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Immediate postpartum cessation of tenofovir did not increase risk of virological or clinical relapse in highly viremic pregnant mothers with chronic hepatitis B infection

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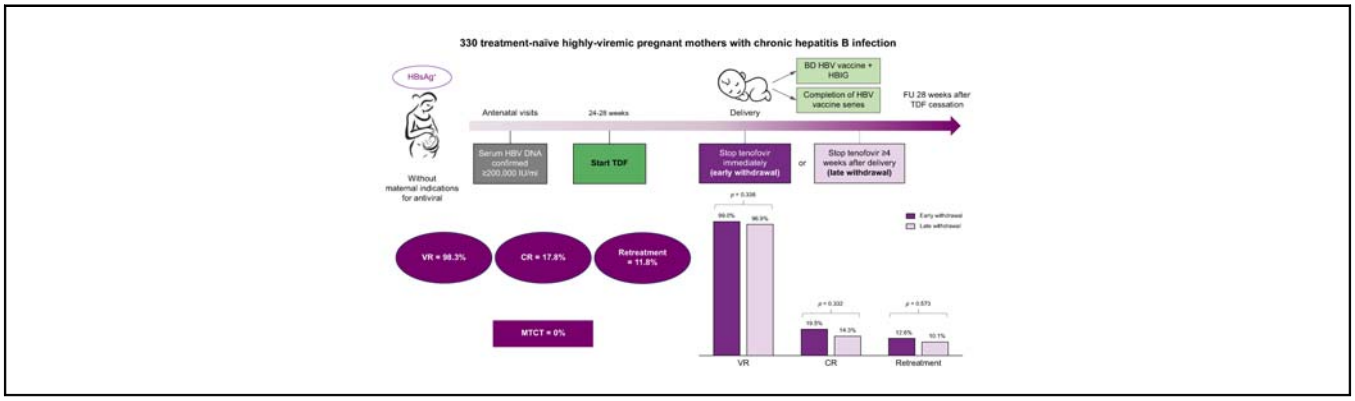
Graphical abstract



Highlights

- The optimal time to stop peripartum antiviral prophylaxis with tenofovir after delivery is unknown.
- Stopping tenofovir immediately at delivery did not increase risk of virological relapse, clinical relapse, or retreatment.
- Transmission of HBV from the mother to the baby was observed in 0% of infants.
- Shortening the duration of tenofovir peripartum prophylaxis from 12 weeks to immediately after delivery can be considered.

Impact and Implications

In pregnant mothers with chronic hepatitis B infection who are started on peripartum tenofovir to prevent mother-to-child-transmission (MTCT), the optimal timing for antiviral withdrawal during the postpartum period remains unknown. This prospective study demonstrates that stopping tenofovir immediately at delivery, compared with longer treatment duration of tenofovir, did not lead to an increased risk of virological relapse, retreatment, or transmission of the virus to the baby. Shortening the duration of peripartum antiviral prophylaxis from 12 weeks to immediately after delivery can be considered. The immediate withdrawal of peripartum tenofovir, combined with standard neonatal immunization schemes, is 100% effective in preventing MTCT among pregnant mothers with CHB who are highly viremic, with a high rate of vaccine response in infants.

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Research article

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Immediate postpartum cessation of tenofovir did not increase risk of virological or clinical relapse in highly viremic pregnant mothers with chronic hepatitis B infection

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Background & Aims: Peripartum prophylaxis (PP) with tenofovir disoproxil fumarate (TDF) is the standard of care to prevent mother-to-child transmission of chronic hepatitis B (CHB) infection in mothers who are highly viremic. We investigated the maternal and infant outcomes in a large Chinese cohort of TDF-treated CHB pregnant participants.

Methods: In this prospective study, treatment-naive mothers with CHB and highly viremic (HBV DNA ≥200,000 IU/ml) but without cirrhosis were treated with TDF at 24–28 weeks of pregnancy. In accordance with Chinese CHB guidelines, TDF was stopped at delivery or ≥4 weeks postpartum. Serum HBV DNA and alanine aminotransferase were monitored every 6–8 weeks to determine virological relapse (VR). Infants received standard neonatal immunization, and HBV serology was checked at 7–12 months of age.

Results: Among 330 participants recruited (median age 30, 82.7% HBeAg+, median HBV DNA 7.82 log IU/ml), TDF was stopped at delivery in 66.4% and at ≥4 weeks in 33.6%. VR was observed in 98.3%, among which 11.6% were retreated with TDF. Timing of TDF cessation did not alter the risk of VR (99.0 *vs.* 96.9%), clinical relapse (19.5 *vs.* 14.3%), or retreatment (12.6 *vs.* 10.1%) (all $p > 0.05$). A similar proportion of patients developed alanine aminotransferase flare five times (1.1 *vs.* 2.1%; $p = 0.464$) and 10 times (0.5 *vs.* 0%; $p = 0.669$) above the upper limit of normal (ULN) in the early withdrawal and late withdrawal groups, respectively. No infants developed HBsAg-positivity.

Conclusions: PP-TDF and neonatal immunization were highly effective in preventing mother-to-child transmission of HBV in mothers who are highly viremic. Timing of cessation of PP-TDF did not affect the risk of VR or retreatment.

Impact and Implications: In pregnant mothers with chronic hepatitis B infection who are started on peripartum tenofovir to prevent mother-to-child-transmission (MTCT), the optimal timing for antiviral withdrawal during the postpartum period remains unknown. This prospective study demonstrates that stopping tenofovir immediately at delivery, compared with longer treatment duration of tenofovir, did not lead to an increased risk of virological relapse, retreatment, or transmission of the virus to the baby. Shortening the duration of peripartum antiviral prophylaxis from 12 weeks to immediately after delivery can be considered. The immediate withdrawal of peripartum tenofovir, combined with standard neonatal immunization schemes, is 100% effective in preventing MTCT among pregnant mothers with CHB who are highly viremic, with a high rate of vaccine response in infants.

Introduction

HBV infection is one of the most important public health problems globally, affecting 316 million people (4.1%) and accounting for 0.5 million deaths from cirrhosis, liver failure, and hepatocellular carcinoma in the year 2019.[1] Mother-to-child transmission (MTCT) is a major route of acquiring HBV in regions of high HBV prevalence. Peripartum prophylaxis (PP) with tenofovir disoproxil fumarate (TDF) is currently the standard of care to reduce the risk of MTCT among pregnant mothers who are highly viremic, defined as having serum HBV DNA >200,000 IU/ml, in addition to neonatal immunization with birth-dose HBV vaccine with or without HBV immunoglobulins (HBIG).[2–4] PP-TDF should be initiated at 24–28 weeks of gestation and continued throughout pregnancy until after delivery. For pregnant HBV carriers who are started on PP-TDF solely for the purpose of preventing MTCT (*i.e.* without maternal

Keywords: HBV; TDF; Mother-to-child transmission; MTCT; Pregnancy; Vaccination.
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indications for HBV treatment), the recommended duration of PP-TDF is not well defined and is heterogeneous across different guidelines.[2–4] The EASL guideline recommends that PP-TDF be stopped at delivery or within the first 3 months after delivery.[3] In comparison, the AASLD guideline[4] and The Asian Pacific Association for the Study of the Liver guideline[5] recommends that PP-TDF be stopped at the time of delivery or up to 4–12 weeks postpartum.

The uncertainty regarding the duration of PP-TDF originates from the potential increased risk of postpartum biochemical flare, which has been well described in the natural history of untreated HBV carriers after delivery in up to 10% within 3 months of delivery.[6,7] Postpartum flares are mostly mild, asymptomatic, and self-limiting, but severe cases requiring liver transplantation have been reported.[8] The underlying mechanisms for postpartum flare are not clear. It is generally believed that pregnancy is a state of immunological tolerance to paternally derived fetal antigens, which reverses once the fetus is delivered.[9] Among antiviral-treated pregnant HBV carriers, biochemical flares could develop during pregnancy (10.9%), although the majority occurred in the postpartum period (45.7%).[10] After cessation of PP-TDF, HBV DNA levels rebounded in virtually all patients, but not all patients would develop biochemical flare (73%) and not all required retreatment (21%).[8]

In view of the scarcity of data on the optimal timing of antiviral withdrawal during the postpartum period, we designed this prospective study to evaluate the maternal and infant outcomes comparing early withdrawal (*i.e.* right after delivery) and late withdrawal (*i.e.* ≥4 weeks after delivery) of PP-TDF among pregnant mothers who are highly viremic with HBV. We assessed maternal outcomes, including risk of virological relapse (VR), clinical relapse (CR), and retreatment with antiviral therapy. We also assessed infant outcomes, including the effectiveness of neonatal immunization plus PP-TDF in the prevention of MTCT, as well as factors associated with vaccine response.

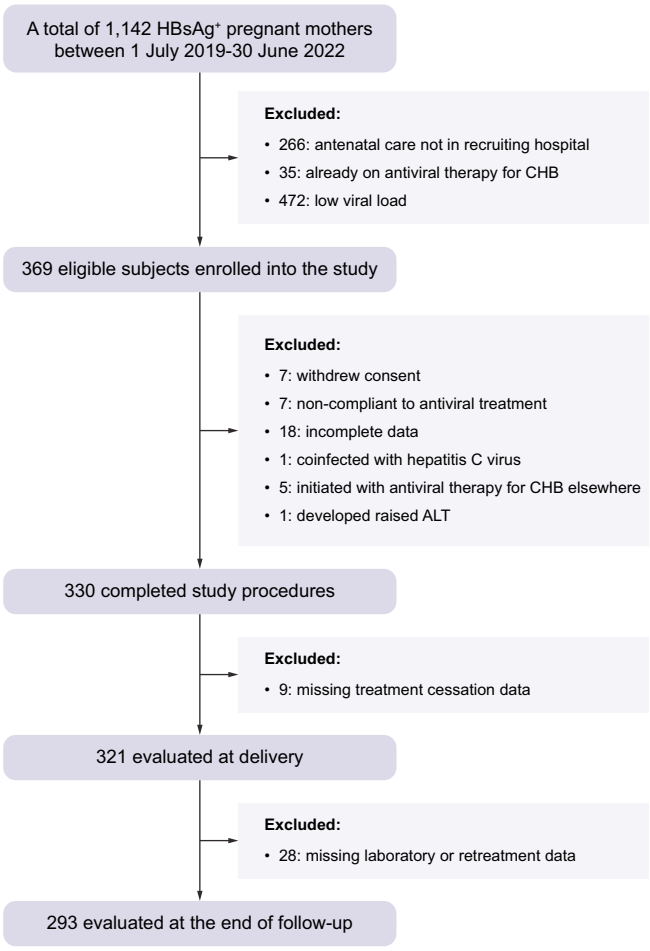

Fig. 1. Patient disposition. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBsAg+, hepatitis B surface antigen positive.

Patients and methods

Patients

This project is a single-center, interdisciplinary clinical study registered on http://www.chictr.org.cn/ (reference number ChiCTR1900027871) involving the clinical units of Hepatology, Obstetrics, and Pediatrics in a tertiary hospital in Shenzhen, China, that provides care for >6,000 pregnant mothers every year. The estimated prevalence of HBV carriers among pregnant mothers under the care of our center is 6.04%. The annual birth rate between 2019 and 2022 in Shenzhen is 13.5–21.6 births per 1,000 persons, which is higher than that of Guangdong province (8–12 per 1,000 persons) and China (6–10 per 1,000 persons).[11] Between July 2019 and June 2022, during the period when China's COVID-19 social distancing restrictions were in place for the majority of the time, we screened all consecutive mothers receiving antenatal care at the recruiting hospital by conducting antenatal blood tests (within 3 months of confirmed pregnancy) for HBsAg, among other tests. For pregnant mothers who were known CHB carriers, only treatment-naive participants were involved in this pathway, whereas those already on antiviral therapy were managed according to usual practice. Fig. 1 depicts the patient disposition.

Pregnant mothers with HBsAg positivity underwent additional assessments such as serum HBV DNA, HBeAg, liver function tests, renal function tests, and transient elastography at 22–26 weeks of gestation. PP-TDF was administered to pregnant women with high HBV DNA levels, defined as >200,000 IU/ml, at 24–28 weeks of gestation to prevent MTCT.[12] After initiation of PP-TDF, participants had blood tests every 4 weeks until delivery to monitor HBV DNA, liver, and renal function tests. HBeAg was also repeated at delivery. Participants continued PP-TDF until delivery, which was either stopped immediately after delivery (early withdrawal) or ≥4 weeks after delivery (late withdrawal) based on patients' preference, rather than through randomization to facilitate recruitment during the COVID-19 restrictions that were in place at that time. Blood tests were monitored every 6–8 weeks until 28 weeks after cessation of PP-TDF to assess maternal outcomes. The mode of delivery (vaginal or Cesarean section), gravidity, parity, and adverse events from PP-TDF were recorded.

Exclusion criteria were as follows: coinfection with HCV or HIV, history of recurrent miscarriage, history of congenital anomalies in previous livebirths, recent pregnancy treated with PP-TDF and <6 months from current episode, renal impairment, hepatocellular carcinoma, advanced fibrosis or cirrhosis, deranged liver function, paternal HBsAg positivity, and concurrent medications including nephrotoxic agents, immunosuppressive therapy, and cytotoxic therapy. All participants provided written informed consent. The study protocol conforms to the

ethical principles in the Declaration of Helsinki and was approved by the Institutional Review Board of The University of Hong Kong – Shenzhen Hospital (reference number: 201801).

Infant management and monitoring

Upon delivery, infants were assessed using the APGAR score, following standard care protocols. Low birth weight was defined as below 2.5 kg, and preterm birth was defined as birth before 37 weeks of gestation. All infants were given standard neonatal immunization, including HBV vaccine (10 μg of recombinant hepatitis B vaccine, *Hansenula polymorpha*, produced by AIM Vaccine Co. Ltd, Beijing, China) within 12 h of birth, at 1 month, and at 6 months. In addition, they were administered HBIG (100 IU of human hepatitis B immunoglobulin, produced by Shenzhen Weiguang Biological Products Co., Ltd, Shenzhen, China). Serum HBsAg, antibody to HBcAg (anti-HBc), and antibody to HBsAg (anti-HBs) were checked at 7–12 months of age.[12]

Serological tests and viral biomarkers

Serum qualitative HBsAg was assessed using ELISA, with an optical density of 0.105 S/CO (positive for ≥0.105 S/CO and negative for <0.105/CO). Serum HBV DNA was measured using real-time PCR (Sansure Biotech Inc. Changsha, Hunan Province, China) with a lower limit of detection (LLOD) of 100 IU/ml. This assay was chosen by the vast majority of pregnant mothers because it was reimbursable. Anti-HBs was measured using ELISA, with an LLOD of 10 IU/L and a linear range of 10–1,000 IU/L. The LLOD of anti-HBc was expressed as 1S/CO (positive for ≥1S/CO and negative for <1S/CO).

Definition of outcomes

For maternal outcomes, VR was defined as HBV DNA >1 log increase following treatment cessation. For participants achieving undetectable HBV DNA, VR was defined as detectable HBV DNA. Clinical relapse (CR) was defined as VR accompanied by a rise in serum alanine aminotransferase (ALT) of more than two times the ULN, where ULN was defined as 40 U/L, at any time point after cessation of PP-TDF. The maximum degree of elevation of ALT relative to baseline ALT and the times above ULN were analyzed. Retreatment with TDF was recommended for participants with CR.

For infant outcomes, MTCT was defined as infant seropositivity for HBsAg >6 months after birth. Vaccine response was defined as infant anti-HBs levels >10 IU/L at >6 months after birth, and strong vaccine response was defined as infant anti-HBs levels >1,000 IU/L. Exposure to HBV was defined as the presence of infant anti-HBc positivity.

The primary outcome of the study was to compare the risks of VR between participants with early withdrawal and late withdrawal of PP-TDF. The secondary outcomes were the risks of CR, retreatment, infant vaccine response, and exposure to HBV. For the sample size calculation of noninferiority between early and delayed withdrawal, we conservatively assumed that the risk of CR was 28% postpartum.[13] With an alpha risk of 0.05, a power of 80%, and a noninferiority margin of 0.15 with the two patient arms recruited in a 2:1 ratio, we needed to recruit 252 patients. Assuming a 20% dropout rate, we aimed to recruit at least 312 patients.

Statistical analysis

Continuous variables were expressed as mean (SD) or median (IQR), as appropriate. Statistical comparisons for continuous variables were conducted with independent-samples *t* test or one-way ANOVA for data with normal distribution or the Mann–Whitney *U* test or the Kruskal–Wallis test for data with non-parametric distribution. Categorical variables, expressed as proportions, were compared using the Chi-square test and Fisher's exact test, as appropriate. Correlations were assessed using Spearman's correlation coefficient. To determine whether relevant factors were independently associated with maternal or infant outcomes, variables with p <0.05 in univariate analyses were entered into multivariate analysis performed by binary logistic regression, with odds ratio (OR) and 95% CIs calculated. A two-tailed p value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences version 27 (SPSS Inc, Chicago, IL, USA).

Results

Participant characteristics

A total of 330 eligible participants were enrolled and started on PP-TDF (*i.e.* baseline) at a median age of 30 (IQR 28–32) years at the 26th (IQR 24–28) week of gestation. Moreover, 66.2% of women experienced their first parity. The majority (82.7%) were HBeAg positive, and the median HBV DNA at baseline was 7.82 (IQR 6.91–8.20) log IU/ml. All enrolled participants had normal ALT (median 17 U/L) and had no cirrhosis, as defined by liver stiffness ≤12 kPa (Table 1). Age showed a weak negative correlation with baseline HBV DNA (r = −0.271, p < 0.001).

At the time of delivery, the median serum HBV DNA was 3.59 (IQR 2.73–4.50) log IU/ml, with a median log reduction of 4.1 (IQR 3.3–4.6). HBeAg seroconversion was observed in 2.8% patients, with no patients undergoing HBsAg seroconversion. Furthermore, 5.9% remained highly viremic, whereas undetectable HBV DNA was achieved in 10.4% (Table 1). Regarding the mode of delivery, 240 (74.8%) underwent vaginal delivery, and 81 (25.2%) underwent Cesarean section.

PP-TDF was stopped right after delivery (*i.e.* early withdrawal) in 213 participants (66.4%). For the remaining 108 participants (33.6%) with late withdrawal of PP-TDF, four (1.2%), two (0.6%), and 102 (31.8%) stopped PP-TDF at 4, 8, and 12 weeks postpartum, respectively. Apart from the earlier initiation of PP-TDF among the late withdrawal group, there were no significant differences observed when comparing with the early withdrawal group (Table 1).

Treatment cessation information was missing in nine participants, and they were excluded from subsequent analysis.

Maternal outcomes

After excluding patients with missing laboratory data or retreatment information, 293 participants were included in the outcome analysis. VR and CR were observed in 288 (98.3%) and 52 (17.7%), respectively. The detailed clinical information of the five participants who did not develop VR is shown in Table S1. The maximal postpartum ALT elevation was at a median of 1.6 (IQR 1.1–2.3) times above baseline, with 15.7%, 8%, and 8.4% experiencing two to three times, three to five times, and more than five times above baseline, respectively. When evaluated against the ULN, 5.6%, 2.1%, and 1.7% experienced elevations of two to three times, three to five times, and more than five times above the ULN, respectively, with only one participant (0.3%) experiencing ALT >10 times above the ULN. A total of 34 participants (11.6%) were retreated with TDF at a median interval of

Table 1. Clinical characteristics of included pregnant mothers who were highly viremic with chronic hepatitis B infection.

Parameter	All (N = 330)	Early withdrawal (n = 213)	Late withdrawal (n = 108)	*p* value
At recruitment				
Age	30 (28–32)	30 (28–32)	30 (28.2–32.7)	0.821
Gestational week at which PP-TDF was started	26 (24–28)	27 (24–28)	25 (24–27)	0.005
First parity	215/325 (66.2%)	139/212 (65.6%)	75/108 (69.4%)	0.531
HBeAg-positive (%)	273/330 (82.7%)	173/213 (81.2%)	91/108 (84.3%)	0.540
HBV DNA (log_{10} IU/ml)	7.82 (6.91–8.20)	7.78 (6.79–8.14)	7.82 (7.12–8.27)	0.184
ALT (U/L)	17 (13–24)	17 (13–24)	17 (13–23)	0.785
Creatinine (μmol/L)	46 (43–51)	46 (42–50)	47 (43–51)	0.525
FIB-4	0.63 (0.52–0.78)	0.64 (0.52–0.79)	0.63 (0.52–0.81)	0.876
Liver stiffness (kPa)*	5.3 (4.5–6.3)	5.4 (4.6–6.4)	5.0 (4.4–6.3)	0.495
Gestational diabetes	41/269 (15.2%)	20/172 (11.6%)	18/90 (20%)	0.095
Maternal BMI (kg/m^2)	25.0 (23.1–26.8)	25.0 (23.3–27.0)	25.0 (23.1–26.7)	0.749
Gestational hypertension	4/301 (1.3%)	1/193 (0.5%)	3/100 (3.0%)	0.117
Dyslipidemia	79/116 (68.1%)	45/72 (62.5%)	33/42 (78.6%)	0.096
HKU-SZH being the source of antenatal referral	300/330 (90.9%)	189/213 (88.7%)	102/108 (94.4%)	0.108
Originated from Guangdong province	165/329 (50.2%)	111/213 (52.1%)	50/107 (46.7%)	0.407
Working class	221/294 (75.2%)	142/187 (75.9%)	73/99 (73.7%)	0.774
At the time of delivery†				
HBeAg-positive (%)	252/308 (81.8%)	166/204 (81.4%)	86/104 (82.7%)	0.876
HBV DNA (log_{10} IU/ml)	3.59 (2.73–4.50)	3.69 (2.77–4.49)	3.54 (2.66–4.51)	0.562
Still highly-viremic‡	16/270 (5.9%)	11/176 (6.3%)	5/94 (5.3%)	1.000
Undetectable DNA§	28/270 (10.4%)	16/176 (9.1%)	12/94 (12.8%)	0.403
Log reduction in DNA	4.1 (3.3–4.6)	4.1 (3.3–4.5)	4.1 (3.4–4.9)	0.081
ALT (U/L)	18 (13–23)	18 (14–24)	16 (13–21)	0.056
Creatinine (μmol/L)	50 (44–56)	49 (33–56)	51 (44–57)	0.243
Plan for breast feeding	288/306 (94.1%)	194/206 (94.2%)	94/100 (94.0%)	1.000

Median values (IQR) or percentages are shown. Statistical comparisons between the early withdrawal group and late withdrawal group were performed using the Mann–Whitney *U* test (for continuous variables) or the Chi-square test (for categorical variables).
* Data available for 114 participants.
† Blood result available for 308 participants.
‡ Defined as serum HBV DNA >200,000 IU/ml.
§ Defined as serum HBV DNA <100 IU/ml. ALT, alanine aminotransferase; PP-TDF, peripartum prophylaxis with tenofovir disoproxil fumarate.

12.6 (IQR 0–25.8) weeks postpartum, with the timing of retreatment among those developing CR depicted in Fig. S1. No patients experienced liver decompensation.

VR was observed in the vast majority of participants (98.3%). Comparing early withdrawal and late withdrawal of PP-TDF, no significant differences could be observed for the risk of VR (99.0 *vs.* 96.9%, respectively; $p = 0.338$). The risks of CR (19.5 *vs.* 14.3%; $p = 0.332$) and retreatment (12.6 *vs.* 10.1%; $p = 0.573$) were similar between patients who stopped PP-TDF right after delivery and those who stopped PP-TDF ≥4 weeks postpartum (Fig. 2). Sensitivity analysis was performed when comparing patients who stopped PP-TDF before 12 weeks and those who stopped PP-TDF after 12 weeks, showing similar rates of VR (99.0 *vs.* 96.7%, respectively; $p = 0.180$), CR (19.9 *vs.* 13.0%, respectively; $p = 0.188$) and retreatment (12.3 *vs.* 10.8%, respectively; $p = 0.847$). When the intention-to-treat approach was used to analyze maternal outcomes (*i.e.* including the seven participants who were non-compliant to antiviral treatment; see Fig. 1), a total of 300 participants with available follow-up data were included, showing similar rates of VR (98.3%), CR (17.6%), and retreatment (11.8%), without significant differences between early and late withdrawal of PP-TDF. The maximal degree of ALT elevation, defined by the number of times above baseline ALT or above the ULN, in the postpartum period was not significantly different between early and late withdrawal of PP-TDF (Fig. 3). Regarding retreatment, as the final decision to retreat among those indicated for retreatment (*i.e.* because of CR) was subject to the participant's personal preference, the actual number of patients who were retreated was lower than the number of patients developing CR (65.4% resumed on TDF). Early withdrawal was associated with a trend for earlier retreatment compared with late withdrawal of PP-TDF ($p = 0.087$; Fig. 4), with a median time to retreatment of 10.1 and 30.9 weeks, respectively

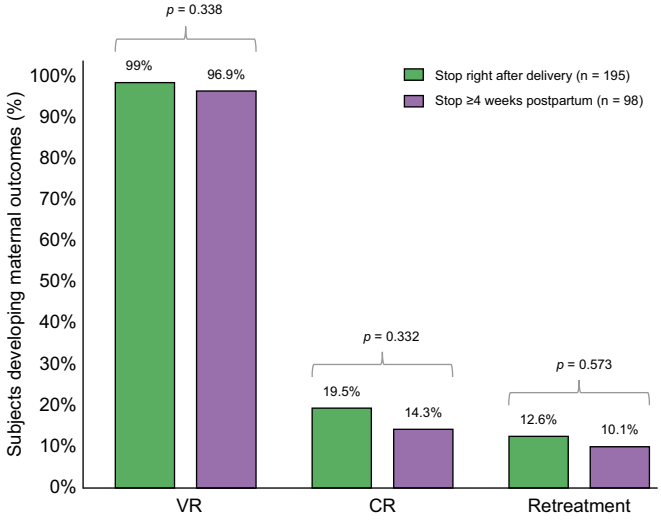

Fig. 2. Risk of VR, CR, and retreatment, stratified by timing of cessation of PP-TDF. Early withdrawal was defined as immediately stopped at delivery, and late withdrawal was defined as cessation ≥4 weeks postpartum. Statistical comparisons between the early and late withdrawal groups were conducted using the Chi-square test. CR, clinical relapse; PP-TDF, peripartum prophylaxis with tenofovir disoproxil fumarate; VR, virological relapse.

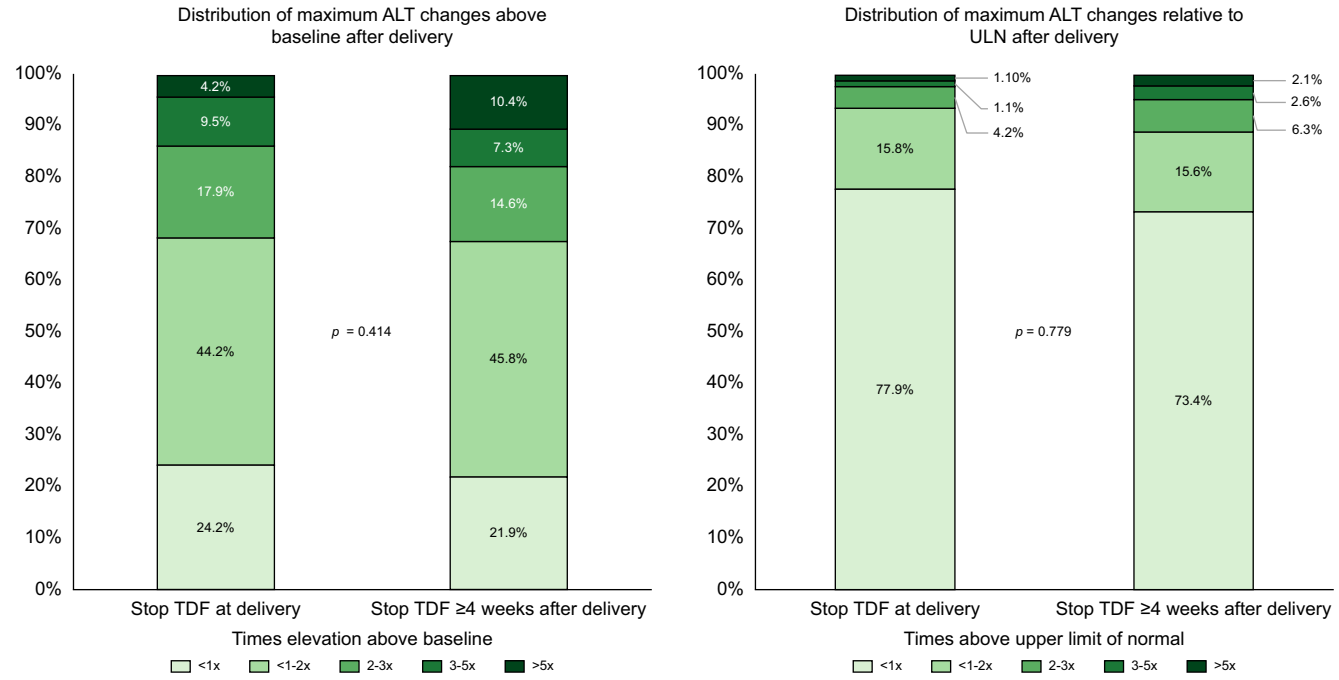

Fig. 3. Degree of maximal ALT changes postpartum, stratified by timing of cessation of PP-TDF. (left) Level defined against baseline ALT. (right) Level defined against the ULN. Statistical comparisons between the early and late withdrawal groups were conducted using the Chi-square test. ALT, alanine aminotransferase; PP-TDF, peripartum prophylaxis with tenofovir disoproxil fumarate; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

($p = 0.025$). In the subgroup of patients who were initiated on PP-TDF beyond 28 weeks of pregnancy (n = 95), the risk of VR (98.8 *vs.* 98.1%; $p = 1.000$), CR (20.9 *vs.* 16.4%; $p = 0.402$), and retreatment (10.2 *vs.* 12.4%; $p = 0.695$) was also similar compared with those who were initiated on PP-TDF before 28 weeks of pregnancy.

No patients developed adverse events from TDF therapy. Serum creatinine remained stable throughout pregnancy: 46 (IQR 43–51) μmol/L at baseline, 46 (IQR 41–52) μmol/L at Week 4 PP-TDF, and 50 (IQR 44–56) μmol/L at delivery.

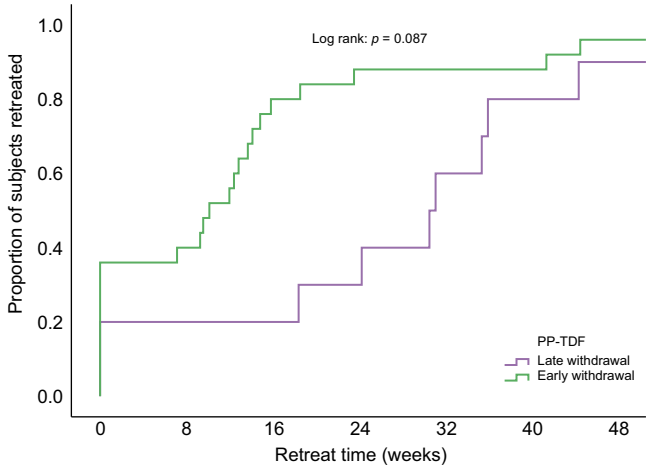

Fig. 4. Kaplan–Meier analysis comparing the time to retreatment in those who were retreated (n = 34) after early *withdrawal vs.* late withdrawal of PP-TDF. Statistical comparison between the early withdrawal group and late withdrawal group was conducted using the log-rank test. PP-TDF, peripartum prophylaxis with tenofovir disoproxil fumarate.

Infant outcomes

A total of 326 livebirths (53% male) with sufficient clinical data were included for analysis. Among them, 5.5% were preterm births, and 4.3% had low birth weight. APGAR score ≥9 was recorded in 95.1% of babies born. The majority of infants received HBIG immediately at birth (77.2%), and the median hours of delay was 0 (IQR 0–0 h). The rest received HBIG within 6 h of birth (Fig. S2). No cases of MTCT (*i.e.* infant HBsAg+ 6 months after birth) were observed. A total of 98.7% of infants developed seroconversion with anti-HBs >10 U/L; 50.5% had anti-HBs >100 U/L, and 32.8% had a strong vaccine response (*i.e.* anti-HBs >1,000 U/L). In addition, 23.1% (69/299) of infants showed seropositivity for anti-HBc (Table 2).

Factors associated with maternal outcomes

For CR, on univariate analysis, only ALT at baseline was a significant variable (OR 1.067, 95% CI 1.030–1.107, $p < 0.001$), whereas timing of PP-TDF cessation was not (Table S2). Multivariate analysis was not performed, as only one significant factor was identified.

Table 2. Summary of clinical data of infants born to HBV+ mothers (n = 326). a.

Parameter	Value
Male	53%
Preterm birth (<37 weeks)	5.5% (18/326)
Low birth weight (<2.5 kg)	4.3% (14/326)
APGAR ≥9	95.1% (310/326)
HBsAg+	0% (0/299)
Anti-HBc+	23.1% (69/299)
Anti-HBs+ (≥10 IU/L)	98.7% (295/299)
Anti-HBs+ (≥100 IU/L)	50.5% (151/299)
Anti-HBs ≥1,000 IU/L	32.8% (98/299)

nti-HBc, antibody to HBcAg; anti-HBs, antibody to HBsAg.

For retreatment, on univariate analysis, age (OR 0.889, 95% CI 0.799–0.989), ALT (OR 1.070, 95% CI 1.027–1.115), maximum ALT elevation above the ULN (OR 3.592, 95% CI 2.242–5.755), and infant anti-HBs >1,000 U/L (OR 0.312, 95% CI 0.116–0.836) were independent variables. In contrast, HBeAg status, HBV DNA level at delivery, being first parity, mode of delivery, timing of PP-TDF cessation, infant birth weight, and preterm birth were not associated with retreatment. Upon multivariate analysis, factors independently associated with retreatment following delivery include the following: baseline ALT (OR 1.054, 95% CI 1.002–1.109, $p = 0.041$), maximum ALT elevation above the ULN after PP-TDF withdrawal (OR 3.565, 95% CI 2.098–6.059), and infant anti-HBs >1,000 U/L (OR 0.258, 95% CI 0.075–0.887, $p = 0.032$) (Table S3).

Among participants with CR, 65.4% agreed to retreatment. Table S4 presents the maternal and infant factors for patients with CR who decided to resume TDF compared with those who refused resumption of TDF. Apart from a trend for higher maximum ALT above ULN (2.2 times *vs.* 1.4 times above the ULN, respectively, $p = 0.06$), other socioeconomic factors (*e.g.* source of referral of antenatal care, geographical origin of mother, employment status, breastfeeding, etc.) and clinical factors (*e.g.* age, time of PP-TDF initiation and withdrawal, viral loads, gestational diabetes mellitus, hypertension, mode of delivery, and infant immune status) were not associated with the decision to retreat among participants with CR.

For the doubling of ALT after delivery (regardless of VR or not), ALT at baseline (multivariate OR 0.929, 95% CI 0.896–0.964, $p < 0.001$), and infant birth weight (multivariate OR 2.152, 95% CI 1.096–4.224, $p = 0.026$) were the only independent variables (Table S5).

Factors associated with infant outcomes

For infantile exposure to HBV (*i.e.* anti-HBc+), on univariate analysis, first parity (OR 1.870, 95% CI 1.005–3.480), infant birth weight (OR 0.427, 95% CI 0.214–0.854), and infant anti-HBs >1,000 U/L (OR 7.498, 95% CI 4.139–13.584) were significant variables. In contrast, maternal age, HBeAg level, HBV DNA at delivery, mode of delivery, timing of PP-TDF cessation, and maternal need for retreatment were not associated with anti-HBc+. Upon multivariate analysis, infant birth weight (OR 0.422, 95% CI 0.195–0.912, $p = 0.028$) and infant anti-HBs >1,000 U/L (OR 7.203, 95% CI 3.931–13.200, $p < 0.001$) remained to be independently associated with infantile exposure to HBV (Table 3).

For strong vaccine response (*i.e.* anti-HBs >1,000 U/L), mother needing retreatment (multivariate OR 0.332, 95% CI 0.116–0.955, $p = 0.041$) and infant anti-HBc (multivariate OR 7.466, 95% CI 4.050–13.763, $p < 0.001$) were the only independent variables (Table S6). Infants with anti-HBs >1,000 U/L, compared with those with lower anti-HBs titers, was also associated with a lower proportion of mothers having postpartum ALT flare more than three times the ULN (2.2 *vs.* 4.5%), although this did not reach statistical significance (Fig. S3).

Discussion

This prospective study included a large cohort of pregnant CHB carriers who were highly viremic to evaluate the maternal and infant outcomes upon either early or late cessation of PP-TDF, in addition to neonatal immunization. The results showed that VR was observed in almost all participants, with only five participants remaining free from VR following TDF cessation without clinical patterns identified (Table S1). Early withdrawal (right after delivery), compared with late withdrawal (≥4 weeks after delivery) of PP-TDF, was not associated with the risk of CR, the degree of maximal ALT elevation, and retreatment. The study also confirmed 100% effectiveness of the guideline-recommend strategy in preventing MTCT regardless of timing of TDF cessation.

Similar studies addressing the clinical question of the timing of PP-TDF cessation reported consistent findings, with the incidence of flare ranging from 22 to 50%, irrespective of the timing of cessation for PP-TDF.[14,15] With the recent suggestion of expanding CHB treatment indications,[16] one can argue that postpartum TDF should simply be continued indefinitely or switched to tenofovir alafenamide for better safety. However, with CR being present in only a minority of patients in our present study, and with regular postpartum monitoring, antiviral withdrawal can be feasible for the majority of patients, reducing the overall pill burden in young patient cohorts.[17]

Although more moderate flares were rare in this cohort, milder elevations of ALT were seen in roughly one-quarter of the participants and were not always associated with VR. Severity of ALT flare was also independent of the timing of PP-TDF cessation.

Table 3. Univariate and multivariate analyses (binary logistic regression) for factors associated with infant anti-HBc+.

	uOR	95% CI	*p* value	mOR	95% CI	*p* value
Age	0.990	0.922–1.062	0.775			
Baseline HBeAg	0.668	0.341–1.310	0.240			
HBV DNA at delivery	0.842	0.671–1.057	0.138			
First parity	1.870	1.005–3.480	0.048	1.682	0.853–3.316	0.134
Vaginal delivery	1.482	0.770–2.851	0.239			
PP-TDF: early withdrawal	0.641	0.367–1.118	0.117			
Mother needing retreatment	0.530	0.196–1.431	0.210			
Infant birth weight	0.427	0.214–0.854	0.016	0.422	0.195–0.912	0.028
Delay in administration of HBIG (per 1 h)	1.189	0.868–1.630	0.282			
Infant anti-HBs >100 U/L	27.209	9.575–77.322	<0.001	*		
Infant anti-HBs >1,000 U/L	7.498	4.139–13.584	<0.001	7.203*	3.931–13.200	<0.001
Breast feeding as main source of milk	5.167	0.674–39/605	0.114			

Variables with $p < 0.05$ in univariate analysis were entered into multivariate analysis performed by binary logistic regression, with OR and 95% CIs calculated. A two-tailed *p* value of <0.05 was considered statistically significant.

* Infant anti-HBs >1,000 U/L (instead of infant anti-HBs >100 U/L) was selected for multivariate analysis. Results were similar if 'infant anti-HBs >100 U/L' was selected instead.

anti-HBc, antibody to HBcAg; anti-HBs, antibody to HBsAg; OR, odds ratio; mOR, OR at multivariate analysis; PP-TDF, peripartum prophylaxis with tenofovir disoproxil fumarate, uOR, OR at univariate analysis.

Interestingly, maternal BMI and infant birth weight were associated with the doubling of ALT in a postpartum mother with CHB (Table S5). Exact mechanisms for these observations are unknown, and further validation studies would be needed to clarify the role of non-HBV-related factors, such as metabolic dysfunction and hepatic steatosis, on ALT flares in the postpartum setting. Strong vaccine response in the infants was found to be negatively associated with retreatment in mothers. Owing to the non-randomized nature of the study, conclusions could not be drawn regarding how the response to neonatal immunization was implicated at retreatment following CR.

Our study has a few limitations. Firstly, this study was not a randomized trial, and the timing of PP-TDF cessation was largely based on clinical decisions. Secondly, not all patients agreed to restart TDF after developing CR despite thorough explanations of the risks and benefits. This could be attributed to the fact that the majority of the study was conducted during the COVID-19 pandemic, which significantly impacted the logistic arrangement of study visits and participants' health-seeking behaviors. Thirdly, only Chinese patients were included, and the study results cannot be generalized to people of other ethnic origins. Lastly, we did not have genotype data or quantitative HBsAg levels for the enrolled participants.

In conclusion, immediate postpartum cessation of TDF was not associated with increased risk of CR, severity of ALT flare, and retreatment when compared with stopping TDF at ≥4 weeks. Shortening the duration of PP-TDF from 12 weeks to immediately after delivery can be considered. This strategy, combined with standard neonatal immunization schemes, has shown to be 100% effective in preventing MTCT among pregnant mothers with CHB who are highly viremic, with a high rate of vaccine response in infants.

Abbreviations

ALT, alanine aminotransferase; anti-HBc, antibody to HBcAg; anti-HBs, antibody to HBsAg; CHB, chronic hepatitis B; CR, clinical relapse; HBIG, HBV immunoglobulin; LLOD, lower limit of detection; MTCT, mother-to-child transmission; PP, peripartum prophylaxis; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; VR, virological relapse.

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Conflicts of interest

MFY received research funding from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Springbank Pharmaceuticals, Sysmex Corporation, and Roche, and is an advisory board member of and/or received research funding from AbbVie, Aligos Therarpeutics, Arbutus Biopharma, Bristol Myer Squibb, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals, and Roche. WKS received speaker's fees from AstraZeneca; is an advisory board member of and received speaker's fees from Abbott; received research funding from Alexion Pharmaceuticals, Boehringer Ingelheim, Pfizer, and Ribo Life Science; and is an advisory board member of and received speaker's fees and researching funding from Gilead Sciences. The other authors have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: CY, YMF, SWK. Clinical care of subjects: CY, THY, YJ, CCB, TAM, LT, WJ, HQ, HH, CKS. Acquisition of data: CY, THY, YJ, CCB, TAM, LT, WJ, HQ, HH, CKS. Analysis and interpretation of data: MLY, SWK. Drafting of manuscript: MLY. Critical evaluation of the manuscript: CY, YMF. Critical revision of the manuscript: THY, YJ, CCB, TAM, LT, WJ, HQ, HH, CKS, SWK. Overall study supervision: SWK. The authors declare they have participated in the preparation of the manuscript and have seen and approved the final version.

Data availability statement

The data that support the findings of this study are available from the corresponding author, WKS, upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101050.

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