

Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection

Mustafa Kemal Celen, Duygu Mert, Müzeyyen Ay, Tuba Dal, Safak Kaya, Necmettin Yildirim, Serda Gulsun, Tunga Barcin, Sevgi Kalkanli, Mehmet Sinan Dal, Celal Ayaz

Mustafa Kemal Celen, Celal Ayaz, Department of Infectious Diseases, Faculty of Medicine, Dicle University, 21280 Yenişehir, Diyarbakir, Turkey

Duygu Mert, State Hospital, 72000 Merkez, Batman, Turkey

Müzeyyen Ay, State Hospital, Kiziltepe, 47500 Mardin, Turkey

Tuba Dal, Department of Medical Microbiology, Faculty of Medicine, Dicle University, 21280 Yenişehir, Diyarbakir, Turkey

Safak Kaya, Department of Infectious Disease, Teaching and Research Hospital, 21100 Diyarbakir, Turkey

Necmettin Yildirim, Department of Infectious Diseases, State Hospital, 47000 Mardin, Turkey

Serda Gulsun, Department of Infectious Diseases, State Hospital, 21100 Diyarbakir, Turkey

Tunga Barcin, Department of Infectious Diseases, Mardin Park Hospital, 47000 Mardin, Turkey

Sevgi Kalkanli, Department of Immunology, Faculty of Medicine, Dicle University, 21280 Yenişehir, Diyarbakir, Turkey

Mehmet Sinan Dal, Department of Internal Medicine, Faculty of Medicine, Dicle University, 21280 Yenişehir, Diyarbakir, Turkey

Author contributions: All authors contributed to this paper.

Correspondence to: Tuba Dal, MD, Associate Professor, Department of Medical Microbiology, Faculty of Medicine, Dicle University, Altunbay 3, 21280 Yenişehir, Diyarbakir,

Turkey. tuba_dal@yahoo.com

Telephone: +90-412-248800 Fax: +90-412-2488042

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Abstract

AIM: To evaluate the effects of tenofovir disoproxil fumarate (TDF) use during late pregnancy to reduce hepatitis B virus (HBV) transmission in highly viremic mothers.

METHODS: This retrospective study included 45 pregnant patients with hepatitis B e antigen (+) chronic hepatitis B and HBV DNA levels $> 10^7$ copies/mL who received TDF 300 mg/d from week 18 to 27 of gestation ($n = 21$). Untreated pregnant patients served as controls (n

$= 24$). All infants received 200 IU of hepatitis B immune globulin (HBIG) within 24 h postpartum and 20 μ g of recombinant HBV vaccine at 4, 8, and 24 wk. Perinatal transmission rate was determined by hepatitis B surface antigen and HBV DNA results in infants at week 28.

RESULTS: At week 28, none of the infants of TDF-treated mothers had immunoprophylaxis failure, whereas 2 (8.3 %) of the infants of control mothers had immunoprophylaxis failure ($P = 0.022$). There were no differences between the groups in terms of adverse events in mothers or congenital deformities, gestational age, height, or weight in infants. At postpartum week 28, significantly more TDF-treated mothers had levels of HBV DNA < 250 copies/mL and normalized alanine aminotransferase compared with controls (62% *vs* none, $P < 0.001$; 82% *vs* 61%, $P = 0.012$, respectively).

CONCLUSION: TDF therapy during the second or third trimester reduced perinatal transmission rates of HBV and no adverse events were observed in mothers or infants.

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Key words: Hepatitis B; Tenofovir; Reverse transcriptase inhibitors; Vertical transmission; Chronic

Core tip: Tenofovir disoproxil fumarate use during late pregnancy reduced hepatitis B virus transmission in highly viremic hepatitis B e antigen positive mothers.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a important medical problem affecting approximately 2 billion people globally^[1]. The vertical transmission of HBV from hepatitis B surface antigen (HBsAg)-positive mothers to their infants at birth or in early infancy has a significant role in the endemicity of HBV infection and causes an increased risk of chronic hepatitis B (CHB)^[2]. The prevention of perinatal or vertical transmission is crucial in the control of hepatitis B endemicity. Without immunoprophylaxis > 90% of infants, born to mothers with hepatitis B e antigen (HBeAg), become chronically infected with HBV. In recent years, active and passive immunoprophylaxis of newborns and universal vaccination programs have reduced the transmission rates of HBV^[1-4]. It was reported that passive or active immunization within 12 h of birth may lead to the prevention of perinatal transmission of HBV^[5]. However, some studies showed that HBV immunoprophylaxis fails in 10%-15% of infants^[6,7], mainly as a result of vertical infection^[8-11]. A high level of maternal viremia is a significant factor in prophylaxis failure. A positive correlation between high maternal serum HBV DNA levels and an increased risk for vaccination breakthrough was found in these studies^[8-11]. These data have introduced the idea of antiviral therapy in pregnant women with a high level of maternal viremia and high maternal serum HBV DNA levels.

Among the oral anti-HBV agents approved by United States Food and Drug Administration (FDA), Tenofovir disoproxil fumarate (TDF) is an effective agent due to its potency and resistance profile^[13-15]. TDF is a nucleotide analog which inhibits reverse transcriptase and blocks HBV replication in liver cells^[2,16]. In over 600 human immunodeficiency virus (HIV) mono-infected and HIV/HBV co-infected mothers, it was reported that TDF had a favorable efficacy and safety profile^[16-18]. However, to our knowledge, there are limited data available in the literature on the safety and efficacy of TDF therapy during pregnancy in highly viremic mothers with chronic hepatitis B and its impact on the perinatal transmission of HBV.

In the current study, we evaluated the efficacy and safety of TDF use during late pregnancy to reduce HBV transmission in highly viremic HBeAg positive mothers.

MATERIALS AND METHODS

Patients

This was a retrospective study conducted in six hospitals in South-east Anatolia, Turkey. A total of 45 pregnant women, who were diagnosed with HBeAg-positive chronic hepatitis B before 12 wk of gestation between February 2010 and January 2012, were included in this study. Twenty-one patients were treated with TDF 300

mg orally once a day (Viread; Gilead Sciences, CA, United States) from week 18 to 27 of gestation ($n = 21$) and served as the treated-group. Twenty-four untreated pregnant women with active hepatitis B infection served as the control group. The treated patients received TDF until the fourth week after delivery.

Eligibility criteria for inclusion in this study were: (1) pregnant women; (2) positive for serum HBsAg and HBeAg for a period of at least 6 mo; (3) HBV DNA levels ≥ 7 log₁₀ copies/mL before initiation of TDF; (4) treatment-naive patients; (5) patients without lamivudine resistance; and (6) patients without gestational diabetes, vaginitis, arrhythmia, anemia or proteinuria.

Forty-five pregnant women met all inclusion criteria and were included in the study. Mothers with HIV co-infection, pregnancy complications, or an abnormal sonographic examination were excluded from TDF therapy. Baseline demographic data and virological characteristics (age, race, HBeAg, and history of prior HBV therapy) of the pregnant women were recorded. Blood and urine beta-HCG were tested in all patients).

HBsAg, HBeAg, anti-HBe, HBV DNA, alanine aminotransferase (ALT), aspartate aminotransferase levels, and creatinine level were measured at intervals of 12 wk. Both the mothers and infants were evaluated at periodic intervals during the intrauterine period.

All newborns were evaluated for congenital malformations, hypothyroidism, and phenylketonuria at birth. Infant Apgar score, anthropometry, birth defects, history of immunoprophylaxis, mode of delivery and complications were evaluated and recorded.

HBV DNA was quantified using the Roche COBAS Amplicor HBV monitor assay which has a low limit of detection (LLD) of 500 copies/mL (Roche Molecular Diagnostics, Branchburg, NJ, United States). This assay was later replaced by the Roche COBAS TaqMan HBV Test with a LLD of 50 copies/mL (Roche Molecular Diagnostics). HBV serological markers were detected by enzyme-linked immunosorbent assay kits (Abbott Labs, North Chicago, IL, United States) on an ARCHITECT 2000 full automatic chemiluminescence immunoassay instrument (Abbott Labs, North Chicago, IL, United States) according to the manufacturer's instructions. Hearing screening was tested by Echo Screen (Madsen, Germering, Germany). Heel blood was taken from the infants after 72 h of breastfeeding and then dried blood-spot specimens on filter paper were sent to the laboratory for congenital phenylketonuria and hypothyroidism screening.

According to national and international treatment guidelines, all infants received 200 IU of hepatitis B immune globulin (HBIG, HyperHEP B solvent/detergent treated; Talecris Biotherapeutic, NC, United States) within 24 h postpartum and 20 μ g of recombinant HBV (Recombivax HB; Merck Sharp and Dohme, NJ, United States) vaccine (4, 8, and 24 wk). Infants were evaluated in terms of serum HbsAg and HBV DNA levels at postpartum weeks 4-28. Vertical transmission was evaluated by HBsAg testing of infant peripheral blood at 4-28 wk of age.

Table 1 Maternal characteristics of the control group and tenofovir disoproxil fumarate-treated group

Maternal characteristics	Control group (n = 24)	Treated group (n = 21)
Mean age (yr)	26.9 ± 2.9	28.2 ± 4.1
HBV DNA (IU/mL)	8.31 log	8.28 log
ALT levels (U/L)	52 (19-77)	56 (22-71)
Serum creatinine levels (mg/dL)	0.81 (0.6-1.0)	0.79 (0.6-0.98)
Compensated cirrhosis	0 (0%)	2 (10%)

HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

Table 2 Maternal outcomes in the control group and tenofovir disoproxil fumarate-treated group n (%)

Maternal outcomes	Control group (n = 24)	Treated group (n = 21)
HBV DNA < 50 IU/mL	0 (0)	13 (62)
Normalized ALT (U/L)	15 (61)	17 (82)
Elevated creatinine kinase (> 165 mg/dL)	0 (0)	1 (4.7)
Spontaneous abortion	1 (4)	0 (0)
Gestational diabetes	0 (0)	1 (4.7)
Vaginitis	0 (0)	1 (4.7)
Arrhythmia	0 (0)	1 (4.7)
Anemia	0 (0)	1 (4.7)
Proteinuria	1 (4.2)	2 (10)

HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

Ethics

All participants gave their written informed consent and did not receive any compensation for taking part in this study. The study conformed to the standards set by the latest revision of the Declaration of Helsinki and was approved by the Ethical Committee.

Statistical analysis

Statistical analysis was performed using Stata software version 10 (Computer Resource Center, Chicago, IL, United States). Measurement data were expressed as mean ± SD and compared with analysis of variance. Fisher's exact test was used for comparison of transmission rate. $P < 0.05$ was considered statistically significant.

RESULTS

Maternal characteristics

HBV DNA levels were > 2000000 IU/mL (10^7 copies/mL) in all patients (treated-group and control group). The median maternal age was 27.7 ± 3.7 years. Serum creatinine levels were within the normal ranges in all patients. Two patients in the treated-group had compensated cirrhosis (10%) (Table 1).

Maternal outcomes

All the mothers in the treated-group continued to receive therapy during the study period. In the treated-group, all pregnant women delivered, however, one patient in the

control group had a spontaneous abortion at week 9.

In the treated-group, gestational diabetes was found in one patient, vaginitis in one patient, arrhythmia in one patient, and anemia in one patient. Three patients (14.3%) had proteinuria in the treated-group. Elevated creatinine kinase (CK) was detected in one (4.7%) patient in the treated-group at week 6, and reached the highest level (341 mg/dL) at week 8. At this time, the patient had no complaints or muscle function loss. Muscle function tests in this patient were normal, and she was diagnosed with asymptomatic CK elevation.

One patient (4.7%) in the treated-group had elevated levels of ALT (258 U/L) at week 7, however, ALT levels were normal at week 11 of treatment.

At postpartum week 28, significantly more TDF-treated mothers had levels of HBV DNA < 50 IU/mL (250 copies/mL) and normalized ALT compared with controls (62% *vs* none, $P < 0.001$; 82% *vs* 61%, $P = 0.012$, respectively). There were no differences in adverse effects in mothers between the groups (Table 2). The treated mothers had no hepatic flares until the fourth week after delivery.

Infant characteristics and outcomes

At the 20th gestational week evaluation, no serious complications were observed in the infants of the treated-group, although 3 (14.3%) infants had growth retardation as shown on ultrasound screening. However, these infants did not show growth retardation at week 24th following ultrasound monitoring.

Birth weight was < 2500 g in two (4.7%) newborn. Hypothyroidism, phenylketonuria and congenital hearing loss were not observed in any of the newborn. At 28 wk, none of the infants whose mothers received TDF had immunoprophylaxis failure, whereas 2 (8.3%) of the infants of control mothers had immunoprophylaxis failure (HBsAg positivity was detected) ($P = 0.022$). Anti-HBs levels were < 100 mIU/mL in one (4.7%) of the vaccinated neonates of treated mothers, while levels were > 100 mIU/mL in the remaining (95%) vaccinated neonates of treated patients. No differences in infant congenital deformities, gestational age, height, or weight between the groups were observed (Table 3).

DISCUSSION

In this retrospective study, we report the efficacy and safety of TDF in the prevention of vertical transmission (VT) in pregnant women with high viremia HBV infection^[15]. Immunoprophylaxis with immediate HBIG and HBV vaccine after delivery effectively prevented VT in these cases. Failure of immunoprophylaxis is generally caused by high maternal viral load^[9,11,15]. It has been clearly demonstrated that there is a correlation between intrauterine serum HBV DNA levels and perinatal transmission of HBV in pregnant women^[15]. HBV DNA level was found to be an independent risk factor for failure of immunoprophylaxis in HBeAg-positive mothers with high HBV DNA levels

Table 3 Outcome of infants born to control mothers and tenofovir disoproxil fumarate-treated mothers *n* (%)

Infant characteristics and outcomes	Infants of control group mothers (<i>n</i> = 23)	Infants of treated group mothers (<i>n</i> = 21)
Birth weight < 2500 g	1 (4.3)	1 (4.7)
Immunoprophylaxis failure	2 (8.3)	0 (0)
Anti-hepatitis B surface levels > 100 mIU/mL	19 (82)	20 (95)
Hypothyroidism	0 (0)	0 (0)
Phenylketonuria	0 (0)	0 (0)
Congenital hearing loss	0 (0)	0 (0)

($\geq 6 \log_{10}$ copies/mL)^[19]. For these reasons we included mothers with high levels of DNA in the present study.

There are many studies on the use of TDF to prevent VT in HIV mono-infected and HIV/HBV coinfecting mothers in the literature^[17,18]. However, there are limited data on the use of TDF in pregnancy and in the prevention of VT in HBV mono-infected mothers. According to previous studies, early post-natal immunoprophylaxis with antiviral therapy in mothers in the third trimester was safe, well-tolerated, and effectively prevented VT of HBV^[2,20]. Among five FDA approved oral anti-HBV agents, TDF and entecavir are the most effective agents due to their resistance profile and potency^[13,15]. TDF and telbivudine are classified as category B (no evidence of risk to humans: either animal findings indicate risk, but human findings do not; or, if no adequate human studies have been conducted, animal findings are negative) for use in pregnancy, whereas lamivudine, entecavir, and adefovir are category C (risk cannot be ruled out: human studies are lacking, and animal studies are either positive for fetal risk, or are lacking). However, potential benefits may justify the potential risk in the FDA drug category for pregnancy^[15].

In a randomized, double-blind, placebo-controlled study with lamivudine, it was found that lamivudine therapy during late pregnancy can reduce HBV perinatal transmission in highly viremic mothers. This study demonstrated that infants in the lamivudine + vaccine + HBIG group had a significant decrease in the incidence of HBsAg seropositivity (10/56, 18% *vs* 23/59, 39%, $P = 0.014$) and in detectable HBV DNA (11/56, 20% *vs* 27/59, 46%, $P = 0.003$) compared to infants who received placebo + vaccine + HBIG. The results of this study suggested that lamivudine reduced HBV transmission from highly viremic mothers to their infants following immunization^[20]. In another prospective, open-label controlled study evaluating the efficacy and safety of telbivudine use during late pregnancy, a striking decline in HBV DNA levels was seen from treatment onset to week 4, and remained at a low level from week 12. According to this study, 33% of the telbivudine-treated mothers and none of the untreated controls had DNA < 500 copies/mL at delivery and seven months after delivery, and the incidence of perinatal transmission was lower in the infants of telbivudine-treated mothers than in the controls (0% *vs* 8%; $P = 0.002$)^[2]. In a case series by Pan *et al*^[15], TDF therapy in the third trimester was evaluated in eleven Asian women with HBV. In their un-

controlled study, a significant reduction in serum HBV-DNA was achieved at delivery compared with baseline, and all infants were HBsAg negative 28-36 wk after birth^[15]. In our controlled study, at postpartum week 28 significantly more TDF-treated mothers had low levels of HBV DNA and none of the infants of 21 treated mothers had immunoprophylaxis failure. In light of these results, we suggest that TDF use in the third trimester is safe and effectively prevents VT of HBV from high viremic HBeAg-positive mothers.

When the potential benefit of an antiviral-agent is evaluated, adverse effects of that antiviral-agent should also be taken into consideration. These adverse effects include teratogenicity, long-term effects on bone development in the infant, post-treatment ALT flares, and HBV-resistant mutations. Studies have indicated that TDF can cause renal events in HIV patients and patients with preexisting renal disease. However, nephrotoxicity was not observed during a three-year period of TDF use in chronic HBV patients with preserved baseline renal function^[21,22]. According to analyzed neonatal safety data from the Antiretroviral Pregnancy Registry (APR), the birth defect prevalence of earliest exposure commencing in the first trimester was 3.1% for lamivudine and 2.4% for TDF; earliest exposure commencing in the second or third trimester was 2.7% for lamivudine and 2.0% for TDF^[23]. A meta-analysis of lamivudine in late pregnancy reported that no significant increase in adverse effects or complications in pregnancy was observed^[24]. In the large-scale controlled study by Han *et al*^[2], no serious adverse events were noted in the telbivudine-treated mothers or their infants. In a Chinese study conducted in eight pregnant HBV women receiving TDF, HBV flares, an increase in creatinine and birth defects were not observed, and all newborn parameters were appropriate for gestational age^[25]. Several clinical studies and the APR have stated that anti-viral agents for hepatitis are safe in pregnancy during the second/third trimester^[15,23]. The relationship between TDF and fetal growth, particularly bone development is a matter of concern. Studies of pregnant monkeys showed that the use of TDF can cause reduced fetal growth and a reduction in fetal bone porosity within two months of starting maternal therapy^[26]. TDF use in HIV-infected children has been reported to result in decreases in bone mineral density^[27,28]. However, long-term safety data in infants perinatally exposed to TDF demonstrated no abnormal bone metabolism or growth impairment in these children^[29,30]. In the study by Pan *et al*^[15], serum creatinine

levels were stable and within the normal range during TDF treatment in all mothers, and they did not encounter any adverse pregnancy outcomes and/or birth defects. Similarly, in the current study we did not observe any differences in adverse events in mothers or infant congenital deformities, gestational age, height, or weight between the groups.

In conclusion, this controlled study revealed that the use of TDF in highly viremic chronic hepatitis B mothers during the second or third trimester of pregnancy reduced the rate of perinatal transmission. Tenofovir disoproxil fumarate produced no adverse events in infants or mothers by 28 wk and is a safe and effective agent in pregnant women with high viremia.

COMMENTS

Background

The vertical transmission of hepatitis B virus (HBV) from hepatitis B surface antigen-positive mothers to their infants at birth or in early infancy has a significant role in the endemicity of HBV infection and causes an increased risk of chronic hepatitis B (CHB).

Research frontiers

Among the oral anti-HBV agents approved by the Food and Drug Administration, tenofovir disoproxil fumarate (TDF) is an effective agent due to its potency and resistance profile. However, there are limited data available in the literature on the safety and efficacy of TDF therapy during pregnancy in highly viremic mothers with CHB and on its impact on the perinatal transmission of HBV. In this study, the authors demonstrated that TDF therapy during the second or third trimester in CHB mothers reduced perinatal transmission rates with no adverse events in mothers and their infants.

Innovations and breakthroughs

This report highlighted the importance of TDF therapy in highly viremic CHB mothers during the second or third trimester to reduce perinatal transmission rates with no adverse events in infants or mothers. This is an important study which shows that TDF can be used in highly viremic mothers. Furthermore, this study suggests that TDF may be used in highly viremic CHB mothers.

Applications

TDF therapy may represent a future strategy for CHB mothers during the second or third trimester.

Terminology

TDF is a nucleotide analog which inhibits reverse transcriptase and blocks HBV replication in liver cells. TDF is a safe and effective agent which can be used during pregnancy in highly viremic mothers with CHB and does not increase perinatal transmission of HBV.

Peer review

The authors studied the influence of TDF use on perinatal transmission of HBV infection. This is an interesting report.

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