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Tenofovir and Hepatitis B Virus Transmission During Pregnancy
A Randomized Clinical Trial

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IMPORTANCE Standard care for preventing mother-to-child transmission (MTCT) of hepatitis B virus (HBV) in highly viremic mothers consists of maternal antiviral prophylaxis beginning at gestational week 28 combined with an HBV vaccine series and HBV immune globulin (HBIG) at birth. However, HBIG is unavailable in some resource-limited areas.

OBJECTIVE To determine whether initiating tenofovir disoproxil fumarate (TDF) at gestational week 16 combined with HBV vaccinations for infants is noninferior to the standard care of TDF at gestational week 28 combined with HBV vaccinations and HBIG for infants in preventing MTCT in mothers with HBV and high levels of viremia.

DESIGN, SETTING, AND PARTICIPANTS An unblinded, 2-group, randomized, noninferiority clinical trial was conducted in 7 tertiary care hospitals in China. A total of 280 pregnant individuals (who all identified as women) with HBV DNA levels greater than 200 000 IU/mL were enrolled between June 4, 2018, and February 8, 2021. The final follow-up occurred on March 1, 2022.

INTERVENTIONS Pregnant individuals were randomly assigned to receive either TDF starting at gestational week 16 with HBV vaccinations for the infant or TDF starting at gestational week 28 with HBV vaccinations and HBIG administered to the infant.

MAIN OUTCOMES AND MEASURES The primary outcome was the MTCT rate, defined as detectable HBV DNA greater than 20 IU/mL or hepatitis B surface antigen positivity in infants at age 28 weeks. Noninferiority was established if the MTCT rate in the experimental group did not increase by more than an absolute difference of 3% compared with the standard care group, as measured by the upper limit of the 2-sided 90% CI.

RESULTS Among 280 pregnant individuals who enrolled in the trial (mean age, 28 years; mean gestational age at enrollment, 16 weeks), 265 (95%) completed the study. Among all live-born infants, using the last observation carried forward, the MTCT rate was 0.76% (1/131) in the experimental group and 0% (0/142) in the standard care group. In the per-protocol analysis, the MTCT rate was 0% (0/124) in the experimental group and 0% (0/141) in the standard care group. The between-group difference was 0.76% (upper limit of the 2-sided 90% CI, 1.74%) in all live-born infants and 0% (upper limit of the 2-sided 90% CI, 1.43%) in the per-protocol analysis. Both comparisons met the criterion for noninferiority. Rates of congenital defects and malformations were 2.3% (3/131) in the experimental group and 6.3% (9/142) in the standard care group (difference, 4% [2-sided 95% CI, −8.8% to 0.7%]).

CONCLUSIONS AND RELEVANCE Among pregnant women with HBV and high levels of viremia, TDF beginning at gestational week 16 combined with HBV vaccination for infants was noninferior to the standard care of TDF beginning at gestational week 28 combined with HBIG and HBV vaccination for infants. These results support beginning TDF at gestational week 16 combined with infant HBV vaccine to prevent MTCT of HBV in geographic areas where HBIG is not available.

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Visual Abstract

Supplemental content

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Approximately 258 million individuals worldwide were infected with the hepatitis B virus (HBV) in 2022, with most new infections occurring through mother-to-child transmission (MTCT).[1] Preventing MTCT is important for eliminating HBV and reducing complications, such as cirrhosis and hepatocellular carcinoma.[2,3] Current management strategies involve testing pregnant individuals for hepatitis B surface antigen (HBsAg) and providing HBV vaccination with HBV immune globulin (HBIG) to their infants.[4,5] Additionally, tenofovir disoproxil fumarate (TDF) therapy is recommended for individuals with HBV DNA levels exceeding 200 000 IU/mL during late pregnancy.[4-6] However, HBIG is unavailable in most countries, particularly in resource-limited regions,[1,7,8] because of the poor availability of refrigeration and high costs. The limited availability of HBIG presents a challenge to HBV elimination in these countries.[1,9-11]

MTCT rates of HBV were 16% to 25% among infants who received only HBV vaccinations and whose mothers were hepatitis B e-antigen (HBeAg)-positive with a typical viral load of more than 200 000 IU/mL.[5,12,13] However, MTCT rates of 2% or less were documented in infants who received only HBV vaccinations and whose mothers had HBeAg-negative infection with a typical viral load of less than 20 000 IU/mL.[14,15] Therefore, it was hypothesized that initiating TDF treatment at gestational week 16 could achieve a target maternal HBV viral load of less than 20 000 IU/mL at delivery in HBeAg-positive mothers, which is similar to viral load levels in most HBeAg-negative mothers, and that HBV vaccination alone, without HBIG administration to infants, could prevent MTCT of HBV with acceptable efficacy. The current noninferiority randomized clinical trial tested whether longer maternal prophylaxis with TDF, beginning at gestational week 16 (experimental group), combined with infant HBV vaccinations was noninferior to TDF beginning at gestational week 28 (standard care group) combined with HBIG administration at birth and HBV vaccinations for the infant. The noninferiority margin was an absolute difference of 3%.

Key Points

Question In pregnant individuals with hepatitis B virus (HBV) and high viremia, is initiation of tenofovir disoproxil fumarate (TDF) at gestational week 16 combined with HBV vaccinations of infants noninferior to initiation of TDF at week 28 combined with HBV vaccinations and HBV immune globulin (HBIG) in preventing mother-to-child transmission?

Findings Initiating maternal TDF therapy at week 16 combined with HBV vaccinations for infants was noninferior to initiating maternal TDF therapy at week 28 combined with HBIG and HBV vaccinations for infants in preventing mother-to-child transmission of HBV (0.76% [1/131] vs 0% [0/142]).

Meaning TDF therapy at gestational week 16 combined with HBV vaccinations of infants avoided the need for HBIG and was noninferior to standard care for preventing HBV transmission from pregnant women to infants.

Methods

Study Design and Oversight

This noninferiority randomized clinical trial was conducted at 7 tertiary care hospitals in China. The study protocol and statistical analysis plan are available online (Supplement 1) and were approved by the Western Institutional Review Board in the US, as well as the ethics committees of each participating hospital (eAppendix 1 in Supplement 2). All pregnant individuals provided written informed consent. All participants identified as women. The trial was monitored through electronic data capture and site visits by a contract research organization, Tigermed Group. Adverse events were monitored by the ethics committees and an independent data and safety monitoring committee, which had the authority to stop the trial for safety concerns (eAppendices 2 and 3 in Supplement 2). This study was reported using the Consolidated Standards of Reporting Trials guidelines.

Inclusion Criteria

Women aged 20 to 35 years with HBeAg-positive chronic hepatitis B and HBV DNA levels of more than 200 000 IU/mL were enrolled.[16] Exclusion criteria included coinfection with HIV; the presence of hepatitis A, C, D, or E, or sexually transmitted diseases; alanine aminotransferase (ALT) levels greater than 200 U/L; total bilirubin greater than 2 mg/dL; decompensated liver disease or cancer; estimated creatinine clearance of less than 100 mL/min[17]; history of kidney dysfunction or fetal abnormalities in a previous pregnancy; clinical signs of threatened miscarriage; and ultrasonographic evidence of fetal abnormalities.

Randomization

The contract research organization, Tigermed Group, performed randomization in a 1:1 ratio and communicated the allocations to the investigators. Randomization was computer generated using permuted blocks of 6, 8, and 10, with block selection done randomly. This process was stratified by hospitals and maternal HBV DNA levels (>9 $\log_{10}$ vs ≤9 $\log_{10}$ IU/mL).

Interventions

Based on the randomization assignment, mothers received 300 mg of TDF daily (VIREAD, Gilead Sciences) from gestational week 16 (experimental group) or week 28 (standard care group) until delivery. The standard care for mothers with chronic hepatitis B is detailed in eAppendix 4 in Supplement 2. Mothers were assessed at gestational weeks 20, 24, 28, 32, 36, and at delivery, and postpartum weeks 4, 8, 12, 24, and 28. Infants were assessed at birth and at weeks 4, 12, 24, and 28. Medication adherence was monitored through pill counts, with nonadherence defined as taking less than 80% of prescribed pills or self-discontinuation of TDF for more than 14 consecutive days (eAppendix 5 in Supplement 2).

All infants received 10 μg of the HBV vaccine within 12 hours of birth, with additional doses administered at 1 and 6 months. Infants in the standard care group also received 100 IU of HBIG at birth. Infants in the experimental group received HBIG if their mother's HBV DNA levels exceeded 200 000 IU/mL either at delivery or at the last available measurement before delivery. This approach provided additional

protection for infants at higher risk of HBV acquisition due to their mother's high viral load, despite the experimental protocol not typically including HBIG administration for these infants.[16,17] The use of TDF from gestational week 16 was based on World Health Organization (WHO) guidelines for HIV-negative pregnant women at risk of acquiring HIV, which recommend TDF therapy throughout pregnancy and breastfeeding, citing no safety-related concerns for the therapy.[18] Breastfeeding was encouraged in this study.[4]

Primary Outcome

The primary end point was the MTCT rate, determined by the percentage of infants with HBV DNA levels greater than 20 IU/mL or HBsAg positivity at age 28 weeks. The upper limit of the 2-sided 90% CI for the between-group difference in MTCT rates was compared with a prespecified noninferiority margin of 3%. In accordance with the US Food and Drug Administration's (FDA) recommendations for noninferiority studies,[19] the lower limits of the 90% and 95% CIs were not assessed for the primary outcome.

Secondary Outcomes

Secondary outcomes in the statistical analysis plan and protocol were not identical. Secondary and other outcomes reported here are based on the statistical analysis plan. The secondary outcomes included the percentage of mothers with HBV DNA levels less than 200 000 IU/mL at delivery, the frequency of seronegativity or seroconversion of maternal HBeAg at postpartum week 28, the frequency of seronegativity or of maternal HBsAg at postpartum week 28, the incidence of congenital malformations or abnormalities among infants, the occurrence of adverse events, the frequency of postpartum maternal ALT elevation to levels more than 5 times the baseline value or more than 10 times the upper limit of normal (40 U/L), and the tolerability of TDF therapy.

Other End Points of Interest

Other outcomes assessed included the percentage of mothers with HBV DNA levels less than 20 000 IU/mL at delivery (a prespecified outcome in the protocol, but not in the statistical analysis plan), the frequency of mild to moderate adverse events in mothers or infants, the frequency of maternal and fetal complications, changes from baseline in maternal creatinine at postpartum week 28, changes from baseline in maternal ALT levels before delivery and at postpartum week 28, the cumulative incidence of TDF-resistant variations in mothers treated with TDF at postpartum week 28, the proportion of mothers who developed maternal or fetal complications at postpartum week 28, and the proportion of infants who developed complications at age 28 weeks.

Statistical Power Considerations

The enrollment of 280 mothers (140 in each group) was estimated to have a statistical power of 80% (1-sided α of .05) to assess noninferiority,[20-22] based on a 3% noninferiority margin and a 1% expected incidence rate of MTCT in both groups.[23,24] The margin was calculated based on the combined effect size of intention-to-treat (ITT) analysis regarding antiviral effects vs no treatment (or placebo) for preventing MTCT reported in 2 large randomized clinical trials from China,[17,25] which demonstrated a 19-percentage point (2-sided 95% CI, 6%-33%) reduction in MTCT rates with maternal antiviral vs no antiviral therapy. The 3% noninferiority margin retained 50% of the reference regimen's effect (corresponding to the lower limit of the 95% CI, ie, 50% of 6% being 3%), as recommended by the FDA guideline for noninferiority trials.[17,19,25] When assessing the primary outcome, the MTCT rate difference between the 2 groups was calculated using the upper limit of a 2-sided 90% CI,[20-22,26] given that the use of the upper limit of a 2-sided 95% CI with a noninferiority margin of 3% would lead to an unrealistic study sample size.[20-22,26]

Statistical Analyses

For the primary outcome, the upper limit of the 2-sided 90% CI for the between-group difference in MTCT rates was compared with a prespecified noninferiority margin of 3%. The primary end point data were analyzed in each group using both per-protocol analysis (including participants who strictly adhered to the protocol, followed the intervention, and completed the study as originally planned) and ITT analysis, which consisted of all live-born infants regardless of adherence to treatment (as outlined in pages 51-53 of the protocol in Supplement 1). The last observation carried forward (LOCF) approach was used for data imputation in the ITT analysis, applied only to the primary efficacy outcome data to reflect the rationale that the infection status at the last available assessment was the best indicator of the final outcome.

Missing data were excluded from secondary efficacy and safety outcome analyses. All secondary outcomes were analyzed for superiority. Proportions of other end points were presented with 2-sided 95% CIs. All continuous end points were summarized using descriptive statistics, while categorical end points were analyzed using frequencies of events or percentages of participants meeting the end point during the trial. The *t* test and χ^2 test or Fisher exact test were used to compare between-group quantitative and categorical variables, respectively. A 2-sided *P* value <.05 was considered statistically significant for the comparison of secondary or exploratory end points. Due to the lack of adjustment for multiple comparisons, results for secondary outcomes should be considered exploratory. Statistical analyses were performed using SPSS software.

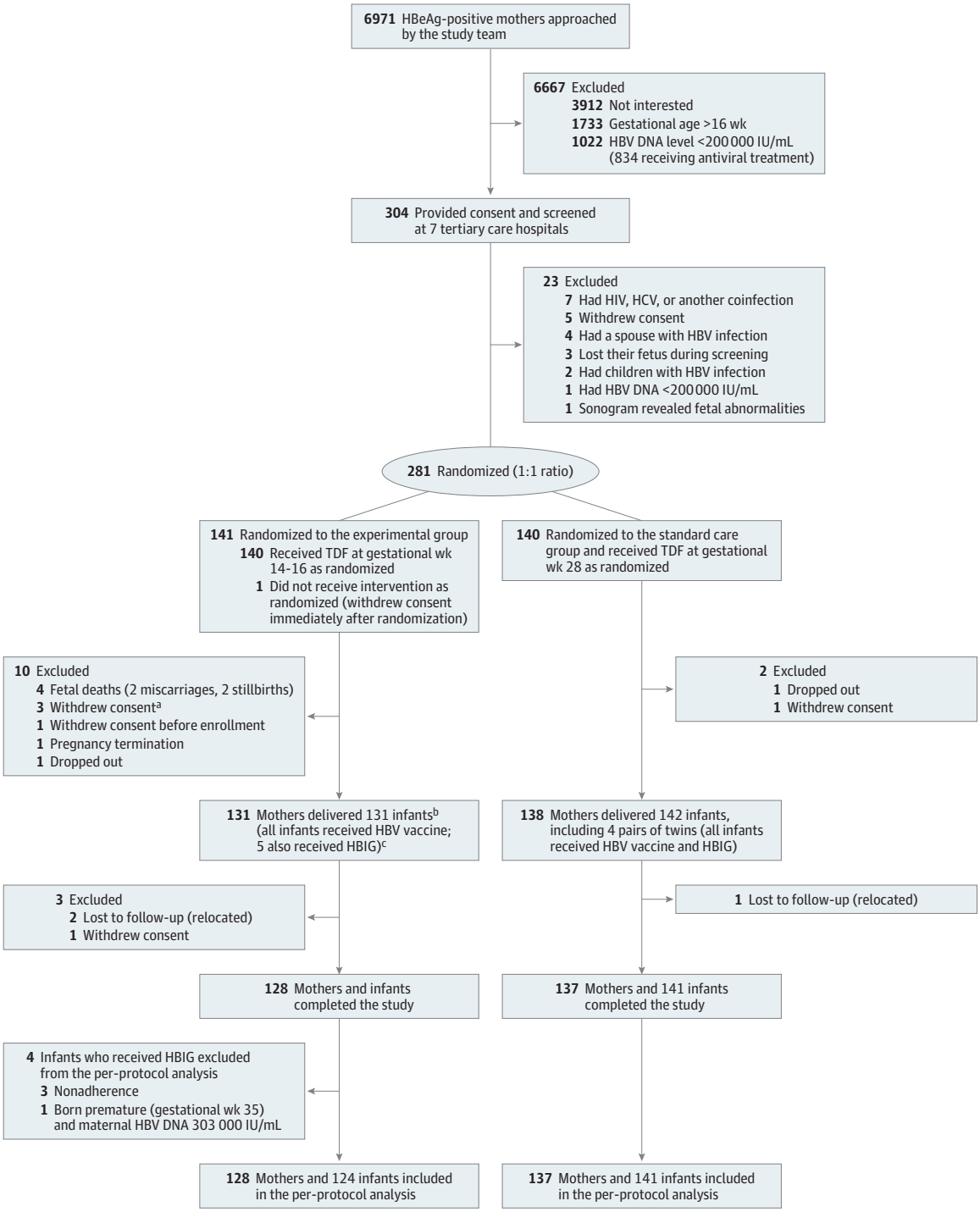
Post Hoc Analyses

In post hoc statistical analyses, the primary outcome measure for the per-protocol analyses and all live-born infants (ITT) was repeated using the upper limit of a 2-sided 95% CI. Additionally, infant data concerning physical growth parameters, bone mineral density, and HBV vaccine response were analyzed.

Results

Of the 304 mothers screened between June 4, 2018, and February 8, 2021, 281 were randomized (**Figure 1**). One mother withdrew consent immediately after randomization, resulting

Figure 1. Flowchart of Patient Enrollment in the Trial



Out of the 281 mothers randomized, 280 were enrolled (1 in the experimental group dropped out before enrollment), resulting in 140 mothers in each group. In the experimental group, 128 mothers with 128 infants completed the study, while in the standard care group, 137 mothers with 141 infants completed the study.

HBeAg indicates hepatitis B e-antigen; HBIG, hepatitis B immune globulin; HBV, hepatitis B virus; HCV, hepatitis C virus; and TDF, tenofovir disoproxil fumarate.

[a]Dropouts and consent withdrawals were mainly due to the COVID-19 pandemic lockdowns and patients changing care facilities.

[b]All mothers in the experimental group had singleton births.

[c]Five infants received HBIG at birth, but only 4 completed the study. All 5 infants who received HBIG were excluded from the per-protocol analysis.

in 280 mothers being enrolled (140 in each group). Participants had a mean (SD) age of 28 (3.1) years and median (IQR) HBV DNA levels of 8.23 (7.98-8.23) $\log_{10}$ IU/mL. Baseline variables for each group are detailed in **Table 1**. Before delivery, 11 mothers were lost to follow-up (9 in the experimental group and 2 in the standard care group). Among these losses, 6 occurred when mothers changed care facilities during the COVID-19 pandemic lockdown, which prevented participants from accessing the research sites. Amniocentesis was not performed for any participants. Among the 273 live births delivered by 269 mothers, 131 were in the experimental group and 142 were in the standard care group. Of these, 265 were singleton births and 8 were twins (all in the standard care group). At age 28 weeks, 269 of 273 infants (98.5%) were available for outcome assessment, including 128 of 131 (97.7%) in the experimental group and 141 of 142 (99%) in the standard care group. Final follow-up occurred on March 1, 2022.

Treatment and Intervention

All mothers received at least 1 dose of TDF after enrollment. The median (IQR) duration of TDF treatment was 162 (155-168) days in the experimental group and 79 (72-84) days in the standard care group ($P < .001$). One mother in the standard care group had a medication possession ratio (the percentage of time when a patient has medication available) of less than 80% (eAppendix 5 in Supplement 2). Changes in maternal HBV DNA, bilirubin, and ALT levels at each visit are detailed in eAppendix 6 in Supplement 2. The median (IQR) time for infants to receive the HBV vaccine after birth was 25 (14-41) minutes. In the standard care group, the at-birth doses of the HBV vaccine and HBIG were administered concurrently. Five infants in the experimental group also received HBIG, including 4 cases of protocol violations, where HBIG was administered by nonresearch staff during the COVID-19 lockdown (3 of these 4 infants completed the study but were excluded from the per-protocol analysis due to these violations). The mothers of these 4 infants had a median HBV DNA level of 893 IU/mL (range, 35-1190) before delivery. The fifth infant received HBIG as a salvage intervention due to premature birth at gestational week 35 and a maternal HBV DNA level of 303 000 IU/mL. Venous blood samples collected from these 5 infants before HBIG administration revealed undetectable HBV DNA levels (<20 IU/mL) and negative HBsAg in 4 infants. One of the 5 infants tested positive for HBsAg but had undetectable HBV DNA and received HBIG at a nonresearch facility. All infants in the per-protocol analysis completed HBV immunization.

Primary Outcome

Among all live-born infants (ITT analysis, n = 273), including 8 infants not analyzed in the per-protocol analysis (7 in the experimental group) (Figure 1), all had undetectable levels of HBV DNA at birth. However, 1 infant in the experimental group with protocol nonadherence tested positive for HBsAg at birth and was classified as a case of HBV infection using the LOCF approach for the analysis of all live-born infants (**Table 2**). This infant was delivered full term at a local hospital due to the unavailability of the research site during the COVID-19 lockdown. The mother took 144 pills of TDF (verified by pill count) over 144 days of therapy (with the last pill taken on the day of delivery) and had HBV DNA levels of 486 000 IU/mL, 4600 IU/mL, 780 IU/mL, 331 IU/mL, and 35 IU/mL at gestational weeks 16, 20, 24, 28, and before delivery, respectively. The remaining 7 infants were HBsAg-negative at birth. Consequently, the MTCT rates were 0.76% (1/131) in the experimental group vs 0% (0/142) in the standard care group. The

Table 1. Baseline Characteristics of Enrolled Mothers and Infants at Birth

Characteristics	Experimental group, No. (%)	Standard care group, No. (%)
Maternal baseline characteristics		
No. of mothers with data	140	140
Age at enrollment, y	28.4 (3.2)	28.0 (3.0)
Gravidity, median, No.	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Maternal height, cm	160.2 (4.8)	160.9 (5.3)
BMI	22.3 (20.3-24.5)	21.9 (20.3-24.1)
Gestational age, wk	16.1 (15.7-16.6)	16.1 (15.9-16.4)
HBeAg titer, S/CO	1353.7 (1209.0-1574.7)	1386.3 (1107.2-1583.3)
HBV DNA, $\log_{10}$ IU/mL	8.2 (8.0-8.2)	8.2 (7.9-8.2)
HBV DNA >9 $\log_{10}$ IU/mL	3/140 (2.1)	1/140 (0.7)
Elevated aminotransferase	15/140 (10.7)	17/140 (12.1)
Creatinine clearance, mL/min/1.73 m^2	155.3 (138.0-177.8)	160.3 (137.6-187.1)
Creatinine clearance within normal range[a]	140/140 (100)	140/140 (100)
Infant characteristics at birth		
No. of infants with data	131	142[b]
Male	59/131 (45.0)	74/142 (52.1)
Female	72/131 (55.0)	68/142 (47.9)
Full-term neonate	124/131 (94.7)	130/142 (91.5)
Body weight, kg	3.3 (3.0-3.5)	3.2 (2.9-3.4)
Small for gestational age	4/131 (3.1)	5/142 (3.5)
Body weight <2500 g	10/131 (7.6)	8/142 (5.6)
Body length, cm	50.0 (49.0-50.0)	50.0 (48.0-50.0)
BMI	13.1 (1.5)	12.9 (1.3)
Head circumference, cm	34.0 (32.0-35.0)	34.0 (32.5-34.0)
Apgar score[c] at 1 min	10 (9-10)	10 (9-10)
Alanine aminotransferase, U/L[d]	9.2 (7.0-14.3)	10.0 (6.4-14.0)
HBsAg positivity at birth	22/131 (16.8)	22/142 (15.5)
HBeAg positivity at birth	121/131 (92.4)	130/142 (91.5)
Detectable HBV DNA at birth[e]	0/131	0/142
Birth dose HBV vaccine time, min	25 (13-42)	26 (15-40)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; S/CO, signal to cutoff.

[a] The normal range for creatinine clearance in females is 88 to 128 mL/min.

[b] Four pairs of twins.

[c] Score assessment on a newborn at 1 minute after birth, which includes appearance (skin color), pulse (heart rate), grimace response (reflexes), activity (muscle tone), and respiration (breathing effort). The scores for each of the 5 criteria (0-2 points) are added together for a total score (7-10, generally normal; 4-6, needs some medical intervention; and 0-3, needs immediate resuscitation).

[d] The upper limit of the normal range for alanine aminotransferase is 40 U/L.

[e] The lowest level of quantitation of HBV DNA is 20 IU/mL. Blood samples at birth were obtained from peripheral veins or arteries.

Table 2. Efficacy Outcome Assessments

HBV infection cases	No./total No. (%) [95% CI][a] Experimental group	Standard care group	Difference in mother-to-child transmission rates, % Upper limit of 90% CI	Upper limit of post hoc 95% CI
Primary outcome (HBV transmission rates in infants aged 28 wk)				
Analysis of all live-born infants (intention-to-treat analysis)[b]	1/131 (0.76)	0/142	0.76 (1.74)	0.76 (2.23)
Per-protocol analysis[c]	0/124	0/141	0 (1.43)[d]	0 (2.15)[d]
			P value	Difference (95% CI), %[e]
Secondary outcomes for mothers				
HBV DNA levels <200 000 IU/mL at delivery	130/131 (99.2) [95.2 to 99.96]	130/138 (94.2) [88.5 to 97.3]	.02[f]	5.00 (0.1 to 10.0)
HBeAg negativity at postpartum week 28	3/140 (2.1) [0.6 to 6.6]	3/140 (2.1) [0.6 to 6.6]	>.99	0 (−3.4 to 3.4)
HBeAg conversion at postpartum week 28	3/140 (2.1) [0.6 to 6.6]	2/140 (1.4) [0.3 to 5.6]	>.99	0.7 (−3.1 to 4.5)
Postpartum ALT >5 × ULN	5/140 (3.6) [1.3 to 8.6]	6/140 (4.3) [1.8 to 9.5]	.76[f]	0.7 (−6.0 to 4.6)
Postpartum ALT >10 × ULN[g]	5/140 (3.6) [1.3 to 8.6]	4/140 (2.9) [0.9 to 7.6]	>.99	0.7 (−4.1 to 5.6)
Other efficacy outcomes for mothers[h]				
HBV DNA levels <20 000 IU/mL at delivery	124/131 (94.7) [88.9 to 97.6]	91/138 (65.9) [57.3 to 73.7]	.001[f]	28.8 (19.2 to 38.3)

Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBIG, HBV immune globulin; HBsAg; hepatitis B surface antigen; HBV, hepatitis B virus; LOCF, last observation carried forward; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

[a] Unless otherwise indicated.

[b] All live-born infants (n = 273) were included in the analysis. This dataset adds 8 infants to the case-completed dataset: 7 from the experimental group (4 received HBIG, 2 were lost to follow-up, and 1 received HBIG before withdrawing from the study 8 weeks after birth) and 1 from the standard care group (dropped out after birth). All 8 infants were HBsAg-negative and had undetectable HBV DNA levels upon testing venous blood at birth before receiving either the HBV vaccine alone or the vaccine plus HBIG, except for 1 infant in the experimental group who was HBsAg-positive at birth without detectable HBV DNA (counted as a case of infection). The LOCF approach was used because newborns who met both criteria of undetectable HBV DNA and negative HBsAg status at birth could be considered noninfected (not having vertical transmission of HBV). Additionally, the missing data assessment indicated that the missing data were completely at random (eAppendix 6 in Supplement 2), further supporting the use of the LOCF approach in all live births (intention-to-treat) analysis.

[c] This case-completed dataset analysis represents the primary outcome analysis, which included all 265 infants who had data at age 28 weeks without protocol nonadherence.

[d] Since the event rates were 0, the Agresti-Caffo method was used to adjust the proportions by adding 1 to both the numerator and denominator for the CI calculation.

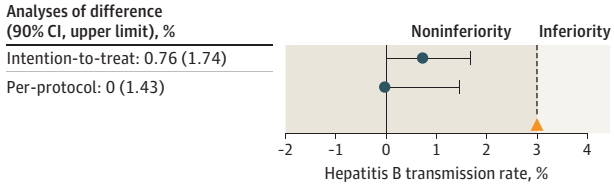
[e] Continuity correction was used when calculating a CI for the difference between the 2 portions.

[f] *P* values were calculated with a χ^2 test.

[g] All mothers (n = 9) exhibited ALT levels of >400 U/L (ULN = 40 U/L) during the first 12 weeks postpartum after TDF cessation at delivery. A detailed assessment of ALT elevation in all mothers is presented in eAppendix 6 in Supplement 2.

[h] This outcome was prespecified in the protocol, but not in the statistical analysis plan.

Figure 2. Assessment of Outcome Difference Between Groups and Noninferiority



The plot illustrates the between-group difference in mother-to child transmission rates and the 2 analyses' upper 1-sided 90% CI. The dashed line indicates the noninferiority margin. The intention-to-treat analysis was based on all live-born infants, including those who withdrew from the study, with missing data imputed using the last observation carried forward approach. The per-protocol analysis was based on the dataset comprising all infants who completed the study at age 28 weeks with protocol adherence. The upper 1-sided 90% CI was used to determine the primary outcome.

difference in MTCT rates between the 2 groups of all live-born infants in the ITT analysis was 0.76%, with an upper limit of the 2-sided 90% CI of 1.74%, which fell within the 3% noninferiority margin.

The per-protocol analysis was conducted in 265 of 273 infants (97.1% of live births). MTCT rates were 0% in the experimental group and 0% in the standard care group, with the upper limits of the 95% CI being 2.93% and 2.58%, respectively. The between-group difference in MTCT rates was 0%, with an upper limit of the 2-sided 90% CI of 1.43%, which is within the 3% noninferiority margin (**Figure 2**).

Secondary Outcomes

Maternal characteristics at delivery are detailed in eAppendix 7 in Supplement 2. A statistically significantly higher percentage of mothers in the experimental group achieved HBV DNA levels of less than 200 000 IU/mL (99.2% vs 94.2%; difference, 5% [2-sided 95% CI, 0.1%-10.0%]; *P* = .02) compared with the standard care group (Table 2). At the 28-week follow-up, no significant differences were observed between the experimental and standard care groups in the following outcomes: maternal prevalence of HBeAg negativity (2.1% vs 2.1%; difference, 0% [2-sided 95% CI, −3.4% to 3.4%]; *P* > .99), HBeAg seroconversion (2.1% vs 1.4%; difference, 0.7% [2-sided 95% CI, −3.1% to 4.5%]; *P* > .99), postpartum

ALT levels more than 5 times the upper limit of normal (3.6% vs 4.3%; difference, 0.7% [2-sided 95% CI, −6.0% to 4.6%]; *P* = .76), postpartum ALT levels more than 10 times the upper limit of normal (3.6% vs 2.9%; difference, 0.7% [2-sided 95% CI, −4.1% to 5.6%]; *P* > .99), and rates of congenital defects or abnormalities in newborns were 2.3% (3/131) in the experimental group and 6.3% (9/142) in the standard care group (difference, 4% [2-sided 95% CI, −8.8% to 0.7%]).

Post Hoc Efficacy Outcomes

The analysis of all live-born infants (ITT) and the per-protocol analysis for the primary outcome were reevaluated using the upper limits of 2-sided 95% CIs. The findings (ITT, 2.23%; per-protocol, 2.15%) were qualitatively similar to those based on the upper limit of the 2-sided 90% CI (ITT, 1.74%; per-protocol, 1.43%). All results remained within the 3% noninferiority margin (Table 2).

Other Outcome of Interest

A statistically significantly higher percentage of mothers in the experimental group achieved HBV DNA levels of less than 20 000 IU/mL (Table 2) (eAppendix 8 in Supplement 2), compared with the standard care group (94.7% vs 65.9%; difference, 28% [2-sided 95% CI, 19.2%-38.3%]; *P* = .001).

Safety Assessments

Maternal TDF therapy was generally well-tolerated, with only 1 mother (0.36%) discontinuing TDF due to nausea. The 3 most common adverse events in the entire cohort (stratified by the experimental group vs the standard care group) were maternal ALT elevation at 25% (23.6% vs 26.4%), upper respiratory infection at 14.6% (11.4% vs 17.8%), and vomiting at 12.9% (16.4% vs 9.3%). In the experimental group, there was 1 pregnancy termination (tetralogy of Fallot) and 4 fetal losses, including 1 miscarriage and 3 stillbirths (**Table 3**) (eAppendix 9 in Supplement 2). These outcomes were determined to be unrelated to TDF therapy, except for 1 case, which was deemed inconclusive. The other losses were attributed to abdominal trauma, an abnormal karyotype, and chorioamnionitis.

Among 9 mothers with severe ALT flares (>400 U/L) following postpartum TDF cessation as per protocol, 3 resolved spontaneously, while 6 restarted TDF with improvement (eAppendix 10 in Supplement 2). Creatinine clearance decreased in 0.71% (1/140) of mothers in the experimental group (to 47.0 mL/min) but normalized within 4 weeks without intervention. The frequency and severity of pregnancy or obstetric complications were similar between the experimental and standard care groups (5% vs 7%; difference, 2% [2-sided 95% CI, −7.7% to 3.5%]). Among live-born infants, the rates of grade III or IV adverse events were similar between groups (Table 3). Grade I or II events in infants are detailed in eAppendix 9 in Supplement 2.

Post Hoc Safety Outcomes

Physical growth parameters, bone mineral density, and HBV vaccine responses were comparable between the 2 infant groups (eAppendix 11 in Supplement 2).

Discussion

In this noninferiority randomized clinical trial, in which all infants received HBV vaccinations at birth, 1 month, and 6 months, MTCT rates at 28 weeks were 0% for infants born to women who received TDF at gestational week 16, compared with 0% for those born to women who received TDF at gestational week 28 combined with HBIG at birth, according to the prespecified primary per-protocol analysis. In the ITT analysis, MTCT rates at 28 weeks were 0.76% among all live-born infants whose mothers received TDF at gestational week 16, compared with 0% among those whose mothers received TDF at gestational week 28 combined with HBIG at birth. The upper limits of the 2-sided 90% CI for the between-group difference in MTCT rates were 1.43% in the primary per-protocol analysis and 1.74% in the ITT analysis, both within the predefined 3% noninferiority margin. The simplicity of this new regimen and the lack of requirement for HBIG at birth may improve the prevention of MTCT of HBV, particularly in resource-limited settings.

The optimal duration of maternal TDF therapy to minimize the use of HBIG in infants is still unclear. Segeral et al studied the initiation of TDF therapy at gestational week 24 in mothers with high levels of HBV viremia and found that 1.5% (4/271) of infants developed chronic hepatitis B.[11] The authors hypothesized that the short duration of TDF treatment may have contributed to HBV infection in infants. Additionally, a short-duration TDF regimen might be inadequate for controlling viremia, especially given the current global preterm birth rate of 11% to 13% (<37 weeks of pregnancy).[27,28] According to a viral kinetic study in women of childbearing age with high levels of HBV viremia, a 24-week course of TDF therapy significantly increased the frequency of achieving HBV DNA levels of less than 200 000 IU/mL or less than 20 000 IU/mL compared with a 12- to 14-week course of TDF treatment.[29]

In this trial, the viremia levels at delivery in mothers who initiated TDF at gestational week 16 were comparable to those observed in HBeAg-negative mothers from previous studies that used only the HBV vaccine for infants, without HBIG, for preventing MTCT.[12,14] These prior trials reported infection rates of less than 2% in infants and suggested omitting HBIG for infants born to HBeAg-negative mothers.[12-15] In the current study, 1 infant born to a mother with an HBV DNA level of 35 IU/mL at delivery tested positive for HBsAg at birth but was lost to follow-up and classified as having HBV infection. Given the undetectable HBV DNA at birth, the likelihood of this infant developing chronic HBV infection was probably below 20%.[30] HBsAg detected at birth is often of maternal origin and typically decreases within 6 months.[30] Pan et al found that none of the newborns (n = 94) with undetectable HBV DNA levels at birth developed chronic hepatitis B at 28 weeks, despite 6% (n = 6) of these infants being HBsAg-positive at birth.[17]

A global registry reported a birth defect rate in women who received TDF during pregnancy that was comparable to the general population: 2.6% (95% CI, 2.0%-3.4%) vs 2.7% (95% CI, 2.68%-2.76%), respectively.[31] Because the WHO 2024 guidelines recommend TDF prophylaxis for all HBsAg-positive

Table 3. Safety Data Including Major Grade III to IV Events Occurring in Mothers or Infants[a]

	Events, No. (%) [95% CI]		Risk difference (95% CI), %[b]
	Experimental group	Standard care group	
Major events regarding fetal safety	140	144	
Stillbirth	3 (2.1) [0.6 to 6.6]	0 [0 to 3.2]	2.1 (−1.0 to 5.2)
Miscarriage	1 (0.7) [0 to 4.5]	0 [0 to 3.2]	0.7 (−1.4 to 2.8)
Pregnancy termination due to fetal abnormality	1 (0.7) [0 to 4.5]	0 [0 to 3.2]	0.7 (−1.4 to 2.8)
Fetal growth restriction[c]	2 (1.4) [0.3 to 5.6]	0 [0 to 3.2]	1.4 (−1.2 to 4.1)
Preterm birth	7 (5.0) [2.2 to 10.4]	11 (7.6) [4.1 to 13.6]	2.6 (−9.0 to 3.7)
SGA	4 (2.9) [0.9 to 7.6]	5 (3.5) [1.3 to 8.3]	0.6 (−5.3 to 4.1)
Birth weight <2500 g	10 (7.1) [3.7 to 13.1]	8 (5.6) [2.6 to 11.0]	1.6 (−4.8 to 8.0)
Congenital defects/abnormalities among live-born infants[b]	131	142	
Duodenal obstruction	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Cutaneous hemangioma	0 [0 to 3.6]	2 (1.4) [0.2 to 5.5]	1.4 (−4.1 to 1.3)
Muscle atonia	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Ureterectasia	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Renal atrophy	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Café au lait spots	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Turner syndrome	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Congenital auricular deformity	1 (0.8) [0 to 4.8]	1 (0.7) [0 to 4.4]	0.1 (−2.0 to 2.2)
Corpus callosum hypoplasia	1 (0.8) [0 to 4.8]	0 [0 to 3.3]	0.8 (−1.5 to 3.0)
Renal pelvicalyceal separation	1 (1.8) [0 to 4.8]	0 [0 to 3.3]	0.8 (−1.5 to 3.0)
Maternal adverse events, grades III-IV	140	140	
Premature rupture of membranes	2 (1.4) [0.3 to 5.6]	0 [0 to 3.3]	1.4 (−1.3 to 4.1)
Threatened preterm labor	2 (1.4) [0.3 to 5.6]	2 (1.4) [0.3 to 5.6]	0 (−2.8 to 2.8)
Intrahepatic cholestasis of pregnancy	1 (0.7) [0 to 4.5]	1 (0.7) [0 to 4.5]	0 (−2.0 to 2.0)
Fetal distress syndrome	1 (0.7) [0 to 4.5]	0 [0 to 3.3]	0.7 (−1.4 to 2.8)
Threatened abortion	1 (0.7) [0 to 4.5]	0 [0 to 3.3]	0.7 (−1.4 to 2.8)
ALT >5 times the ULN before or at delivery[d]	1 (0.7) [0 to 4.5]	0 [0 to 3.3]	0.7 (−1.4 to 2.8)
Adverse events for infants, grades III-IV	131	142	
Pathologic jaundice	1 (0.8) [0 to 4.8]	0 [0 to 3.3]	0.8 (−1.5 to 3.0)
Severe oral ulcers	1 (0.8) [0 to 4.8]	0 [0 to 3.3]	0.8 (−1.5 to 3.0)
Apnea	1 (0.8) [0 to 4.8]	0 [0 to 3.3]	0.8 (−1.5 to 3.0)
Transient tachypnea of the newborn	1 (0.8) [0 to 4.8]	1 (0.7) [0 to 4.4]	0.1 (−2.0 to 2.1)
Pneumonia/bronchopneumonia	1 (0.8) [0 to 4.8]	1 (0.7) [0 to 4.4]	0.1 (−2.0 to 2.1)
Bronchitis	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Neonatal hyperbilirubinemia	3 (2.3) [0.6 to 7.1]	1 (0.7) [0 to 4.4]	1.6 (−2.1 to 5.2)
Newborn respiratory distress syndrome	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Nasal obstruction with vomiting	0 [0 to 3.6]	1 (0.7) [0 to 4.4]	0.7 (−2.8 to 1.4)
Prolonged hospitalization due to preterm birth/SGA/ lower body weight	5 (3.8) [1.4 to 9.1]	6 (4.2) [1.7 to 9.4]	0.4 (−5.5 to 4.7)

Abbreviations: ALT, alanine aminotransferase; SGA, small for gestational age; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

[a] For a more comprehensive report on safety data, including grades I-II adverse events for both mothers and infants, refer to eAppendix 9 in Supplement 2.

[b] The difference in proportion was analyzed with continuity correction.

[c] The fetal growth restriction may be due to a single umbilical artery occurring in the same case.

[d] ULN for ALT = 40 U/L. One patient undergoing TDF treatment in the experimental group had an ALT level of 434 U/L at gestational week 28 after receiving a diagnosis of intrahepatic cholestasis at gestational week 24.

mothers during pregnancy when HBeAg or HBV DNA testing is unavailable, initiating TDF at gestational week 16 or earlier may be appropriate to control viremia and simplify infant immunoprophylaxis with an HBV vaccination–only regimen in resource-limited areas. A 2024 meta-analysis of 27 studies (5 randomized clinical trials and 22 cohort studies) involving 2588 highly viremic mothers receiving TDF to prevent MTCT found that cessation of TDF immediately after delivery was safe for mothers who did not have postpartum indications for continued HBV treatment.[32]

Limitations

This study has several limitations. First, the primary outcome was based on a relatively short-term follow-up period. Second, the results from this Chinese population may not be generalizable to other populations. Third, the clinical trial was unblinded. Fourth, the use of a 2-sided 90% CI for interpreting noninferiority is wide, potentially making it less definitive. Fifth, some participants in the intervention group received HBIG, which may have biased the study toward a finding of noninferiority.

Conclusions

Among pregnant women with HBV and high levels of viremia, initiating TDF at gestational week 16 combined with HBV vaccination for infants was noninferior to the standard care of TDF at gestational week 28 with both HBV vaccination and HBIG for infants. These results support starting TDF at gestational week 16 combined with infant HBV vaccination to prevent MTCT HBV transmission in regions where HBIG is not available.

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