Size Estimation, Statistical Analysis, and Ethics Evaluation

These sections are included in the Supplementary Materials.

RESULTS

Participants

A total of 1066 chronic HBV-infected pregnant women were assessed for eligibility from January 1 to July 31, 2019 (Fig. 1), and 232 mothers were eventually enrolled 1:1 for treatment with TAF or TDF. Among the 116 TAF-treated mothers with a mean age of 29.6 (± 4.5) years, 107 (92.2%) were HBeAg positive, and 9 (7.8%) were negative (Table 1). Mothers initiated TAF therapy at a mean gestational age of 28.2 (± 2.1) weeks; notably, 6 (5.2%) of them started between 33 and 35 gestational weeks. The TDF group had characteristics comparable to those of the TAF group at the timepoint of treatment initiation (Table 1). In total, 117 live newborns, including one pair of twins, were born in the TAF group, and 116 live newborns were born in the TDF group (Supplementary Table 1). Based on the mothers' personal preferences, 46 (39.3%) and 43 (37.1%) infants received breast milk in the TAF and TDF groups, respectively.

Safety of the Mothers

All 232 mothers completed the full course of TAF or TDF treatment, i.e., from baseline to delivery. In the TAF group, the mean treatment duration was 11.0 (± 2.5) weeks, and the shortest and longest treatment periods were 2 and 16 weeks, respectively; in the TDF group, the mean treatment duration was 11.1 (± 1.9) weeks, and the shortest and longest treatment periods were 5 and 16 weeks, respectively. TAF was well tolerated in the pregnant women, no mothers discontinued therapy because of adverse events (Table 2), and all discontinued therapy naturally at delivery. The most common perinatal adverse events and complications were nausea (19.0%) and premature rupture of

membranes (12.9%). None of the mothers received amniocentesis during pregnancy. The TDF group had comparable adverse events and complications with the TAF group during treatment (Table 2).

In terms of laboratory abnormalities at delivery (Table 3), 35 (30.2%) mothers had anemia in the TAF group, and 14 (12.1%) of them were diagnosed with moderate anemia, which was defined as a hemoglobin concentration ranging from 70-99 g/L [14]. One (1.1%) and 3 (2.6%) mother(s) had an ALT higher than the ULN at delivery (51 U/L) and postpartum month 3 (47, 56, 60 U/L) in the TAF group, respectively. At postpartum month 6, 9 (7.8%) mothers had an ALT level higher than the ULN, with a mean level of 72.7 (± 18.0) U/L in the TAF group, a peak level of 100 U/L, and no mothers had ALT flares (in either group). Additionally, no significant differences were observed for serum creatinine levels between the timepoints of baseline, delivery, and postpartum months 3 and 6 (all $P > 0.05$) in the TAF group. The TDF group had laboratory abnormalities comparable to those of the TAF group at delivery and at postpartum months 3 and 6 (Table 3, no significant difference was found, *P* value data are not shown).

Safety of the Infants

In terms of infant safety, the mean gestational age of the 117 infants was 39.2 (± 1.4) weeks in the TAF group, 56 (47.9%) of them were born by cesarean section, and 4 (3.4%) of them were preterm infants (Supplementary Table 1). No infant had an Apgar score of less than 8 at 1 minute of birth in the TAF group. No congenital defects or malformations were observed in the TAF group. No severe abnormal signs or symptoms were observed among infants from birth to 7 months in the TAF group (Supplementary Table 2). The TDF group had characteristics and abnormal conditions comparable to those of the TAF group (Supplementary Tables 1 and 2).

The most common abnormal condition was prolonged (neonatal) jaundice in both groups [15], which was defined as neonatal jaundice lasting more than 2 weeks in term infants and more than 3 weeks in preterm infants, and it occurred in 15 (12.8%) and 13 (11.2%) infants in the TAF and TDF groups, respectively. These 28 infants with prolonged jaundice were either spontaneously resolved or

cured by phototherapy alone before 2 months. The infants' physical and neurological development at birth and at 7 months in the TAF group were comparable to those in the TDF group or even slightly higher than the China national standards and WHO standards for children's growth (Table 4).

On-time Rate of Immunoprophylaxis

Among the 117 newborns in the TAF group, the time from birth to administration of the first doses of immunoprophylaxis was 6.6 (± 4.5) hours (Supplementary Table 1). Of the newborns, 89 (76.1%) received the first doses of HBIG and HBV vaccine within 12 hours of birth, and the remaining 28 (23.9%) received injections within 13-19 hours of birth because of the vaccination stations being closed at night (commonly from 18:00 to 08:00). For the second dose of HBV vaccine, 91 (77.8%) infants were injected at 1 month, 18 (15.4%) infants received injections 2-4 days after the one-month target because of personal reasons or that the vaccination stations were closed on weekends or holidays, and 8 (6.8%) were delayed for 2-4 weeks because of prolonged neonatal jaundice. With regard to the third dose of HBV vaccine, 101 (86.3%) infants were injected at 6 months, and 16 (13.7%) were delayed for 1-4 weeks because of personal reasons or traffic influenced by the coronavirus disease 2019 in Henan Province, China [16]. The TDF group had comparable on-time rates of immunoprophylaxis with the TAF group (Supplementary Table 1).

Effectiveness in the Mothers and Infants

The mean decreases in serum HBV DNA levels in TAF- and TDF-treated mothers were 4.3 (± 0.6) $\log_{10}$ IU/ml and 4.4 (± 0.7) $\log_{10}$ IU/ml, leading to mean viral loads of 3.5 (± 0.9) $\log_{10}$ IU/ml and 3.4 (± 1.0) $\log_{10}$ IU/ml at delivery, respectively (Table 3). Upon delivery, 100% (232/232) of mothers achieved HBV DNA levels < 200,000 IU/ml in both groups. No mother had HBeAg or HBsAg clearance at delivery or at postpartum months 3 and 6 in either group. At the 7-month visit for infants, no infant was positive for HBsAg in either group: the MTCT rate was 0%. Additionally, 115 (98.3%)

and 115 (99.1%) infants had positive anti-HBs, with mean anti-HBs levels of 444.4 (± 302.9) mIU/ml and 447.7 (± 277.8) mIU/ml, and 41 (35.0%) and 39 (33.6%) infants had positive anti-HBc at 7 months in the TAF and TDF groups, respectively.

DISCUSSION

Recently, as an updated version or successor of TDF [17], TAF has increasingly been used for CHB [18-21]. However, TAF is not currently recommended during pregnancy in patients with HIV and HBV infections because of limited pharmacokinetic and safety data [9-12]. Nevertheless, TAF is likely to become a potential first-line antiviral agent for use in pregnant women in the future [9]. In China, the drug label for TAF indicates its usage during pregnancy, which enabled this investigation in a real-world setting. This study demonstrates the safety and effectiveness of short-term TAF treatment in pregnant women who are chronic HBV carriers.

TAF can selectively concentrate in target cells and has greater affinity and distribution to hepatocytes to maximize its antiviral effectiveness, potency, and clinical safety [22]. Meanwhile, compared to TDF, TAF achieves approximately 90% lower systemic exposures of tenofovir [23], which are associated with a lower risk of decline in glomerular filtration rate, renal tubular toxicity, and decreased bone mineral density with long-term use [24, 25]. Additionally, recent studies found that children of HBV- or HIV-infected mothers who received TDF treatment during pregnancy had normal long-term growth, renal function, and bone development up to 1 to 6-7 years after delivery [26-28]. Currently, initial pregnancy data suggest that TAF-containing fixed-dose drug combinations have high efficacy and a low risk of adverse effects during pregnancy [9]. Notably, it remains unclear whether higher intracellular tenofovir diphosphate concentrations would increase the risk of

congenital anomalies and adverse pregnancy outcomes [9]; however, until now, the number of patients with TAF reported in the HIV Antiretroviral Pregnancy Registry has been insufficient to draw any reasonable conclusions on the association between TAF and any congenital anomalies [9].

Given that the safety profile of TAF is potentially more favorable than that of TDF, and our study indicates that pregnant women with chronic hepatitis B who require longer-term treatment and women of childbearing age suffer from kidney and bone diseases, TAF may be the preferred treatment over TDF.

To date, only one recent study has reported the safety and efficacy of TAF treatment for HBV-infected mothers [29]; however, that study was a retrospective study and lacked a control group, which may limit the understanding of the safety and efficacy concerns of TAF to some extent. The current TDF-controlled prospective study indicated that the safety of TAF use was favorable for both mothers and infants. The most severe maternal complication in the TAF group was threatened miscarriage, which occurred in one mother; however, she was diagnosed before taking TAF (Table 2). Other perinatal complications and adverse events presented in Table 2 also commonly occurred in the TDF group or other real-world and placebo-controlled studies using TDF [7, 8, 30, 31]. Generally, 38% of pregnant women were anemic [14]; in the current study, only 30.2% of mothers had anemia (Table 3), and these data indicate that the anemia may not have been caused by TAF therapy. For abnormal conditions in infants, prolonged jaundice was relatively common in both groups (Supplementary Table 2), which indicates that jaundice may not be associated with TAF therapy; however, the reason is unknown. Additionally, no congenital defects or malformations were observed in either group, and when compared with the TDF group and China national and WHO standards for children's growth, the infants' growth was not affected at birth or 7 months in the TAF group, as manifested by their comparable or even slightly higher levels of growth parameters.

Generally, the recommendation of antiviral prophylaxis to pregnant women with HBV DNA > 200,000 IU/ml from gestational weeks 24-32 to delivery is widely followed in actual clinical practice in China [30, 32], and this is currently the standard procedure recommended by the 2019 Chinese CHB guidelines [12]. However, in real-world settings, not all highly viremic pregnant women needing prevention have an awareness of antiviral prophylaxis during their second or third trimester of pregnancy, which may result in delayed treatment or even no treatment, and the 12 mothers who initiated treatment from 33 to 35 gestational weeks in the current study were the typical examples. For infants, the timeliness of the first doses of immunoprophylaxis is relevant [31]. However, not all infants can receive immunoprophylaxis on time, as expected. Notably, 39.3% (46) and 37.1% (43) of infants received complete or partial breastfeeding until 7 months in the TAF and TDF groups, respectively, and none of them was infected with HBV at 7 months, indicating that breastfeeding may not increase the risk of infection, although their mothers had a high rebound of viral loads at postpartum month 3 (Table 3).

The primary limitation of the current study is the potential selection bias of the mothers, and two factors may be involved. First, there is age. We only included mothers aged more than 20 years because it is illegal for a woman to be married under 20 years in China. Meanwhile, we excluded mothers aged more than 40 years because the probability of relevant maternal or postpartum complications may increase with increasing age, which may further lead to the following bias of results or conclusions in the current study. Second, there is the drug cost. No randomization for the antiviral agents and the subsequent drug cost introduced potential selection bias, which may be the major weakness of the study. During the enrollment of the current study, TDF and TAF costs were approximately 69 USD (490 RMB) and 167 USD (1,180 RMB) per bottle (30 tablets), respectively, with an expected price difference of approximately 300 USD for 3 bottles. The actual influence of 300 USD for mothers is unclear, and TAF-treated mothers may be wealthier than TDF-treated mothers. Notably, according to the discussion with the mothers and their families, almost all of them considered that the total price difference of 300 USD between TAF and TDF was negligible and that

having a healthy baby without HBV infection was most important. Therefore, the selection bias based on the drug cost may be minimal. The other limitation of this study is that the follow-up period of infants is relatively short; therefore, the eventual effects on growth and bone abnormalities might be difficult to observe, and we will continue the follow-up in the future.

In conclusion, we demonstrated that TAF was generally safe for highly viremic pregnant women during the second or third trimester of pregnancy and for their infants until 7 months; furthermore, TAF reduced the MTCT rate to 0% in combination with standard immunoprophylaxis. The current study provides justification for the administration of TAF to prevent perinatal HBV transmission. Future randomized controlled trials are needed.

Notes

Author contributions.

Qing-Lei Zeng, Zu-Jiang Yu, and Fu-Sheng Wang contributed to the conception and design of this study. All authors contributed to the data collection, analysis, interpretation, drafting and revision of this manuscript. All authors approved the final version of this manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Acknowledgments.

The authors sincerely thank the pregnant mothers and their families for their cooperation regarding the on-treatment and follow-up evaluations. The authors would like to thank Professor Yuan Shen from the Department of Statistics, Xi'an Jiaotong University Health Science Center, and Professor Kai-Juan Wang from the Department of Epidemiology and Biostatistics, School of Public Health, Zhengzhou University, for their valuable help regarding the estimation of the sample size in the current study.

Financial support.

This study was supported by National Natural Science Foundation of China (Nos. 81970517 and 81902470), Zhongyuan (Henan Province) Thousand Outstanding Talents Plan (No. ZYQR201912179), National S & T Major Project for Infectious Diseases (No. 2017ZX10302201-004-007), and Key Scientific Research Project of Henan Higher Education Institutions of China (Nos. 20B320028 and 14B320022). The funders had no role in the design and conduct of the study,

collection, management, analysis, interpretation of the data, preparation, review, approval of the manuscript, or the decision to submit the manuscript for publication.

Conflict of interest statement.

The authors declare that they do not have anything to disclose regarding funding or conflicts of interest with respect to this manuscript. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic Hepatitis B Infection: A Review. JAMA **2018**;319:1802-13.
2. Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol **2020**;5:167-228.
3. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. Hepatology **2014**;60:2099-108.
4. Jing W, Liu J, Liu M. Eliminating mother-to-child transmission of HBV: progress and challenges in China. Front Med **2020**;14:21-9.
5. Greenup AJ, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. J Hepatol **2014**;61:502-7.
6. Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology **2015**;62:375-86.
7. Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med **2016**;374:2324-34.
8. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. Hepatology **2014**;60:468-76.
9. Eke AC, Brooks KM, Gebreyohannes RD, Sheffield JS, Dooley KE, Mirochnick M. Tenofovir alafenamide use in pregnant and lactating women living with HIV. Expert Opin Drug Metab Toxicol **2020**;16:333-42.
10. Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol **2017**;67:370-98.
11. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology **2018**;67:1560-99.
12. Chinese Society of Infectious Diseases CMA, Chinese Society of Hepatology CMA. The guidelines of prevention and treatment for chronic hepatitis B (2019 version). Zhonghua Gan Zang Bing Za Zhi (Chinese Journal of Hepatology) **2019**;27:938-61.
13. Capital Institute of Pediatrics. 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 (Chinese Journal of Pediatrics) **2018**;56:192-9.

14. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet **2016**;387:907-16.
15. McKiernan P. Neonatal jaundice. Clin Res Hepatol Gastroenterol **2012**;36:253-6.
16. Zeng QL, Li GM, Ji F, Ma SH, Zhang GF, Xu JH, et al. Clinical course and treatment efficacy of COVID-19 near Hubei Province, China: A multicentre, retrospective study. Transbound Emerg Dis **2020**;published online June 12.
17. De Clercq E. Tenofovir alafenamide (TAF) as the successor of tenofovir disoproxil fumarate (TDF). Biochem Pharmacol **2016**;119:1-7.
18. Buti M, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, 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.
19. Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, 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**;1:185-95.
20. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol **2018**;68:672-81.
21. Lampertico P, Buti M, Fung S, Ahn SH, Chuang WL, Tak WY, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol **2020**;5:441-53.
22. Ruane PJ, DeJesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. J Acquir Immune Defic Syndr **2013**;63:449-55.
23. Ray AS, Fordyce MW, Hitchcock MJ. Tenofovir alafenamide: A novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. Antiviral Res **2016**;125:63-70.
24. Podany AT, Bares SH, Havens J, Dyavar SR, O'Neill J, Lee S, et al. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. AIDS **2018**;32:761-5.
25. Baxi SM, Scherzer R, Greenblatt RM, Minkoff H, Sharma A, Cohen M, et al. Higher tenofovir exposure is associated with longitudinal declines in kidney function in women living with HIV. AIDS **2016**;30:609-18.
26. Kapito-Tembo AP, Bauleni A, Wesevich A, Ongubo D, Hosseinipour MC, Dube Q, et al. Growth and neurodevelopment outcomes in HIV, tenofovir and efavirenz exposed breastfed infants in PMTCT Option B+ program in Malawi. J Acquir Immune Defic Syndr **2020**;published online Oct

5.
27. Wen WH, Chen HL, Shih TT, Wu JF, Ni YH, Lee CN, et al. Long-term growth and bone development in children of HBV-infected mothers with and without fetal exposure to tenofovir disoproxil fumarate. J Hepatol **2020**;72:1082-7.
28. Salvadori N, Fan B, Teeyasoontranon W, Ngo-Giang-Huong N, Phanomcheong S, Luvira A, et al. Maternal and Infant Bone Mineral Density 1 Year After Delivery in a Randomized, Controlled Trial of Maternal Tenofovir Disoproxil Fumarate to Prevent Mother-to-child Transmission of Hepatitis B Virus. Clin Infect Dis **2019**;69:144-6.
29. Ding Y, Cao L, Zhu L, Huang Y, Lin C, Wang Y, 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**;52:1377-86.
30. Wang M, Bian Q, Zhu Y, Pang Q, Chang L, Li R, et al. Real-world study of tenofovir disoproxil fumarate to prevent hepatitis B transmission in mothers with high viral load. Aliment Pharmacol Ther **2019**;49:211-7.
31. Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al. Tenofovir versus Placebo to Prevent Perinatal Transmission of Hepatitis B. N Engl J Med **2018**;378:911-23.
32. Zeng QL, Xu GH, Wang B, Li ZQ, Yu ZJ. Prophylactic antiviral therapy for the prevention of mother-to-child transmission of hepatitis B virus can be stopped at delivery. J Viral Hepat **2018**;25:612-3.
33. World Health Organization. Anthro for personal computers, version 3.2.2, 2011: Software for assessing growth and development of the world's children. Geneva: World Health Organization, 2010 (http://www.who.int/childgrowth/software/en/).

Figure 1. Enrollment of participants.

HBV, hepatitis B virus; MTCT, mother-to-child transmission; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 1. Characteristics of the mothers at treatment initiation

Characteristics	TAF group (n = 116)	TDF group (n = 116)	*P* value
Age, years	29.6 ± 4.5	29.3 ± 4.2	0.647
Gestational age, weeks	28.2 ± 2.1	28.2 ± 1.8	0.695
24-27	31 (26.7)	31 (26.7)	-
28-32	79 (68.1)	79 (68.1)	-
33-35	6 (5.2)	6 (5.2)	-
Primipara	86 (74.1)	83 (71.6)	0.658
Hemoglobin, g/L	119.8 ± 10.6	119.1 ± 10.0	0.586
< 110	17 (14.7)	19 (16.4)	0.717
100-109	11 (9.5)	13 (11.2)	0.666
90-99	6 (5.2)	6 (5.2)	-
Platelets, $\times 10^9$/L	230.5 ± 43.8	224.8 ± 48.9	0.186
< 100	0 (0)	0 (0)	-
Alanine aminotransferase, U/L	17.4 ± 7.8	17.2 ± 6.8	0.671
> 40	0 (0)	0 (0)	-
Total bilirubin, μmol/L	8.0 ± 3.4	7.8 ± 3.0	0.648
> 17.1	0 (0)	0 (0)	-
Creatinine, μmol/L[†]	45.7 ± 9.6	46.7 ± 10.1	0.450
> 115	0/102 (0)	0/105 (0)	-
Hepatitis B e antigen status			
Positive	107 (92.2)	107 (92.2)	-
Negative	9 (7.8)	9 (7.8)	-
HBV DNA, $\log_{10}$ IU/ml	7.8 ± 0.7	7.8 ± 0.7	0.703
< 2×10^5 IU/ml	0 (0)	0 (0)	-
2×10^5 - 1×10^6 IU/ml	7 (6.0)	8 (6.9)	0.789
1×10^6 - 1×10^7 IU/ml	8 (6.9)	9 (7.8)	0.801
1×10^7 - 1×10^8 IU/ml	53 (45.7)	49 (42.2)	0.597
1×10^8 - 1×10^9 IU/ml	48 (41.4)	50 (43.1)	0.790

Data are presented as the mean ± standard deviation, n (%), or n/N (%), where N is the total number of cases with available data. [†]A total of 102 and 105 mothers with available data in the tenofovir alafenamide and tenofovir disoproxil fumarate groups, respectively. The upper limits of the normal ranges for alanine aminotransferase, total bilirubin, and creatinine were 40 U/L, 17.1 μmol/L, and 115 μmol/L, respectively, and the lower limits of the normal ranges for hemoglobin and platelets were 110 g/L and 100 × 10^9/L, respectively. HBV, hepatitis B virus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 2. **Adverse events and complications of the mothers during treatment**

Parameters	**TAF group (n = 116)**	**TDF group (n = 116)**	***P* value**
Maternal adverse events			
Nausea	22 (19.0)	24 (20.7)	0.742
Anorexia	18 (15.5)	17 (14.7)	0.854
Fatigue	14 (12.1)	14 (12.1)	-
Vomiting	8 (6.9)	7 (6.0)	0.789
Headache	6 (5.2)	5 (4.3)	0.757
Dizziness	4 (3.4)	5 (4.3)	1.000
Insomnia	2 (1.7)	2 (1.7)	-
Maternal complications			
Premature rupture of membranes	15 (12.9)	14 (12.1)	0.843
Preterm labor	4 (3.4)[†]	4 (3.4)	-
Gestational hypertension	2 (1.7)	1 (0.9)	1.000
Gestational diabetes mellitus	1 (0.9)	2 (1.7)	1.000
Threatened abortion	1 (0.9)[†]	0 (0)	1.000
Postpartum hemorrhage	0 (0)	0 (0)	-

Data are presented as n (%). [†]One mother was diagnosed with threatened miscarriage at gestational week 24, was treated at gestational week 28 (HBV DNA 30,600,000 IU/ml) and prematurely delivered at gestational week 30 (HBV DNA 90,900 IU/ml) by means of cesarean section. TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 3. Maternal laboratory parameters at delivery, postpartum month (PPM) 3, and 6

Parameters	TAF group (n = 116)			TDF group (n = 116)		
	Delivery	PPM 3[†]	PPM 6	Delivery	PPM 3[†]	PPM 6
Hemoglobin, g/L	114.6 ± 11.0	118.6 ± 8.0	123.4 ± 7.8	116.1 ± 11.0	119.6 ± 8.2	124.0 ± 6.8
< 110	35 (30.2)	14 (12.1)	5 (4.3)	34 (29.3)	12 (10.3)	4 (3.4)
100-109	21 (18.1)	12 (10.3)	4 (3.4)	21 (18.1)	10 (8.6)	3 (2.6)
80-99	14 (12.1)	2 (1.7)	1 (0.9)	13 (11.2)	2 (1.7)	1 (0.9)
Platelets, $\times 10^9$/L	225.0 ± 43.9	233.6 ± 36.0	231.9 ± 37.8	229.5 ± 43.0	228.8 ± 39.1	233.5 ± 38.1
< 100	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ALT, U/L	17.0 ± 7.1	16.8 ± 8.5	21.0 ± 16.9	17.3 ± 7.6	17.0 ± 9.6	22.3 ± 24.5
> 40	1 (0.9)	3 (2.6)	9 (7.8)	1 (0.9)	4 (3.4)	10 (8.6)
TBIL, μmol/L	8.0 ± 3.2	6.3 ± 2.1	9.0 ± 4.3	7.7 ± 2.8	6.3 ± 2.2	9.3 ± 3.1
> 17.1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)
Creatinine, μmol/L[‡]	43.8 ± 9.5	46.0 ± 9.4	43.7 ± 10.0	44.7 ± 9.8	46.3 ± 10.0	45.1 ± 11.1
> 115	0/114 (0)	0/115 (0)	0/113 (0)	0 (0)	0/115 (0)	0/114 (0)
HBeAg status						
Positive	107 (92.2)	107 (92.2)	107 (92.2)	107 (92.2)	107 (92.2)	107 (92.2)
Negative	9 (7.8)	9 (7.8)	9 (7.8)	9 (7.8)	9 (7.8)	9 (7.8)
HBV DNA, $\log_{10}$ IU/ml	3.5 ± 0.9	7.7 ± 1.0	7.8 ± 0.8	3.4 ± 1.0	7.7 ± 0.9	7.8 ± 0.8
< 2×10^5 IU/ml	116 (100)	4 (3.4)	0 (0)	116 (100)	3 (2.6)	1 (0.9)
2×10^5 - 1×10^6 IU/ml	0 (0)	7 (6.0)	7 (6.0)	0 (0)	6 (5.2)	5 (4.3)
1×10^6 - 1×10^7 IU/ml	0 (0)	10 (8.6)	7 (6.0)	0 (0)	11 (9.5)	8 (6.9)
1×10^7 - 1×10^8	0 (0)	47 (40.5)	51 (44.0)	0 (0)	46 (39.6)	49 (42.2)

IU/ml						
1×10^8 - 1×10^9 IU/ml	0 (0)	48 (41.4)	51 (44.0)	0 (0)	50 (43.1)	53 (45.7)

Data are presented as the mean ± standard deviation, n (%), or n/N (%), where N is the total number of cases with available data. †Postpartum months 2, 3, and 4 were generally regarded as the timepoint of postpartum month 3 in consideration of 5 (4.3%), 93 (80.2%), and 18 (15.5%) TAF-treated mothers as well as 4 (3.4%), 96 (82.8%), and 16 (13.8%) TDF-treated mothers who had available data at postpartum months 2, 3, and 4, respectively, and those mothers were tested ahead of schedule or with delay because of the vacations of Chinese New Year and influence of the coronavirus disease 2019 (COVID-19) pandemic at the beginning of 2020 in Henan Province, China [16]. ‡A total of 114, 115, and 113 TAF-treated mothers as well as 116, 115, and 114 TDF-treated mothers had available data on serum creatinine at delivery and at postpartum months 3 and 6, respectively. The upper limits of the normal ranges for alanine aminotransferase, total bilirubin, and creatinine were 40 U/L, 17.1 μmol/L, and 115 μmol/L, respectively, and the lower limits of the normal ranges for hemoglobin and platelets were 110 g/L and 100×10^9/L, respectively. Pregnant women with hemoglobin concentrations of 100-109 g/L and 70-99 g/L were diagnosed with mild and moderate anemia, respectively [14]. Serum HBV DNA (lower limit of quantification was 15 or 25 IU/ml, depending on the institute's settings) was measured using COBAS® AmpliPrep/COBAS® TaqMan® tests (Roche Molecular Systems, Inc., NJ, USA).

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; TAF, tenofovir alafenamide; TBIL, total bilirubin; TDF, tenofovir disoproxil fumarate.

Table 4. Anthropometric indexes of infants at birth and 7 months

Parameters	TAF group (n = 117)	WHO z scores†	TDF group (n = 116)	WHO z scores†	National standards‡	*P* value§	*P* value¶
At birth							
Boys' weight, kg	3.47 ± 0.46	0.27 ± 0.98	3.50 ± 0.30	0.39 ± 0.61	3.38 ± 0.40	0.912	0.040
Boys' height, cm	50.59 ± 1.86	0.63 ± 1.09	50.86 ± 1.24	0.84 ± 0.61	50.40 ± 1.60	0.372	0.280
Boys' head circumference, cm	34.72 ± 0.92	0.13 ± 0.73	34.79 ± 0.82	0.23 ± 0.62	34.0 ± 1.40	0.699	< 0.001
Girls' weight, kg	3.36 ± 0.36	0.31 ± 0.77	3.43 ± 0.37	0.45 ± 0.77	3.26 ± 0.40	0.226	0.008
Girls' height, cm	49.57 ± 1.32	0.51 ± 0.71	49.92 ± 1.38	0.69 ± 0.73	49.80 ± 1.60	0.217	0.072
Girls' head circumference, cm	34.06 ± 0.84	0.07 ± 0.71	34.20 ± 0.63	0.17 ± 0.53	33.70 ± 1.30	0.334	< 0.001
At 7 months							
Boys' weight, kg	8.68 ± 0.38	0.41 ± 0.40	8.56 ± 0.35	0.37 ± 0.28	8.68 ± 0.94	0.167	1.000
Boys' height, cm	70.0 ± 1.79	0.70 ± 0.82	69.71 ± 1.97	0.66 ± 0.87	69.50 ± 2.30	0.751	0.005
Boys' head circumference, cm	44.56 ± 0.95	0.47 ± 0.77	44.68 ± 1.09	0.68 ± 0.74	43.80 ± 1.30	0.397	< 0.001
Girls' weight, kg	8.05 ± 0.32	0.42 ± 0.32	8.04 ± 0.24	0.39 ± 0.20	8.03 ± 0.90	0.839	0.580
Girls' height, cm	67.98 ±	0.60 ±	68.18 ±	0.66	67.90 ±	0.456	0.573

	1.42	0.61	1.32	±0.55	2.30		
Girls' head circumference, cm	43.04 ± 0.99	0.16 ± 0.75	43.06 ± 0.86	0.15 ± 0.60	42.60 ± 1.20	0.953	< 0.001

Data are presented as the mean ± standard deviation. †Anthropometric z scores for the infants' growth of the two groups were based on WHO standards (https://www.who.int/childgrowth/standards/en/), including the weight-for-age (at birth and 7 months), head circumference-for-age (at birth and 7 months), and length/height-for-age (at birth and 7 months) z-scores in the current study and were calculated by WHO Anthro Software (version 3.2.2) [33]; it was found that the anthropometric z scores of the infants in the current study were slightly higher than WHO standards. ‡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" [13] in which a total of 2,264 boys and 2,147 girls were involved for analysis at birth, and 1,901 boys and 1,884 girls were included for analysis at 7 months. §Anthropometric indexes of the infants were compared between the TAF and TDF groups. ¶Anthropometric indexes of the infants were compared between the TAF group and the national standards of China. TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

Figure 1