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Use of Tenofovir Disoproxil Fumarate in Highly Viremic, Hepatitis B Mono-Infected Pregnant Women

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Abstract

Background—Antiviral therapy in addition to immunoprophylaxis at birth has been shown to further reduce perinatal transmission of hepatitis B virus (HBV) in highly viremic women.

Aims—The aim of this study was to describe the use of tenofovir disoproxil fumarate (TDF) prophylaxis to reduce maternal HBV DNA levels and potentially vertical transmission in highly viremic women.

Methods—After receiving IRB approval, we performed a retrospective chart review of mothers positive for hepatitis B surface antigen (HBsAg) who delivered between 2009 and 2012. We identified women with HBV DNA levels ≥ 6 log copies/mL who were treated with TDF in pregnancy.

Results—There were 22 women identified. The majority were of Micronesian ethnicity. All were negative for hepatitis C antibody and HIV infection. The median gestational age of TDF initiation

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was 31 weeks with a median duration of treatment of 45 days. There was a reduction in median HBV DNA levels from baseline 9.0 ± 2.0 to 5.4 ± 1.1 log copies/mL after treatment. There were five (22.7 %) preterm deliveries and five (22.7 %) cesarean deliveries. All infants received immunoprophylaxis at birth. Postnatal HBsAg testing at 9–12 months was available for 13 infants, 12 of which were negative. There was one case of perinatal transmission.

Conclusions—This is the second published case series to date on the use of TDF prophylaxis in HBV mono-infected, highly viremic mothers. This series suggests the use of TDF in pregnancy reduces maternal HBV DNA levels and is well tolerated.

Keywords

Hepatitis B virus; Pregnancy; Perinatal transmission; Tenofovir

Introduction

Chronic hepatitis B virus (HBV) infection affects approximately 400 million people worldwide and caused 786,000 deaths in 2010 [1, 2]. In the USA, it is estimated that 800,000 to 1.4 million people are infected with chronic HBV [3]. Among pregnant women, the prevalence of positive hepatitis B surface antigen (HBsAg) ranges from 0.6 to 5.8 % and varies by maternal race/ethnicity [4]. Prevalence rates among Asian populations are much higher than those among whites, Hispanics, and blacks. Perinatal transmission is the most common route of infection in endemic areas, particularly in the Asia–Pacific regions [5, 6]. The introduction of HBV passive–active immunoprophylaxis with HBV vaccine and hepatitis B immunoglobulin (HBIG) has been shown to reduce perinatal transmission of HBV by greater than 90 % [7–9]. Immunoprophylaxis failure has been noted in women with high maternal HBV DNA levels and the presence of HBeAg [10, 11]. Congenital HBV infection rates of 8–14 % have been reported in children who received newborn immunoprophylaxis and were born to mothers with high DNA levels and positive for HBeAg [11–14].

The use of antiviral medications, in particular lamivudine and telbivudine, in the third trimester of pregnancy in addition to passive–active immunoprophylaxis has been shown to further reduce the vertical transmission rate in women with high HBV DNA levels (usually defined as greater than 6–8 log copies/mL) [11, 15]. The efficacy of TDF to reduce perinatal transmission has not yet been studied in any prospective trials. Its use has been favored by many experts due to its efficacy seen in HBV and HIV in the non-pregnant population. Its safety has been well documented for the treatment of human immunodeficiency virus (HIV) infection in pregnancy and has been classified as category B medication by the Food and Drug Administration. TDF is also the drug of choice for the treatment of non-pregnant chronic HBV patients due to its low drug resistance and high efficacy profile [16, 17]. Due to the limited data on TDF in the prevention of HBV perinatal transmission in mono-infected women, the purpose of this retrospective case series was to describe its use for reducing HBV DNA levels and potentially perinatal transmission in highly viremic pregnant women.

Methods

After obtaining approval from Western Institutional Review Board (Protocol #2012-083), we performed a retrospective chart review of mothers positive for hepatitis B who delivered at Kapiolani Medical Center for Women and Children in Honolulu, Hawaii. ICD-9 codes indicating positive hepatitis B infection (070.20–070.33) were searched in all births between 2009 and 2012. Of the women identified using ICD-9 codes for hepatitis B infection, electronic medical records were reviewed for inclusion and exclusion criteria. The inclusion criteria included HBV mono-infected pregnant women with HBV DNA levels ≥ 6 log copies/mL who were treated with TDF 300 mg orally once a day (Viread; Gilead Sciences, CA, USA) during pregnancy. Cases were excluded if the infant did not receive HBV vaccine and HBIG within 12 h of delivery and there was presence of maternal HIV infection and/or maternal hepatitis C infection.

Maternal data including age, race/ethnicity, parity, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and hepatitis B surface antigen (HBsAg) status were collected. Neonatal and delivery data including birth weight, sex, Apgar scores, presence of birth defects, gestational age at delivery, mode of delivery, and immediate postpartum breastfeeding status were also collected. Maternal HBV DNA levels before and after the initiation of TDF were compared. Gestational age at TDF initiation, total duration of treatment, drug side effects, and postpartum prescription of TDF were also examined. Outpatient electronic medical records of the infants were reviewed for the presence of serum HBsAg at 9–12 months of age.

Results

Out of the 24,377 births that occurred between 2009 and 2012, there were 82 women identified as having hepatitis B infection. Of the 82 cases, 22 women met inclusion and exclusion criteria (Fig. 1). The maternal characteristics, pre- and post-TDF treatment serum HBV DNA levels, and estimated duration of therapy during pregnancy for the 22 women are shown in Table 1. Maternal age ranged from 18 to 40 years, and the median age was 28 ± 7.5 years. Twelve (54.5 %) women were of Micronesian/Marshallese descent, five (22.7 %) women were of Chinese descent, and five (22.7 %) women were of other Asian descent, which included Thai, Korean, Filipina, and Vietnamese. There was one spontaneous twin gestation. One woman had elevated AST and ALT levels prior to treatment initiation. All were negative for hepatitis C antibody and HIV infection. All were positive for hepatitis B e antigen. The median gestational age of TDF initiation was 31 weeks with a median duration of treatment of 45 ± 31.3 days or 6.4 ± 4.5 weeks. There was a reduction in median HBV DNA level from baseline 9.0 ± 2.0 to 5.4 ± 1.1 log copies/mL after treatment. Only one woman reported a side effect, which was nausea and vomiting. She stopped the medication after 2 weeks (patient number 20). In one patient (patient number 17), there was no reduction in HBV DNA levels after appropriate duration (71 days) of treatment. There was a significant reduction in the maternal DNA level of 3.4 log copies/mL in one patient (patient number 8) after just 19 days of treatment.

There were no stillbirths among the 22 women. There were a total of five (22.7 %) preterm births, one early and four late. All were due to spontaneous preterm labor. There were five (22.7 %) cesarean deliveries, three were elective due to breech, previous cesarean section, and placental previa, and two were after onset of labor. All 22 infants received hepatitis B vaccination and HBIG within 12 h of delivery. Postnatal HBsAg testing at 9–12 months was available for 13 infants. The delivery and infant data of these 13 cases are summarized in Table 2. One infant tested positive and was referred to a pediatric gastroenterologist for management. The mother of this infant was treated with TDF for only 17 days due to non-compliance with prenatal care. She was lost to follow-up until 35 weeks' gestation, where at that time TDF was started. She delivered at 37 5/7 weeks' gestation via spontaneous vaginal delivery and breast-fed during her hospital stay. There was a birth defect, hypospadias, in infant A of the twin gestation (patient number 11). All birth weights were appropriate for gestational age. Eighty-two percent of the women in our study breast-fed their infants while in the hospital. Ten out of 22 patients (45.4 %) of our case series were prescribed TDF postpartum. Of those who breast-fed, 7 out of 18 (38.9 %) were on TDF postpartum.

Discussion

TDF treatment has been well studied in HIV-infected pregnant women and HBV-infected non-pregnant women [16–25]. Data on the use of TDF in HBV mono-infected pregnant women are limited. Our results are consistent with the first published case series from Pan et al. [26], who reported their experience treating 11 women with TDF in the third trimester. They also reported a reduction in mean HBV DNA level from baseline of 8.9 ± 0.5 to 5.3 ± 1.8 log copies/mL at delivery. We saw a similar mean reduction in our study; however, one patient did not have any reduction in her HBV DNA level. This was suspected to be a result of non-compliance with the medication as previous literature noted minimal to no change in viral load levels during pregnancy in women not treated with antiviral medications [11, 27]. Pan et al. did not observe any obstetric complications in their cohort, and all patients were delivered at term. This is in contrast to our cohort where we did observe a higher preterm birthrate. This may be due to the fact that our institution has the largest level III neonatal intensive care unit in the state of Hawaii and is a high-risk obstetric referral center. Many of our patients have other risk factors for preterm delivery, such as history of preterm birth, maternal hypertension, and maternal diabetes. Preterm birthrates among Asian and Pacific Islanders in Hawaii have been shown to be higher than those among white women [28]. Since the majority of our patients with hepatitis B were of Asian and Pacific Islander descent, the higher preterm birthrate in our cohort was not unexpected. The one patient with early preterm birth in our study delivered at 30 6/7 weeks' gestation had a previous preterm delivery at 26 5/7 weeks' gestation. While Pan et al. reported no birth defects, we did see one minor birth defect of hypospadias, which we do not suspect to be the result of TDF exposure. In Pan et al.'s study, all infants were negative for HBsAg at 28–36 weeks of age, while we found one case of perinatal transmission. The case of perinatal transmission in our series is postulated to be from an inadequate duration of treatment of only 17 days prior to delivery. Studies on antiviral treatment to prevent perinatal transmission suggest starting treatment in early third trimester (28–32 weeks) to allow an adequate reduction in maternal

HBV DNA levels prior to delivery [11, 27]. In patients at increased risk of preterm delivery, earlier initiation of antiviral treatment may be warranted.

Our series is the second published case series to demonstrate promising preliminary data on the use of TDF for preventing perinatal transmission of HBV infection in highly viremic pregnant women. A high maternal HBV DNA level is an independent risk factor for perinatal transmission of HBV, despite appropriate infant HBV immunoprophylaxis. In Taiwan, Wen et al. [14] noted that children born to mothers with high viral loads compared to those born to mothers with low viral loads were 3.5 times more likely to be infected with HBV (OR 3.49; 95 % CI 1.63–7.48). They estimated rates of HBV transmission by maternal HBV DNA levels. At 8 log copies/mL, the transmission rate was 14.6 % (95 % CI 5.6–23.6 %) versus 5 log copies/mL, where the transmission rate was 0.9 % (95 % CI 0.9–2.7 %). In China, Zou et al. [13] also noted higher immunoprophylaxis failure rates with higher maternal HBV DNA levels. At maternal HBV DNA levels >8 log copies/mL, the perinatal transmission was 7.6 % at 7–12 months of age. In Australia, Wiseman et al. [12] found a 9 % transmission rate of infants at 9 months in cases of maternal HBV DNA levels >8 log copies/mL. Antiviral medications, such as lamivudine and telbivudine, prescribed during pregnancy have been shown to further decrease the perinatal transmission rate [11, 27, 29–33].

TDF is currently considered to be first-line treatment for chronic HBV infection and HIV infection in adults. It has been shown to be more efficacious compared to other antiviral medications [16, 17]. The 2013 World Health Organization (WHO) guidelines recommend the use of TDF-containing regimen as first-line therapy in treating HIV infection in adults [19]. TDF-containing antiretroviral regimen is also recommended as first-line therapy for pregnant women coinfecting with HIV and HBV by the National Institute of Health [34]. Although bone demineralization and growth restriction with TDF treatment were reported in animal studies and pediatric studies of HIV-infected children [35, 36], safety studies of TDF use in human pregnancies have been reassuring [20, 24, 37]. Siberry et al. [24] examined infants exposed to TDF-containing regimen versus those without in HIV-infected pregnant women and found no difference in the incidence of small-for-gestational-age and low birth weight infants. There were slightly lower mean length-for-age and head circumference-for-age z-scores at one year of age, but this difference was not seen at birth. Gibb et al. [20] examined pregnancy outcomes of TDF-exposed pregnancies in HIV-infected women from Uganda and Zimbabwe and noted no difference in infant mortality, congenital anomaly, renal toxicity, and growth abnormality rates.

Potential maternal complications with the use of TDF in pregnancy include hepatitis flare and renal toxicity. Elevations in ALT have been seen during lamivudine treatment during pregnancy and after abrupt postpartum cessation of the medication [32, 38]. Forty-five percent of the patients in our study continued TDF immediately postpartum. We were unable to access outpatient records to evaluate the length of TDF treatment postpartum and whether hepatitis flares were seen. Nephrotoxicity is another potential complication from the use of TDF and has been seen in the treatment of HIV-infected patients [39]. Renal impairment at the time of delivery was not seen in our study. Renal function should be monitored closely in all patients on TDF.

Studies on perinatal HBV transmission have not identified breast-feeding as a risk factor [14, 40, 41]. The American Academy of Pediatrics recommends breast-feeding for HBV-infected women as long as their neonates receive appropriate immunoprophylaxis. Data on breast-feeding in women taking TDF are limited. Although animal studies show that TDF is excreted into breast milk, there are no human data available. Pharmacologically, TDF is converted into its metabolite, tenofovir, prior to being excreted into breast milk. Tenofovir is not absorbed by the adult GI tract [42]. We can speculate that tenofovir is also not absorbed by the gut of the neonate. Seventy-seven percent of the women in our study breast-fed their infants while in the hospital. Based on the available literature, we do not discourage breast-feeding in hepatitis B mono-infected mothers as long as the neonates receive both HBV vaccine and HBIG, regardless of whether they continue TDF. Patients are counseled regarding the scarcity of information on breast-feeding and TDF use as well as the known benefits of breast-feeding.

The primary strength of this retrospective case series is that it demonstrates a realistic clinical perspective of the use of TDF in the prevention of HBV perinatal transmission. Similar to real-life clinical scenarios, some women in our series may have been non-compliant with prenatal care and with medication intake and/or have difficulty accessing care or medications. Compliance with TDF could not be measured in this case series and is a limitation. Non-compliance with medication may be suspected if there is no reduction in HBV DNA levels. Han et al. [11] noted that every patient out of the 135 women they treated with telbivudine had a drop in serum HBV DNA levels below 3 log copies/mL. Pan et al. [26] also noted in their case series that every woman had a reduction in serum HBV DNA level after treatment with TDF. Other limitations include the small sample size and no comparison group that were not prescribed antiviral medication or were prescribed placebo. The variation in management, such as timing of TDF initiation, serum HBV DNA levels, and postpartum continuation of TDF, was also a limitation. We are in the process of developing a standard protocol for the treatment of highly viremic HBV-infected pregnant women at our institution.

In conclusion, this is the second published case series to date on the use of TDF prophylaxis in HBV mono-infected, highly viremic mothers. This series suggests that the use of TDF in the third trimester reduces maternal HBV DNA levels and is well tolerated by pregnant women. Initiation of TDF in the third trimester in highly viremic women to reduce vertical transmission should be considered. Randomized controlled trials are needed to completely evaluate the efficacy of TDF for the prevention of vertical transmission of hepatitis B infection.

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Fig. 1.
Patient selection

Table 1

Maternal data

Subject	At TDF initiation		After TDF treatment			
	Age (years)	GA (weeks)	HBV DNA (log copies/mL)	TDF duration before repeat HBV DNA (days)	Repeat HBV DNA (log copies/mL)	Total duration of TDF in pregnancy (days)
1	37	32 3/7	>8.81	40	5.01	39
2	26	38 1/7	>8.81	7	7.37	8
3	36	36 0/7	>8.81	*	*	29
4	22	35 2/7	>8.81	*	*	17
5	21	27 3/7	>8.81	*	*	24
6	28	28 6/7	>8.81	33	6.38	52
7	26	34 6/7	>8.81	*	*	38
8	21	30 1/7	>8.81	19	5.39	71
9	36	31 1/7	7.01	55	3.37	38
10	34	34 0/7	>8.81	42	6.54	55
11	40	29 3/7	>8.23	42	6.1	57
12	21	32 4/7	>8.81	35	5.26	54
13	25	31 5/7	>8.81	35	6.18	57
14	34	26 5/7	>8.81	62	5.39	80
15	26	29 4/7	>8.81	42	6.27	51
16	18	33 0/7	>8.23	15	7.79	15
17	28	28 1/7	>8.81	71	>8.81	71
18	26	30 3/7	8.99	39	6.27	54
19	28	28 0/7	6.22	*	*	70
20	28	27 4/7	8.99	*	*	14
21	28	35 0/7	8.99	25	4.6	19
22	29	35 6/7	>8.81	*	*	30
Median $\pm$ IQR	28 $\pm$ 7.50	31 3/7 $\pm$ 5.67	8.99 $\pm$ 1.98	39 $\pm$ 13.00	5.44 $\pm$ 1.06	45 $\pm$ 31.25

GA gestational age, IQR interquartile range, TDF tenofovir disoproxil fumarate

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Table 2

Birth and infant data

Subject no.	GA	Mode of delivery	BW (g)	Gender	Apgar scores (1/5 min)	Breast milk exposure	HBsAg at 9–12 months
1	38 0/7	SVD	3,379	M	8,9	Yes	Negative
2	39 2/7	CD	3,096	F	8,8	Yes	Negative
3	39 2/7	CD	3,379	M	8,9	Yes	Negative
4	37 5/7	SVD	3,419	F	8,9	Yes	Positive
6	36 2/7	CD	2,985	M	8,9	No	Negative
7	40 2/7	SVD	3,606	M	8,9	Yes	Negative
8	41 3/7	SVD	3,359	M	8,8	No	Negative
9	36 3/7	CD	3,161	F	8,9	No	Negative
10	39 0/7	CD	3,697	F	8,9	Yes	Negative
11-A	37 4/7	CD	2,574	M	8,9	Yes	Negative
11-B			1,785	M	8,9	Yes	Negative
21	40 6/7	SVD	3,649	M	8,9	No	Negative
22	39 1/7	VAVD	3,249	F	8,9	Yes	Negative
Median ± IQR	39 0/7 ± 1.80		3,359 ± 323				

GA gestational age, BW birth weight, SVD spontaneous vaginal delivery, CD cesarean delivery, FAVD forceps-assisted vaginal delivery, VAVD vacuum-assisted vaginal delivery, HBsAg hepatitis B surface antigen, IQR interquartile range