

## Evaluation of the Efficacy and Safety of Tenofovir Disoproxil Fumarate in Intercepting Mother-to-Child Transmission of Hepatitis B Virus

Dongxiang Han<sup>a§</sup>, Jianxiu Du<sup>b§</sup>, Wei Wang<sup>a</sup>, and Cui Wang<sup>c\*</sup>

Departments of <sup>a</sup>Obstetrics, <sup>b</sup>Laboratory Medicine, <sup>c</sup>Functional, Shijiazhuang Maternity & Child Healthcare Hospital, Shijiazhuang 050091, China

Vertical transmission of hepatitis B virus (HBV), especially in Asia, is a key target in the global elimination of HBV. This study assessed the effects of tenofovir disoproxil fumarate (TDF) in pregnant women for mother-to-infant transmission of HBV. A total of 122 pregnant women at our hospital met the inclusion criteria for high HBV DNA viral loads. They were randomly divided into TDF-treatment (n=70) and placebo (n=52) groups. Maternal liver function and serum HBV DNA load were tested before and after treatment. Clinical and laboratory data of infants were assayed at delivery and 7-months post-partum visit and compared between the two groups. There was no difference in clinical characteristics of participants between the two groups. There were no significant differences in liver function markers, including alanine aminotransferase, total bilirubin, blood creatinine, and blood urea nitrogen levels before and after TDF treatment. The serum HBV DNA viral load of the TDF-treated group became significantly lower than those of the control group and their own pre-medication levels. Infants showed no significant difference in body growth, including weight, height, head size, and five-min Apgar score. At 7 months after birth, 94.29% of infants in the TDF group and 86.54% of control-group infants had protective HBsAb levels  $\geq 10$  mIU/ml ( $p > 0.05$ ). The HBV infection rate of infants in the TDF-treated group was lower than that in the non-treated group. In high-HBV-DNA-load pregnant women, TDF administered from 28 weeks gestational age to delivery was associated with a lower risk of mother-to-infant transmission of HBV.

**Key words:** mother-to-infant transmission, tenofovir disoproxil fumarate, hepatitis B virus

Viral hepatitis is caused by a diverse collection of hepatotropic viruses, such as hepatitis B virus (HBV) [1]. Currently, the global prevalence of viral hepatitis is about 3.9%, manifesting as about 290 million people infected [1, 2]. HBV is the most prevalent form of viral hepatitis, and HBV and hepatitis C virus are responsible for 96% of all deaths from hepatitis [3, 4]. It is reported that in 2020, the rate of newly reported chronic hepatitis B was almost 12 times higher among the Asian/Pacific Islander population than

among non-Hispanic Caucasians [5]. As the world's most populous country, China is considered a pivotal country in the global elimination of hepatitis B [6]. There are two major modes of HBV transmission, perinatal transmission (vertical transmission) and horizontal transmission [7]. If expectant mothers are positive for the HBV antigen or have very high levels of HBV DNA ( $> 200,000$  IU/ml in the blood), perinatal transmission occurs universally [8]. About two million children (less than 5 years) acquire HBV infection through vertical transmission [9], and most of these transmis-

Received March 6, 2023; accepted June 20, 2023.

\*Corresponding author. Phone and Fax: +86-0311-66063777

E-mail: wangcuicw@163.com. (C. Wang)

§These authors contributed equally to this work.

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

sions occur at or near the time of delivery. More significantly, the population who acquire chronic HBV infection by perinatal transmission is prone to severe liver diseases and a poor response to antiviral therapy [10]. All this information underlines the importance of interrupting perinatal transmission.

Strategies to prevent vertical transmission of HBV during pregnancy include maternal screening, vaccination against HBV, immunoglobulin, and antiviral treatment [11]. Maternal screening can identify the woman's hepatitis B phase and determine the possible treatment during or after pregnancy [12]. An accelerated hepatitis B vaccination schedule at 0-, 1-, and 4 months during pregnancy is safe and effective to passively transfer maternal antibodies across the placenta to newborns, especially for pregnant women who are at high risk for HBV infection [13]. Nevertheless, up to 10% of infants are born with HBV infection despite their mothers or themselves receiving hepatitis B immune globulin (HBIG) and the HBV vaccine. Furthermore, the doses and routes of hepatitis B immunoglobulins administration are quite heterogeneous. Previous research concluded the uncertainty of the benefit of hepatitis B immunoglobulins in preventing perinatal transmission as compared with no intervention [14]. This makes additional interventions reasonable to decrease the transmission rate, such as antiviral treatment during the pre-birth phase. Antiviral treatment has been recommended in pregnant women with HBV DNA levels of more than  $2 \times 10^5$  IU/mL [15]. One of the aims of maternal antiviral therapy is to reduce HBV DNA levels, thereby improving the chances of immunoprophylaxis at the time of delivery. Among these antiviral drugs, telbivudine and lamivudine have a low genetic barrier to resistance [16]. Therefore, tenofovir disoproxil fumarate (TDF) becomes a preferred choice for HBV-positive mothers due to not only its potent antiviral activity but also the high genetic barrier to resistance [17]. Of course, the efficacy and safety of TDF in HBV-positive expectant parturients need to be evaluated before recommending its use.

The present study was designed to assess the efficacy and safety of TDF therapy for pregnant women who load high HBV DNA, to prevent mother-to-infant transmission of HBV.

## Methods

**Target population.** This is a placebo-controlled and single-blind clinical trial conducted in Shijiazhuang Maternity & Child Healthcare Hospital (Fig. 1) in Hebei Province of China. Participants were recruited into this study from the files of expectant mothers at our hospital from January 2021 to June 2021 according to the following inclusion criteria: pregnant women; 20 to 35 years of age; singleton pregnancy at 20 to 28 weeks; HBsAg and HBeAg-positive, and HBV DNA  $\geq 1.0 \times 10^6$  IU/ml; an alanine amino transferase (ALT) level of  $\leq 30$  IU/L at first screening; no HIV and/or other kinds of hepatitis infection (C, D, E); no history of TDF treatment at any time; no anti-HBV treatment during the current pregnancy; no proteinuria or normoglycemic glycosuria; no evidence of a fetal anomaly incompatible with life. The gravida was excluded if she had received other nucleotide analog treatments previously, was co-infected with other kinds of hepatitis infection, or took immunosuppressive/cytotoxic/corticosteroid drugs at any time during her pregnancy.

Approval was obtained from the ethics committee of

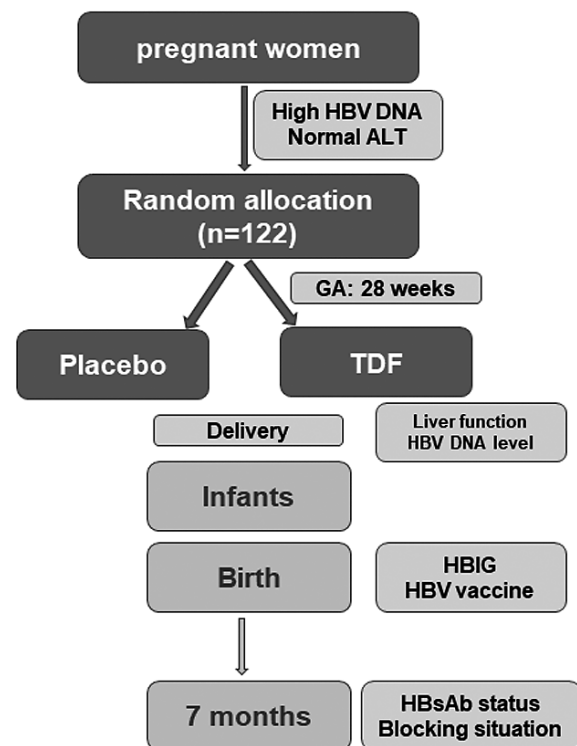


Fig. 1 Flow diagram of this study.

Shijiazhuang Maternity & Child Healthcare Hospital. The procedures used in this study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

**Study design and treatment regimens.** The enrolled pregnant women were divided into two groups based on the subjects' willingness to be treated for HBV or not and a comprehensive assessment of individual patient status by physicians. Ultimately, the control group included 52 patients and the TDF group had 70. The case numbers were different in the two groups because of grouping criteria. Participants were blind to treatment, while the physician in charge was aware of the grouping. The participants were initiated on a placebo or TDF (manufactured by GSK Plc, Tianjin, China) 300 mg once daily at 28 weeks of gestation (+/-5 days). Both groups received therapy until the day of delivery. All infants were vaccinated with 200 IU of HBIG within 6 hours after birth, and 20 mg of hepatitis B vaccine three times: within 12 h after birth, at 4 weeks, and at 24 weeks of age.

**Measures.** Data on age, body-mass index (BMI), adverse pregnancy (e.g., eclampsia, premature rupture of membranes, and premature delivery), postpartum hemorrhage, and delivery mode were collected from all participants. The maternal alanine aminotransferase (ALT), total bilirubin (TBIL), serum creatinine, and blood urea nitrogen were tested before and after treatment. At delivery, the infant's birth status, birth height/weight, 5-minute APGAR scores, birth defects, HBsAg, HBeAg, and HBV DNA were documented. Serum HBsAb status of infants at 7 months was tested. The same laboratory technician who was blinded to subject names and grouping conducted the laboratory examinations to control for potential bias.

**Statistical analysis.** Distributions of maternal

and infantile characteristics were compared using the Wilcoxon rank-sum test for continuous variables and chi-squared test for categorical or discrete variables. The maternal liver function indexes and HBV DNA viral load before and after intervention were compared using paired *t*-test. All *p*-values were two-sided, and <0.05 was significant.

## Results

**Participants' baseline characteristics.** Table 1 summarizes the disposition of the pregnant women included in the study. Fifty-two were assigned to the placebo group and 70 to the TDF group. None of the baseline characteristics were significantly different between the placebo- and TDF-treated groups, including age, BMI, adverse pregnancy, postpartum hemorrhage, delivery mode, HBsAg titer, and HBV DNA loading.

**Maternal liver function before and after treatment.** The levels of ALT, TBIL, serum creatinine, and blood urea nitrogen were obtained before and after treatment to assess maternal liver function. There were no significant differences in ALT, TBIL, serum creatinine, or blood urea nitrogen levels before medication when compared to those just prior to childbirth (the last dose) (Fig. 2). This indicates that TDF had no adverse influence on liver function during pregnancy.

**Maternal serum HBV DNA viral load before and after treatment.** Dynamic changes in maternal serum HBV DNA level are shown in Fig. 3. The maternal serum HBV DNA level declined significantly after treatment in the TDF group (*p*<0.001) and became lower than that of the placebo-treated group (*p*<0.001).

**Safety of TDF for infants.** Characteristics of the 70 infants born to the TDF-treated mothers are sum-

**Table 1** Basic information statistics of pregnant women

item	Control group (n=52)	Treatment group (n=70)	<i>P</i> -value
Age (year)	27.63 ± 3.21	26.68 ± 2.66	0.077
BMI (kg/m <sup>2</sup> )	22.91 ± 2.30	23.10 ± 2.09	0.617
Adverse pregnancy (n/%)	3/5.77	5/7.14	0.762
Postpartum hemorrhage (n/%)	6/11.54	8/11.43	0.985
Cesarean section (n/%)	12/23.08	20/28.57	0.495
HBsAg titer	3,107.0 ± 291.5	3,234.5 ± 409.3	0.058
HBV DNA (lg IU/ml)	7.96 ± 0.74	7.79 ± 0.37	0.107

All data in the table were presented as mean ± standard deviation or n/%.

marized in Table 2. Their growth measures at delivery, including weight, height, head size, and five-min Apgar score, were similar to those in infants born to women without TDF treatment. Furthermore, none of the newborns in either group had birth defects. The seropositive percentage of HBsAg and HBeAg in infants born to the TDF-treated mothers was statistically lower than that observed in infants born to the placebo-treated mothers ( $p < 0.01$ ). There was also a significantly lower HBV DNA viral load in infants born to the TDF-treated

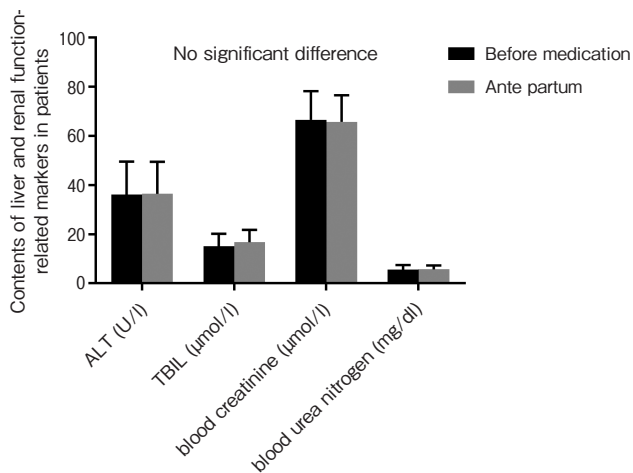
mothers compared to the infants born to placebo-treated mothers ( $p < 0.001$ ).

#### **Efficacy of TDF in mother-to-child transmission.**

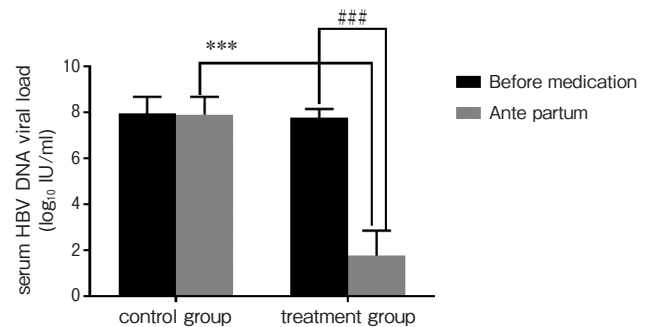
At 7 months after birth, 94.29% of infants in the TDF group had protective HBsAb levels  $\geq 10$  mIU/ml, a higher percentage than that (86.53%) in the control group ( $p = 0.042$ , Table 3). The difference in the HBV infection rate between the TDF-treated (0%) and control group (11.54%) was statistically significant ( $p = 0.04$ ).

## Discussion

Deepening understanding of the failure to prevent vertical HBV transmission has suggested that joint



**Fig. 2** Maternal alanine aminotransferase (ALT), total bilirubin (TBIL), serum creatinine, and blood urea nitrogen levels were tested before and after treatment. There were no significant differences in these levels between the control group and the TDF-treatment group at either time point.



**Fig. 3** Dynamic changes of maternal serum HBV DNA levels. The HBV DNA viral load in the TDF-treatment group was significantly lower than that in the control group or the level before medication administration. \*\*\* $P < 0.001$  vs the control group. ### $P < 0.001$  vs before medication.

**Table 2** Differences in the indicators of infants

	Control group (n=52)	Treatment group (n=70)	P-value
Weight (g)	3,346.51 $\pm$ 417.13	3,322.13 $\pm$ 396.21	0.743
Height (cm)	49.56 $\pm$ 1.56	49.67 $\pm$ 1.06	0.656
Head size (cm)	32.73 $\pm$ 1.08	33.03 $\pm$ 1.08	0.131
Five-min Apgar score	9.77 $\pm$ 0.43	9.84 $\pm$ 0.37	0.308
Birth deformity	0	0	
HBsAg			<0.001
Seropositive (n/%)	10/19.23	0/0.00	
Seronegative (n/%)	42/80.77	70/100.00	
HBeAg			0.001
Seropositive (n%)	8/15.38	0/0.00	
Seronegative (n%)	44/84.62	70/100.00	
HBV DNA (IU/ml)			<0.001
$\leq 1000$	42/80.77	70/100.00	
$> 1000$	10/19.23	0/0.00	

All data in the table were presented as mean  $\pm$  standard deviation or n/%.

**Table 3** Follow-up of two groups of infants infected with HBV

Items	Control group (n=52)	Treatment group (n=70)	P-value
HBsAb staus at 7 months (n/%)			0.042
< 10 mIU/ml	7/13.46	4/5.71	
10~100 mIU/ml	20/38.46	17/24.29	
≥100 mIU/ml	25/48.07	49/70.00	
Blocking situation at 7 months (n/%)			0.004
successful	46/88.46	70/100.00	
failure	6/11.54	0/0.00	

All data in the table were presented as mean ± standard deviation or n/%.

mother-newborn immunization may effectively control the HBV infection during and after delivery but has no blocking effect on intrauterine infection [18,19]. Previous studies have shown that the mother-to-child transmission rate of HBeAg-positive pregnant women is higher than that of HBeAg-negative pregnant women [20,21]. Positive HBeAg can be regarded as one of the important risk factors for intrauterine infection. In addition, research shows that a high viral load is another important risk factor for mother-to-child transmission of HBV [22]. Therefore, pregnant women who are positive for HBsAg and HBeAg, with a high HBV DNA viral loads, have occasion to receive treatment during pregnancy to block mother-to-child transmission [23]. The present study was a single-center, placebo-control clinical study that investigated the influence of TDF administration on pregnant women with high HBV DNA loads, as well as the outcomes in their born infants, in safely reducing HBV mother-to-child transmission. In the present study, our findings showed no vertical transmission by pregnant women receiving TDF treatment, while a vertical transmission rate of 11.54% occurred in women receiving the placebo. This finding confirmed the role of antiviral agents in the prevention of HBV vertical transmission.

A study has predicted China will achieve the HBV-elimination target by 2029, which may even be advanced to 2024 by the further addition of tenofovir administration to HBeAg-positive pregnancies [24]. In general, HBV DNA > 2,000 IU/ml, elevated ALT, and/or at least moderate histological damage are typical indications for treatment [25]. The prevention of vertical transmission in pregnant women with high viremia is an additional indication for chemotherapy. TDF is the preferred agent, not only due to its effective characteristics but also its general safety even in patients with

decompensated disease [26]. The initiation of antiviral prophylaxis with TDF has been recommended at week 24-28 of gestation in pregnant women with high HBV DNA levels or HBsAg levels [25]. Therefore, the 70 expectant mothers assigned to this study's treatment group were initiated on TDF at 28 weeks of gestation. HBV DNA levels mostly represented the natural history of chronic HBV infection. Notably, HBV DNA level serum assay is key to the treatment decision and subsequent monitoring of patients. In this study, all enrolled patients achieved virological remission defined as HBV DNA < 2,000 IU/ml. This was in line with a previous 8-year study, which showed 99% of HBeAg-negative chronic hepatitis B patients achieved virological response by treatment with TDF [27]. There is strong evidence that TDF therapy significantly improves liver function [28]. Here, we tested the patient's liver function markers and found that TDF had no adverse effect on liver function. This supports the findings of a previous study showing no evidence of liver impairment during follow-up of a TDF-treated group [29].

Reproduction studies performed in both animals and humans under TDF treatment have revealed no evidence of harm to the fetus [30]. In our trial, no significant safety concerns associated with TDF were observed in the infants. Infant growth did not differ significantly between TDF and placebo groups. This is consistent with a recent perinatal HBV study showing that TDF administration for the prevention of HBV mother-to-child transmission had no impact in infants on long-term growth [31]. Among the available agents for HBV mothers, TDF is preferred due to a better resistance profile and more extensive safety data [25]. It has been known that infants born to women with high HBV DNA levels are prone to carry disease despite HBIG and vaccine blocking measures. Utilizing TDF

can reduce maternal viremia levels and increase the effectiveness of HBIG and vaccination [32]. Our study confirmed the potential advantage of TDF in stopping HBV transmission at delivery. The rate of HBV transmission at delivery was 0% in the maternal group treated with TDF from gestational week 28, while it was 11.54% in the placebo-treated control group.

This study offers important evidence but has several limitations. First, the number of patients included in this research was small. This was partly the result of another limitation, namely that the patients were enrolled from a single hospital. Another limitation was the lack of subgrouping of delivery mode (*e.g.*, vaginal vs. elective and non-elective cesarean section). We also regret the lack of collection for invasive testing history, such as amniocentesis.

In conclusion, this trial showed that treatment of high HBV-viral-DNA-load pregnant mothers with TDF, in addition to the administration of HBIG and vaccine to infants, significantly lowered the mother-to-infant HBV transmission rate.

**Funding.** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## References

- Castaneda D, Gonzalez AJ, Alomari M, Tandon K and Zervos XB: From hepatitis A to E: A critical review of viral hepatitis. *World journal of gastroenterology* (2021) 27: 1691–1715.
- Odenwald MA and Paul S: Viral hepatitis: Past, present, and future. *World journal of gastroenterology* (2022) 28: 1405–1429.
- Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, Al-Raddadi R, Alvis-Guzman N, Amoako Y, Artaman A, Ayele TA, Barac A, Bensenor I, Berhane A, Bhutta Z, Castillo-Rivas J, Chittheer A, Choi JY, Cowie B, Dandona L, Dandona R, Dey S, Dicker D, Phuc H, Ekwueme DU, Zaki MS, Fischer F, Fürst T, Hancock J, Hay SI, Hotez P, Jee SH, Kasaeian A, Khader Y, Khang YH, Kumar A, Kutz M, Larson H, Lopez A, Lunevicius R, Malekzadeh R, McAlinden C, Meier T, Mendoza W, Mokdad A, Moradi-Lakeh M, Nagel G, Nguyen Q, Nguyen G, Ogbo F, Patton G, Pereira DM, Pourmalek F, Qorbani M, Radfar A, Roshandel G, Salomon JA, Sanabria J, Sartorius B, Satpathy M, Sawhney M, Sepanlou S, Shackelford K, Shore H, Sun J, Mengistu DT, Topór-Mądry R, Tran B, Ukwaja KN, Vlassov V, Vollset SE, Vos T, Wakayo T, Weiderpass E, Werdecker A, Yonemoto N, Younis M, Yu C, Zaidi Z, Zhu L, Murray CJL, Naghavi M and Fitzmaurice C: The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA Oncology* (2017) 3: 1683–1691.
- Brody H: Hepatitis B. *Nature* (2022) 603: S45.
- Schmit N, Nayagam S, Thursz MR and Hallett TB: The global burden of chronic hepatitis B virus infection: comparison of country-level prevalence estimates from four research groups. *International journal of epidemiology* (2021) 50: 560–569.
- Liu J, Liang W, Jing W and Liu M: Countdown to 2030: eliminating hepatitis B disease, China. *Bull World Health Organ* (2019) 97: 230–238.
- Nelson NP, Easterbrook PJ and McMahon BJ: Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease. *Clin Liver Dis* (2016) 20: 607–628.
- Veronese P, Dodi I, Esposito S and Indolfi G: Prevention of vertical transmission of hepatitis B virus infection. *World J Gastroenterol* (2021) 27: 4182–4193.
- Terrault NA, Levy MT, Cheung KW and Jourdain G: Viral hepatitis and pregnancy. *Nature reviews Gastroenterology & hepatology* (2021) 18: 117–130.
- Li J, Dong XQ, Wu Z, Ma AL, Xie SB, Zhang XQ, Zhang ZQ, Zhang DZ, Zhao WF, Zhang G, Cheng J, Xie Q, Li J, Zou ZQ, Liu YX, Wang GQ and Zhao H: Unsatisfying antiviral therapeutic effect in patients with mother-to-child transmitted chronic hepatitis B virus infection: a prospective multi-center clinical study. *Chinese medical journal* (2019) 132: 2647–2656.
- Liu JF, Chen TY and Zhao YR: Vertical transmission of hepatitis B virus: propositions and future directions. *Chinese medical journal* (2021) 134: 2825–2831.
- Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Jr., Bzowej NH and Wong JB: Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* (Baltimore, Md) (2018) 67: 1560–1599.
- Dionne-Odom J, Tita AT and Silverman NS: #38: Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission. *American journal of obstetrics and gynecology* (2016) 214: 6–14.
- Eke AC, Eleje GU, Eke UA, Xia Y and Liu J: Hepatitis B immunoglobulin during pregnancy for prevention of mother-to-child transmission of hepatitis B virus. *The Cochrane database of systematic reviews* (2017) 2: Cd008545.
- Sirilert S and Tongsong T: Hepatitis B Virus Infection in Pregnancy: An Update on Evidence-Based Management. *Obstetrical & gynecological survey* (2020) 75: 557–565.
- Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S and Atkins M: Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *Journal of viral hepatitis* (2009) 16: 94–103.
- Hyun MH, Lee YS, Kim JH, Je JH, Yoo YJ, Yeon JE and Byun KS: Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. *Alimentary pharmacology & therapeutics* (2017) 45: 1493–1505.
- Pan CQ, Duan ZP, Bhamidimarri KR, Zou HB, Liang XF, Li J and Tong MJ: An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. *Clinical gastroenterology and hepatology: Clin Gastroenterol Hepatol* (2012) 10: 452–459.
- Chen T, Wang J, Feng Y, Yan Z, Zhang T, Liu M, Bai Y, Song H, Liu H, Yang Y, Liu J, He Y, Chen Y, Zhang S, Zhuang G, Liang X, Liu Z, Xu X, Chen W, Liu Y and Zhao Y: Dynamic changes of HBV markers and HBV DNA load in infants born to HBsAg(+) mothers: can positivity of HBsAg or HBV DNA at birth be an indicator for HBV infection of infants? *BMC Infect Dis* (2013) 13: 524.

20. Ott JJ, Stevens GA and Wiersma ST: The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions. *BMC Infect Dis* (2012) 12: 131.
21. Gentile I and Borgia G: Vertical transmission of hepatitis B virus: challenges and solutions. *Int J Womens Health* (2014) 6: 605–611.
22. Liu CP, Zeng YL, Zhou M, Chen LL, Hu R, Wang L and Tang H: Factors associated with mother-to-child transmission of hepatitis B virus despite immunoprophylaxis. *Internal Medicine (Jpn Soc Internal Med)* (2015) 54: 711–716.
23. Hou J, Cui F, Ding Y, Dou X, Duan Z, Han G, Jia J, Mao Q, Li J, Li Z, Liu Z, Wei L, Xie Q, Yang X, Zhang H and Zhuang H: Management Algorithm for Interrupting Mother-to-Child Transmission of Hepatitis B Virus. *Clinical gastroenterology and hepatology: Clin Gastroenterol Hepatol* (2019) 17: 1929–1936. e1921.
24. Hui Z, Nayagam S, Chan P, Fuzhen W, Thursz M, Zundong Y, Ning M, Xiaojin S, Cui F, Guomin Z and Hallett TB: Progress towards elimination of mother-to-child transmission of hepatitis B virus infection in China: a modelling analysis. *Bull World Health Organ* (2021) 99: 10–18.
25. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* (2017) 67: 370–398.
26. Miquel M, Núñez Ó, Trapero-Marugán M, Díaz-Sánchez A, Jiménez M, Arenas J and Canós AP: Efficacy and safety of entecavir and/or tenofovir in hepatitis B compensated and decompensated cirrhotic patients in clinical practice. *Annals of hepatology* (2013) 12: 205–212.
27. Parallel 34: Hepatitis B: Outcomes of Approved Therapy. *Hepatology* (Baltimore, Md) (2014) 60: 313A–317A.
28. Jang JW, Choi JY, Kim YS, Woo HY, Choi SK, Lee CH, Kim TY, Sohn JH, Tak WY and Han KH: Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. *Hepatology* (Baltimore, MD) (2015) 61: 1809–1820.
29. Wang T, Smith DA, Campbell C, Mokaya J, Freeman O, Salih H, McNaughton AL, Cripps S, Várnai KA, Noble T, Woods K, Collier J, Jeffery K, Davies J, Barnes E and Matthews PC: Hepatitis B virus (HBV) viral load, liver and renal function in adults treated with tenofovir disoproxil fumarate (TDF) vs. untreated: a retrospective longitudinal UK cohort study. *BMC infectious diseases* (2021) 21: 610.
30. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *Journal of hepatology* (2012) 57: 167–185.
31. Liegeon G, Ngo-Giang-Huong N, Salvadori N, Bunpo P, Cressey R, Achalapong J, Kanjanavikai P, Patamasingh Na Ayudhaya O, Prommas S, Siriwachirachai T, Sabsanong P, Yves Mary J and Jourdain G: Proximal tubular dysfunction in pregnant women receiving tenofovir disoproxil fumarate to prevent mother-to-child transmission of hepatitis B virus. *The Journal of antimicrobial chemotherapy* (2022) 77: 1111–1118.
32. Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, Zhang H, Zou H, Zhu B, Zhao W and Jiang H: Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *The New England journal of medicine* (2016) 374: 2324–2334.