Tenofovir rescue therapy in pregnant females with chronic hepatitis B

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Abstract

AIM: To evaluate the safety and efficacy of tenofovir monotherapy in pregnant females resistant to lamivudine or telbivudine. The effect of tenofovir on the fetus was also assessed.

METHODS: The clinical data of 17 females were reviewed in this study. Adverse events and pregnancy outcomes from January 1, 2011 to June 30, 2013 were evaluated in the Department of Gynecology and Obstetrics of Beijing Ditan Hospital, Capital Medical University, Beijing, China. These pregnant females developed lamivudine (LAM)- or telbivudine (LdT)-resistant chronic hepatitis B and received tenofovir (TDF) therapy (300 mg/d), and its curative effect, maternal and perinatal adverse events, fetal growth and development, and neonatal prognosis were evaluated.

RESULTS: The median hepatitis B virus (HBV) DNA level in the pregnant females with LAM or LdT resistance was 5.9 (range, 4.2-7.2) log_{10} copies/mL before the initiation of TDF. Ten of these females had abnormal alanine aminotransferase (ALT) levels. The patients were treated with TDF for a median of 24 wk (range, 12-40 wk). Fourteen females (82.4%) had an HBV DNA level of < 500 copies/mL at the time of delivery. This decrease was statistically significant ($P < 0.0001$). Serum ALT levels were normalized in all subjects with an elevated serum ALT level at baseline ($P = 0.0003$). There were no significant changes in serum creatinine and phosphorus levels during TDF treatment. In addition, no adverse events related to TDF treatment were observed. Seventeen females delivered 17 live infants, and all infants had good Apgar scores. The mean birth weight was 3226.5 ± 331.7 g, and the mean length at birth was 50.4 ± 1.1 cm. The growth and development of the infants was normal at birth, and no infants had birth defects related to TDF treatment. Eleven infants completed HBV vaccination and had no evidence of vertical transmission.

CONCLUSION: The use of TDF in pregnant females with chronic HBV and LAM or LdT resistance was safe and effective.

Key words: Pregnancy; Chronic hepatitis B; Tenofovir; Safety; Birth defects

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Core tip: Tenofovir (TDF) is effective for treating chronic hepatitis B virus (HBV) patients with lamivudine (LAM) or telbivudine (LdT) resistance. It is classified as category B during pregnancy. There are very few reports regarding the safety of TDF treatment in pregnant patients with LAM or LdT resistance. The present study reports the safety of TDF monotherapy in pregnant females with chronic HBV and LAM or LdT resistance. This study provides preliminary evidence regarding the efficacy and safety of TDF during pregnancy. It also sets an example for further studies exploring the safety profiles of nucleos(t)ide analogs in pregnant females.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem. Approximately two billion people worldwide have a history of or current HBV infection, and 240 million are chronic HBV carriers. Around one million people die annually of sequelae related to HBV infection including liver failure, cirrhosis, or primary hepatocellular carcinoma.[1] The hepatitis B surface antigen (HBsAg)-positive rate among fertile females in high epidemic areas such as Africa and South Asia is 9.2%-15.5%.[2-4] Approximately 30% of HBV-infected females progress to chronic hepatitis B (CHB) and require antiviral therapy. However, some females become pregnant during nucleos(t)ide analog therapy.[5,6] Lamivudine (LAM) and telbivudine (LdT) were introduced into China in 1999 and 2007, respectively. However, some pregnant females receiving LAM or LdT[5,6] have developed drug resistance. Tenofovir (tenofovir disoproxil fumarate, TDF) is effective in the treatment of CHB patients with either LAM or LdT-resistance. It is classified as a category B drug. However, there are very few reports evaluating the safety of TDF treatment during pregnancy, particularly since the emergence of LAM or LdT resistance. We performed a retrospective study assessing the efficacy and safety of TDF rescue therapy in pregnant females with chronic CHB after developing resistance to LAM or LdT.

MATERIALS AND METHODS

Ethics

Data were collected retrospectively from pregnant females at Beijing Ditan Hospital, an affiliate of Capital Medical University, from January 2011 to June 2013. The Ditan Hospital Ethical Committee approved the study protocol (Ethics: Beijing ethics code [2013] 37), and each patient signed written informed consent before the study began.

Patient tissues

Eligibility criteria were as follows: (1) pregnant females; (2) a diagnosis of CHB was made before pregnancy and was treated using either LAM or LdT; (3) serum HBV DNA rebound during pregnancy (defined as a 10-fold increase from the treatment nadir and a serum HBV DNA > 10^5 copies/mL); and (4) the patient accepted treatment with 300 mg/d TDF. The exclusion criteria were as follows: (1) patients with human immunodeficiency virus (HIV), hepatitis C (HCV), hepatitis D virus (HDV), syphilis, toxoplasmosis, herpes virus, rubella virus, or cytomegalovirus infection; (2) duration of TDF treatment < 12 wk during pregnancy (beginning treatment after 28 wk of pregnancy); and (3) the use of other antiviral agents.

All participants were screened every 12 wk during pregnancy using biochemical testing and HBV DNA determination. Adverse events, neonatal abnormalities, and the vertical transmission of HBV were recorded. All infants received passive-active immunoprophylaxis with 200 IU hepatitis B immunoglobulin (HBIG) and three doses of 10 μg hepatitis B vaccine (at 0, 1, and 6 mo), according to the guidelines for the prevention and treatment of CHB.[7] HBV serology was measured 1 mo after completion of HBV vaccination. All infants also underwent a physical examination, hearing screening, and testing for congenital phenylketonuria and hypothyroidism at birth. Infants were also observed to identify any effects on their growth rate.

Laboratory testing

Biochemical tests and HBV serology were performed in the clinical laboratory of our hospital. HBV DNA was detected using an HBV real-time PCR amplification kit (Kehua Biological Company, Shanghai, China), which can detect as few as 500 HBV DNA copies/mL (< 2.7 log_{10} copies/mL). HBV markers were detected using enzyme-linked immunosorbent assay kits (Abbott Labs, North Chicago, IL, United States) and an ARCHITECT i2000 automatic immunoassay analyzer (Abbott), according to the manufacturer’s instructions. An HBV surface antigen level < 0.05 IU/mL, HBV e antigen levels < 1.0 signal/cutoff (S/CO), antibodies against HBV surface antigen < 10 mIU/mL, HBV e antibody level > 1 S/CO, and an HBV core antibody level > 1 S/CO were considered negative results. Blood biochemistry parameters were determined using a Hitachi 7600-020 automatic biochemical analyzer. The normal range of alanine aminotransferase (ALT) was 0-40 U/L of serum. The normal range of creatinine in females was 45-84 μmol/L. Serum inorganic phosphorus levels were determined using the molybdate direct method; the normal range was 0.81-1.45 mmol/L.
LAM: Lamivudine; ETV: Entecavir; ADV: Adefovir; LdT: Telbivudine; INF: Interferon; TDF: Tenofovir; GW: Gestational week; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; Cr: Creatinine; Pho: Serum phosphorus.

Hearing screening was performed using ECHO-SCREEN from the Madsen Company (Denmark). Heel blood was taken from the infants after 72 h of breastfeeding. A dried spot of blood on filter paper was then sent to the Beijing Neonatal Disease Screening Center to rule out congenital phenylketonuria and hypothyroidism.

Statistical analysis
Categorical variables are summarized as numbers or percentages. Continuous variables are presented as mean (± standard deviation) or median (range). HBV DNA levels were logarithmically transformed for analysis. Student’s t-tests were used to compare normally distributed continuous variables. A rank-sum test was used to compare variables without normal distribution. \( \chi^2 \) tests were used to compare the HBV DNA negative conversion rate and the recovery rate of ALT before and after treatment. Stata 10 software (Stata, Computer Resource Center, United States) was used for statistical analyses. A value of \( P < 0.05 \) was considered statistically significant.

RESULTS
Maternal characteristics
Seventeen pregnant females with LAM or LdT resistance were enrolled between January 2011 and June 2013. One hundred and twenty-eight females became pregnant during LAM treatment. Of these, 17 (13.3%) developed drug resistance during pregnancy. Eight pregnant females were switched to treatment with 300 mg/d TDF. Six of these were included in the study, and two were excluded (one because of serum HBV DNA levels < 4 \( \log_{10} \), and the other because of treatment with TDF for < 12 wk during pregnancy. One hundred and twenty-four females became pregnant during LdT treatment. Of these, 12 (9.7%) developed drug resistance during pregnancy. Eleven females were switched to treatment with 300 mg/d TDF, and all of these met the inclusion criteria. The characteristics of the patients at baseline and at delivery are shown in Table 1.

The median maternal age was 30.6 years (range, 23-45 years). All females were of Chinese ethnicity. Sixteen were primiparous, and one was multiparous. All patients had CHB. One individual had compensated cirrhosis and was started on nucleotide analog treatment before pregnancy. One female was HBeAg-negative, and 16 were HBeAg-positive. One husband was HBsAg positive, 15 were negative, and the status of one was unknown.

Five pregnant females developed resistance to LAM or LdT before pregnancy. In addition, the HBV DNA levels rebounded between the 8th and 24th gestational weeks in 12 patients. The patients were diagnosed with resistance to LAM or LdT after excluding poor compliance with treatment. TDF was started at the median gestational age (GA) of 15 wk (range, 0-28 wk). The median duration of TDF treatment before delivery was 24.4 wk (range, 12-40 wk).

Maternal outcomes
The median HBV DNA level before the initiation of TDF was 5.9 \( \log_{10} \) copies/mL (range, 4.2-7.2 \( \log_{10} \) copies/mL). Ten of the 17 females had abnormal ALT levels; of these, levels were elevated to > 5-times the upper limit of normal (ULN) in three. One of these patients...
HBV is one of the most common infectious diseases globally. Although there are some effective antiviral drugs, most patients require long-term treatment. Some females may become pregnant during treatment\(^{8-10}\). TDF is a fumaric acid salt form of the bis-isopropoxycarbonyloxyethyl ester derivative of tenofovir. TDF has been available in the United States for the treatment of HIV since 2001, and was approved for the treatment of chronic HBV in 2008\(^{11}\). Although TDF is an FDA category B drug, it was recommended by the European Association for the Study of the Liver for use during pregnancy when the benefits outweigh the risks\(^{12}\). A large number of patients have taken or are taking LAM or LdT, which are commonly associated with development of resistance\(^{13,14}\). In the current study, 13.3% of females treated with LAM and 9.7% of those treated with LdT developed resistance. Resistance is generally associated with an increase in serum HBV DNA levels. Resistance is often defined as a 10-fold increase in HBV DNA levels compared with the treatment nadir. Viral rebound often coincides with an increase in serum ALT levels. In some cases there is also a marked increase in aminotransferases and a hepatitis flare (aminotransferase > 5 times ULN) with hepatic decompensation\(^{13,14}\). The deterioration of liver function in pregnant females can affect the health of the mother and fetus\(^{15}\). In the current study, abnormal ALT levels were found in 10 (58.8%) patients, three of who had a hepatitis flare. One patient was hospitalized with an ALT level of 1701.6 U/L. The development of resistance, even in pregnant females, should be treated\(^{14,16}\). Rescue therapy after the development of LAM or LdT resistance usually consists of the addition of either adefovir (ADV) or TDF, or switching to TDF\(^{7,17-19}\). ADV is classified as a category C drug, and so is not recommended for use during pregnancy. As such, switching to TDF is the preferred option during pregnancy after the development of LAM or LdT resistance. However, there are few data available regarding the use of TDF monotherapy in this patient population.

Pharmacokinetic studies have shown that the clearance of TDF was significantly higher during pregnancy. Pregnant females had a 39% higher apparent clearance than non-pregnant females\(^{20}\). Peaks, troughs, and the area under the curve (AUC 0-24 h) of TDF were significantly lower during the third trimester compared with postpartum. The magnitude of the decrease in the AUC in pregnancy was only about 15% overall\(^{21}\). A previous study reported that the pharmacokinetic exposure to TDF during the third trimester of pregnancy was about 25% lower than postpartum, including AUCO-24 h, maximum concentration (C\(_{\text{max}}\)), and 24 h concentration (C\(_{\text{ave}}\))\(^{22}\). Although TDF exposure is lower during pregnancy, standard dosing results in sufficient exposure for most females, and a dose modification during pregnancy is not recommended. Based on these findings, Benaboud suggested that an increase in the TDF dose should be
considered for females during the second and third trimester\cite{20}. However, it was argued that the lower pharmacokinetic exposure during pregnancy was not associated with virological failure, and did not result in mother-to-child transmission\cite{21}; therefore, it was not necessary to change the dose of TDF during pregnancy\cite{21}. In the current study, TDF monotherapy using standard dosing (300 mg/d) was associated with effective treatment. Specifically, 82.4% of pregnant females achieved a complete virological response after a median of 24 wk (range, 12-40 wk) of TDF treatment. All individuals had undetectable serum HBV DNA levels and normal liver function test results. As such, these findings did not support the use of an increased dose of TDF during pregnancy.

Vertical transmission is believed to be correlated with the mother’s serum HBV DNA levels\cite{22-24}. The serum HBV DNA levels of females typically rebound with the development of LAM or LdT resistance. TDF can effectively suppress HIV replication and reduce HBV DNA to low or undetectable levels before delivery, thereby reducing the risk of intra-uterine and perinatal transmission of HBV when combined with passive and active immunization using HBIG and HBV vaccination in newborn infants\cite{26-28}. Eleven infants treated in the current study completed the entire course of HBV vaccination, and all were negative for HBV serum markers. Therefore, TDF effectively reduced the risk of vertical transmission in pregnant females with LAM or LdT resistance.

TDF is an FDA category B drug\cite{19}. Reproductive studies have been performed in rats and rabbits using doses 14-19 times higher than that used in humans, with no evidence of impaired fertility or harm to the fetus\cite{29}. There were also no effects on fertility, mating performance, or early embryonic development when TDF was administered to male rats (600 mg/kg per day; equivalent to 10 times the human dose based on body surface area) for 28 d before mating, or to female rats for 15 d before mating until day 7 of gestation. However, there was an alteration of the estrous cycle in female rats administered 600 mg/kg/day\cite{29}. TDF pharmacokinetic studies have shown that TDF has good placental transfer (about 60% of the total dose)\cite{30}. The median cord blood to maternal plasma concentration ratio is about 1, and ranges from 0.6-1.7\cite{21}. Studies assessing HIV infection in pregnant females have shown that fetal exposure to TDF is good. The exposure to TDF during pregnancy does not impair growth patterns and bone health, and does not increase the risk of premature or low birth weight infants\cite{30-32}. The current study revealed no significant changes in serum creatinine and phosphorus levels during TDF treatment. All adverse events were common complications of pregnancy, and no adverse events appeared to be related to TDF treatment. No spontaneous abortions or altered fetal growth were observed. None of the infants evaluated were born prematurely or had a low birth weight. One baby girl had a congenital dislocation of the knee, but this was thought to be unrelated to TDF treatment\cite{33}. One baby had a patent foramen ovale that closed spontaneously by six months after birth; this was not a birth defect, as defined by the Antiretroviral Pregnancy Registry Steering Committee\cite{34}. Therefore, we concluded that TDF treatment was safe for pregnant mothers and their fetuses.

The use of TDF in pregnant females with chronic HBV infection and LAM or LdT resistance was safe and effective. Nevertheless, larger studies are needed with longer follow-up to confirm these findings.

**REFERENCES**

1. World Health Organization. Hepatitis B. World Health Organization Fact Sheet 204 dex. Revised 2012-06. Available from: URL: http://www.who.int/mediacentre/factsheets/fs204/en/

2. Makuwa M, Caron M, Souquière S, Malonga-Mouelet G, Mahé A, Kazanji M. Prevalence and genetic diversity of hepatitis B and delta viruses in pregnant women in Gabon: molecular evidence that hepatitis delta virus clade 8 originates from and is endemic in central Africa. J Clin Microbiol 2008; 46: 754-756 [PMID: 18077651 DOI: 10.1128/JCM.02142-07]

3. Lin CC, Hsieh HS, Huang YJ, Huang YL, Ku MK, Hung HC. Hepatitis B virus infection among pregnant women in Taiwan: comparison between women born in Taiwan and other southeast countries. BMC Public Health 2008; 8: 49 [PMID: 18254978 DOI: 10.1186/1471-2458-8-49]
5 Yi W, Liu M, Cai HD. Safety of lamivudine treatment for chronic hepatitis B in early pregnancy. World J Gastroenterol. 2012; 18: 6645-6650 [PMID: 23252640 DOI: 10.3748/wjg.v18.i45.6645]

6 Liu M, Cai H, Yi W. Safety of telbivudine treatment for chronic hepatitis B for the entire pregnancy. J Viral Hepat 2013; 20 Suppl 1: 65-70 [PMID: 23458527 DOI: 10.1111/jhj.12066]

7 Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association. [The guideline of prevention and treatment for chronic hepatitis B (2010 version)]. Zhonghua Gan Zang Bing ZaZhi 2011; 19: 13-24 [PMID: 21272453 DOI: 10.3760/cma.j.issn.1007-3418.2011.01.007]

8 Pawl CQ, Lot EM. Antiviral therapy for chronic hepatitis B in pregnancy. Semin Liver Dis 2013; 33: 138-146 [PMID: 23749670 DOI: 10.1055/s-0033-1347518]

9 Bzowej NH. Optimal Management of the Hepatitis B Patient Who Desires Pregnancy or Is Pregnant. Curr Hepat Rep 2012; 11: 82-89 [PMID: 22707918 DOI: 10.1007/s11882-011-0130-x]

10 Pol S, Corouge M, Fontaine H. Hepatitis B virus infection and pregnancy. Clin Res Hepatol Gastroenterol 2011; 35: 618-622 [DOI: 10.1016/j.clinre.2011.03.013]

11 Reynaud L, Carleo MA, Talamo M, Borgia G. Tenofovir and its potential in the treatment of hepatitis B virus. Ther Clin Risk Manag 2009; 5: 177-185 [PMID: 19436619]

12 European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]

13 Pawlotsky JM, Dusheiko G, Hatzakis A, Lau D, Lau G, Liang TJ, Locarnini S, Martin P, Richman DD, Zoulim F. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach. Gastroenterology 2008; 134: 405-415 [PMID: 18242209 DOI: 10.1016/gastro.2007.11.036]

14 Lok AS, Zoulim F, Locarnini S, Bartholomeeusen A, Ghany MG, Pawlotsky JM, Maïc F, Mizokami N, Kuenen C. Antiviral drug-resistant HBV: stabilization of nomenclature and assays and recommendations for management. Hepatology 2007; 46: 254-265 [PMID: 17596850 DOI: 10.1002/hep.21698]

15 Galluzzo C, Liotta G, Andreotti M, Luigiana R, Jere H, Tan PK, Greco G, Mancinelli A, Capparelli E. Implications of gender and pregnancy for antiretroviral drug dosing. Curr Opin HIV AIDS 2008; 3: 277-282 [PMID: 19372979 DOI: 10.1097/COH.0b013e3282f979e]

16 Colbers AP, Hawkins DA, Ginkelmaier A, Kabeya K, Rockstroh JK, Wyen C, Weizsäcker K, Sagad JT, Ivanovic J, Giaquinto C, Taylor GP, Moltó J, Burger DM. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. AIDS 2013; 27: 739-748 [PMID: 23169329 DOI: 10.1097/QAD.0b013e32835c208b]

17 Wiseman E, Fraser MA, Holdens S, Glass A, Kidson BL, Heron LG, Maley MW, Ayres A, Locarnini SA, Levy MT. Perinatal transmission of hepatitis B virus: an Australian experience. Med J Aust 2009; 190: 489-492 [PMID: 19413519]

18 Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S, Atkin M. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomised, double-blind, placebo-controlled study. J Viral Hepat 2009; 16: 94-103 [PMID: 19175878 DOI: 10.1111/j.1365-2893.2008.01056.x]

19 Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012; 19: e18-e25 [PMID: 22393517 DOI: 10.1111/j.1365-2833.2011.01492.x]

20 Pan CQ, Mi LJ, Bunchorntavakul C, Karsdon J, Huang WM, Singhvi G, Ghany MG, Reddy KR. Tenofovir disoproxil fumarate for prevention of vertical transmission of hepatitis B virus infection by highly viremic pregnant women: a case series. Dig Dis Sci 2012; 57: 2423-2429 [PMID: 22543886 DOI: 10.1007/s10620-012-2187-3]

21 Celen MK, Mert D, Ay M, Kaya S, Yildirim N, Gulsun S, Barcin T, Ayaz C. The efficacy and safety of tenofovir disoproxil fumarate for the prevention of vertical transmission of HBV infection. 23th Asian Pacific Association for the Study of the Liver (APASL). Hepatol Int Berlin 2013; 7 Suppl 1: 216

22 Greenup AJ, TanPK, Lawlor J, Glass A, Chatterjee U, Davison S, Smith L, Ayres A, Locarnini S, Levy MT. Tenofovir use in pregnant women with chronic Hepatitis B: virological efficacy and mother and child safety. 23th Asian Pacific Association for the Study of the Liver (APASL). Hepatol Int Berlin 2013; 7 Suppl 1: S266

23 Gilead Sciences I. Product Monograph: Viread® (Tenofovir disoproxil fumarate Tablets). 2012-10-12. Available from: URL: http://www.gilead.com/23

24 Hirt D, Urien S, Ekouevi DK, Rey E, Arrévé E, Blanche S, Amann- Bosce C, Nerrinet E, Gray G, Kone M, Leang SK, McIntyre J, Dabis F, Tréluyer JM. Population pharmacokinetics of tenofovir in HIV-uninfected children born to HIV-infected mothers and their neonates (ANRS 12109). Clin Pharmacol Ther 2009; 85: 182-189 [PMID: 18987623 DOI: 10.1038/cpt.2009.201]

25 Viganò A, Mora S, Giacomet V, Stucchi S, Manfredini V, Gabiano C, Salvini F, Cellini M, Tamburini E, Puzzovio M, Zuccotti GV. In utero exposure to tenofovir disoproxil fumarate does not impair growth and bone health in HIV-uninfected children born to HIV-infected mothers. Antivir Ther 2011; 16: 1259-1266 [PMID: 22155907 DOI: 10.3851/IMP1909]

26 Siberry GK, Williams PL, Mendez H, Seage GR, Jacobson DL, Hazra R, Rich KC, Griner R, Tassopoulous K, Kacanek D, Mofenson LM, Miller T, DeMiglio LA, Watts DH. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. AIDS 2012; 26: 1151-1159 [PMID: 22382151 DOI: 10.1097/QAD.0b013e32835d1335]

27 Abdelaziz TH, Samir S. Congenital dislocation of the knee: a protocol for management based on degree of knee flexion. J Child Orthop 2011; 5: 143-149 [PMID: 22468158 DOI: 10.1007/s11832-011-0333-7]

28 Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2011. Available from: URL: http://www.APRegistry.com

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