Poster 584LB

TDF TO PREVENT PERINATAL HEPATITIS B VIRUS TRANSMISSION: A RANDOMIZED TRIAL (ITAP)

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Background

- 8% to 12% of infants born to hepatitis B infected mothers with high-level viremia or with HBeAg are infected despite prophylaxis with passive (HBIg) and active (HB vaccine) immunization starting at birth.[1-6]
- Antivirals inhibiting HBV replication such as lamivudine, tenofovir disoproxil fumarate (TDF), and telbivudine, prescribed to pregnant women with high HBV loads at the end of pregnancy and during the early postpartum period, may reduce the risk of hepatitis B mother to child transmission[1-3,5]

Objectives

Primary

- To assess the efficacy and safety of a short course of maternal tenofovir disoproxil fumarate (TDF), from 28 weeks gestation through 2 months postpartum, among women with HBeAg, a marker of high viral load, for the prevention of mother-to-child of HBV.

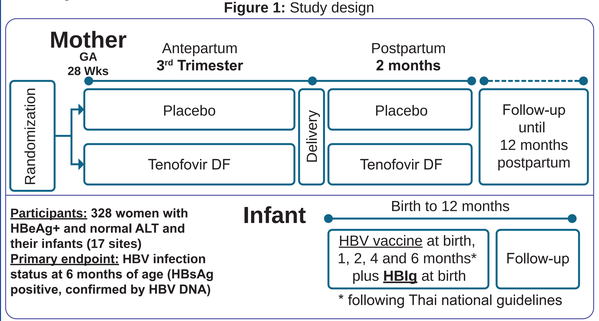
Secondary

- To assess the risk of postpartum hepatic disease exacerbation after discontinuing treatment
- Maternal and infant safety

Study design

- Phase III, double-blind, randomized clinical trial in pregnant inwomen with HBV infection (HBsAg and HBeAg positive) compairing TDF300 mg once daily or placebo (1:1) in 17 sites in Thailand7
- See Figure 1

Figure 1: Study design



Treatments and infant feeding

Maternal study treatment

- Participants were enrolled at 28 weeks gestation (+/−10 days), and randomly assigned to receive study treatment (manufactured by Gilead Sciences Inc.), i.e. either TDF 300 mg once daily or a matching placebo, from 28 weeks gestation through 2-months postpartum.
- Double-blind was maintained throughout the study.

Vaccine

- Infants received hepatitis B vaccine (10 ug) at birth, 1, 2, 4 and 6 months through the national expanded program for immunization (after the blood draw for assessment of HBV infection)

HB Immune Globulin

- The study provided all infants with HBIg (Grifols, Spain) immediately after birth.

Breastfeeding

- Infants were breastfed.

Inclusion criteria

- Pregnant women ≥18 years of age
- positive HBsAg and HBeAg tests
- alanine aminotransferase (ALT) ≤30 IU/L (confirmed ≤60 IU/L on a subsequent blood draw)
- Not HIV and not hepatitis C infected
- Cockcroft-Gault creatinine clearance ≥50 mL/min
- No proteinuria (dipstick ≤1+ / ≤30 mg/dL)
- No normoglycemic glucosuria
- No evidence of fetal anomalies incompatible with life.
- No history of TDF treatment

Evaluations

Primary endpoint

- Detection of HBsAg confirmed by HBV DNA at 6 months of age for efficacy assessment

Secondary endpoints

- Maternal or infant adverse events (SAEs and grade 3/4 signs and symptoms)
- Maternal hepatic flares (ALT >300 IU/L) following study treatment discontinuation
- Infant growth (WHO weight, height and head-circumference Z-scores-for-age) at 6 months.

Statistical considerations

- Target sample size: 156 evaluable mother/infant pairs per arm to detect a difference in HBV infected infants of 3% (TDF) vs. 12% (placebo) with 90% power accounting for 1 interim efficacy analysis, using a one-sided Fisher's exact test.

Results

Results: women

- 331 women (168 TDF, 163 placebo) enrolled from January 2013 to August 2015
- Age: 26.1 years (22.9, 30.0)
- Gestational age: 28.3 weeks (range: 26.6 to 29.6)
- Weight at entry: 61.2 kg (55.5, 69.7)
- HBV DNA load at enrollment: 8.0 log10IU/mL (7.1, 8.5)
- HBV DNA load at delivery: 3.9 log10 IU/mL (3.0, 4.8) on TDF, versus 7.8 log10 IU/mL (6.8, 8.5) on placebo

Values are medians (IQR) or frequencies (%) unless otherwise specified

Results: deliveries and infants

- 322 (97%) on-study deliveries (85 Cesarean, 26%)
- 323 live births (including 2 twin pairs) and 1 stillbirth (TDF arm)
- Gestational age at delivery: 38.9 weeks (38.1, 39.9)
- Preterm newborns: 21 (7%) (8 TDF, 13 placebo)
- Birth weight: 3050 g (2796, 3352): 3028 g (TDF) and 3061 g (placebo)

Values are medians (IQR) or frequencies (%) unless otherwise specified

Administration of HBIg and vaccine

- 320 (99%) infants received HBIg a median of 1.3 hours after birth
- 322 (>99%) HB vaccine a median of 1.2 hours after birth

Efficacy

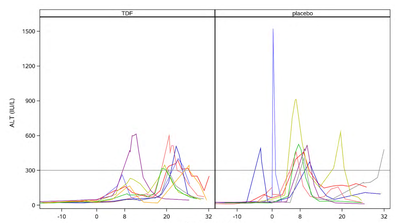
- In the primary complete case analysis at 6 months, 0/147 infants had HBV infection in the TDF arm versus 3/147 (2.0%) in the placebo arm (p=0.12). All 3 infected infants' mothers had HBV DNA >7.8 log10 IU/mL at delivery.

Efficacy endpoints at 6 months	TDF N	TDF Event	TDF Percent (95% CI)	Placebo N	Placebo Event	Placebo Percent (95% CI)	P-value Fisher's one-sided exact test
HBV Infection: Primary analysis	147	0	0.0 (0.0,2.5)	147	3	2.0 (0.4,5.8)	0.12
HBV Infection (Sensitivity analysis: Missing considered as infected)	167	20	12.0 (7.5,17.9)	163	19	11.7 (7.2,17.6)	0.60
Anti-HB antibodies ≥10IU/L	147	147	100.0 (97.5,100.0)	147	145	98.6 (95.2,99.8)	0.25

Safety endpoints, 6 months after delivery

- There were one stillbirth in the TDF arm, and one newborn with gross abnormalities who died soon after birth in the placebo arm.
- Following study treatment discontinuation, 9 (6%) women experienced an ALT >300 IU/mL in the TDF arm vs. 5 (3%) in the placebo arm (two-sided p=0.29).
- Nine women ever had ALT >300 IU/mL during the trial in the TDF arm, and 8 in the placebo arm (See Figure 2).
- The proportions of maternal and infant adverse events, and infant growth were similar between arms.

Figure 2: ALT over time by randomized arm for women >300 IU/L during the trial



Safety Endpoints Categorical endpoints	TDF N	TDF Event	TDF Percent (95% CI)	Placebo N	Placebo Event	Placebo Percent (95% CI)	P-value Fisher's two-sided exact test
Women: Grade 3/4 adverse events or serious adverse events	168	41	24 (18,32)	163	44	27 (20,34)	0.62
Women: ALT >300 U/L after treatment discontinuation	154	9	5.8 (2.7,10.8)	157	5	3.2 (1.0,7.3)	0.29
Infants: Grade 3/4 adverse events or serious adverse events	161	43	27 (20,34)	160	38	24 (17,31)	0.61

Infant growth WHO Z-scores at 6 months	N	Mean (SD)	N	Mean (SD)	Student's two-sided T-test
Weight-for-age	148	-0.4 (1.1)	146	-0.2 (1.1)	0.09
Length-for-age	148	-0.2 (1.2)	146	-0.2 (1.2)	0.67
Head circumference-for-age	148	-0.6 (1.1)	146	-0.6 (0.9)	0.76

Conclusions

- In this study where mothers were HBsAg and HBeAg positive, HBV mother-to-child transmission was only 2% in infants who received HBIg and HBV vaccine
- TDF resulted in a small non-significant reduction in perinatal HBV transmission beyond the low risk achieved with HBIg and HBV vaccine
- TDF appeared safe for pregnant women and infants and there was no evidence of impaired infant growth.

Discussion

- **Transmission rate in the placebo arm**
  - To date, no study has reported a transmission rate as low as 2% among untreated women with HBeAg whose infants received only hepatitis B vaccine and HBIg
  - The timing of HBIg and vaccine may be crucial but was not systematically reported in previous studies
  - The Thailand infant vaccination program (5 doses) may have contributed to decreased transmission in the placebo group
- **Sample size**
  - Our study sample size was the largest of published studies in this setting. It was calculated for >90% power to detect a difference in transmission between treatment arms of 12% and 3% or between 8% and 1%.
  - In Pan *et al*[8] open label study, a rate of mother-to-child transmission of 20% was assumed in the control group for determination of the sample size. However, a 7% transmission rate was observed (95% CI, 2 to 12; 6 of 88 infants).
  - To show a difference between 0.1% and 2% a much larger sample size (>1,600) would be required.

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Acknowledgements

- We would like to thank all the study participants as well as the study staff for their contributions to the study at clinical sites and at the PHPT laboratory and coordination center.
- We would like to express our gratitude to the members of the Data and Safety Monitorring Board: Kenneth McIntosh (Chair, Harvard University, Boston, MA, USA), Marc Bulterys (Center for Diseases Control and Prevention, USA), Suwachai Intaraprasert (Mahidol University, Bangkok, Thailand), Jean-Yves Mary (INSERM, Paris, France), Mark Mirochnick (Boston University, Boston, MA, USA), Yong Poovorawan (Chulalongkorn University, Bangkok, Thailand), and Tawesak Tanwandee (Mahidol University, Bangkok, Thailand).
- The study was supported by a grant from the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD) (U01HD071889) under a cooperative agreement between NICHD, the Centers for Disease Control and Prevention, United States of America, and *Institut de recherche pour le développement*, France.
- Study drugs (tenofovir disoproxil fumarate and matching placebo) were donated by Gilead Sciences Inc., CA, United States of America.