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Vemlidy® (tenofovir alafenamide) Use in Pregnancy and Lactation

This document is in response to your request for information regarding the use of Vemlidy® (tenofovir alafenamide [TAF]) for the treatment of HBV during pregnancy and lactation.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/vemlidy/vemlidy_pi.

Summary

Product Labeling[1]

In animal studies, no adverse embryo-fetal developmental effects were observed with TAF.

ARV Pregnancy Exposure Registry[2]

Based on safety data from the APR, the prevalence of birth defects with first-trimester exposure to TAF was 3.9%, and that with second-/third-trimester exposure was 4.7%.

Available Data: TAF Use in Pregnancy and Lactation

In a meta-analysis that included four studies that evaluated TAF use in pregnant participants with CHB, rates of MTCT and pregnancy complications were similar to those observed with TDF (pooled RR of 1.09 [95% CI: 0.16–7.61]). Infant safety outcomes were generally similar between the TAF and TDF treatment groups.[3]

In nine studies of pregnant women with HBV,[4-12] treatment with TAF during pregnancy resulted in 0% MTCT at the last follow-up in seven studies.[4-8,11,12] In a prospective, multicenter study that evaluated 8 vs 12 weeks of TAF in pregnant women, the MTCT rates in infants at 7 months of age were 7.1% and 0% in the ITT and PP populations, respectively.[10] In another prospective, multicenter study that evaluated effectiveness of TAF vs TDF in pregnant women, 1 infant in each of the TAF (n=81) and TDF (n=55) groups was HBsAg+ at Months 6 and 12.[9]

- Infant growth and development were normal. TAF was generally well tolerated, with no discontinuations due to AEs. Additional safety outcomes are provided below.[4-6,8-12]

PK Data: TAF Use in Pregnancy and Lactation

In a PK study that evaluated infant exposure and the PK of TAF and TFV in women with CHB who were breastfeeding, TAF levels were below the LoQ in breast milk and maternal plasma within 6 to 8 hours after a dose. The RID of TAF was 0.005% of the maternal dose.[13]

Product Labeling[1]

Pregnancy

Animal data

Embryonic fetal development studies performed in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. The embryo-fetal no observed adverse effect levels in rats and rabbits occurred at TAF exposures similar to and 51 times higher than, respectively, the exposure in humans at the recommended daily dose. TAF is rapidly converted to TFV; the observed TFV exposure in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human TFV exposures at the recommended daily dose.

TAF was administered orally to pregnant rats (25, 100, or 250 mg/kg/day) and rabbits (10, 30, or 100 mg/kg/day) through organogenesis (on gestation Days 6–17, and 7–20, respectively). No adverse embryo-fetal effects were observed in rats and rabbits at TAF exposures approximately similar to (rats) and 51 (rabbits) times higher than the exposure in humans at the recommended daily dose of TAF. TAF is rapidly converted to TFV; the observed TFV exposures in rats and rabbits were 54 (rats) and 85 (rabbits) times higher than human TFV exposures at the recommended daily dose. Since TAF is rapidly converted to TFV and a lower TFV exposure in rats and mice was observed after TAF administration compared to TDF, another prodrug for TFV administration, a pre/postnatal development study in rats was conducted only with TDF. Doses up to 600 mg/kg/day were administered through lactation; no AEs were observed in the offspring on gestation Day 7 (and lactation Day 20) at TFV exposures of approximately 12 (18 at lactation Day 20) times higher than the exposures in humans at the recommended daily dose of TAF.

Lactation

Data from the published literature report the presence of TAF and tenofovir in human milk. Data from the published literature have not reported adverse effects of TAF on a breastfed child. There are no data on the effects of TAF on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAF and any potential adverse effects on the breastfed infant from TAF or from the underlying maternal condition.

ARV Pregnancy Exposure Registry[2]

Safety data for TAF in pregnant women are derived primarily from outcomes in the HIV-infected population. The APR is an international, voluntary, prospective, exposure-registration cohort study of predominantly women with HIV-1 and no concomitant infections to monitor major teratogenic effects of ARV drugs, including anti-HBV drugs, following exposure during pregnancy. Healthcare providers are encouraged to register patients in the APR (http://www.APRegistry.com).

The APR began to systematically collect HBV infection status in 2003. Since the addition of the HBV indication, the APR has received 1125 prospective reports of patients diagnosed with HBV, with or without concurrent HIV infection, all of which are included in the overall primary prospective analysis. Through July 31, 2024, a total of 887 prospective reports of

HBV-monoinfected pregnancies with outcomes have been reported. Among the 887 reports, there were 832 live births, including 683 live births with initial exposure during the first trimester of pregnancy; 3 stillbirths; 33 spontaneous abortions; and 28 induced abortions. Among the 832 live births, 12 birth defect cases were reported. There was no pattern among the types of birth defects reported.

Data from the APR through July 31, 2024, for the overall (n=24,074) prospective reports with follow-up data showed that birth defect prevalence with exposure to any of the ARV therapies included in the registry at any time during pregnancy was 2.9% (2.9 birth defects per 100 live births; Table 1). This was not substantially different from that reported by the Centers for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (2.72%) and the Texas Birth Defects Registry.

For TAF, data from the APR showed that there have been 52 first-trimester birth defect cases with exposure to TAF-containing regimens (Table 1). The prevalence of birth defects with first-trimester exposure to TAF-containing regimens was 3.7% (95% CI: 2.7–4.8%). Sufficient numbers of TAF first-trimester exposures have been monitored to detect at least a 1.5-fold increase in the risk of overall birth defects and a 2-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. No such increases were detected.

In an exposure registration study, rates of drug-associated AEs cannot be extrapolated to reflect true rates in the potential target population. Since reports of exposures in the APR are voluntary, they are subject to numerous potential selection biases.

Table 1. APR: Birth Defect Prevalence by Trimester of Earliest Exposure Through July 31, 2024[2a]

Earliest Drug Exposure	Outcome/Prevalence	All APR-Registered ARVs	TAF-Containing Regimens
First trimester	Defects/live births, n/N	370/12,586	52/1420
	Prevalence, % (95% CI)	2.9 (2.7–3.3)	3.7 (2.7–4.8)
Second/third trimester	Defects/live births, n/N	289/10,200	15/347
	Prevalence, % (95% CI)	2.8 (2.5–3.2)	4.3 (2.4–7)
Any trimester	Defects/live births, n/N	661/22,789	–
	Prevalence, % (95% CI)	2.9 (2.7–3.1)	–

[a]Exposures are not mutually exclusive across individual ARVs.

Available Data: TAF Use in Pregnancy and Lactation

Meta-Analysis of TAF vs TDF for MTCT Prevention in Mothers With High VLs

Study design

A systematic review and meta-analysis were conducted to compare the rates of MTCT and safety between TAF-treated, TDF-treated, and control groups within randomized controlled trials (n=6) and controlled, retrospective or prospective cohort (n=25) studies. Eligible studies were those that included pregnant participants with CHB and HBV DNA VL ≥200,000 IU/mL, immunoprophylaxis administration to infants and TAF or TDF to women in one study arm during pregnancy, and reported clinical outcomes, including MTCT rate (HBsAg+ and/or detectable HBV DNA after 6 months) and maternal and infant safety. Study investigators excluded animal or translational studies; studies with participants who had

comorbid HIV, HAV, HCV, HDV, or HEV; studies with treatment arms containing <10 participants or those providing second-line treatment with telbivudine, adefovir, or lamivudine; and cohort studies with a high risk of bias (ie, Newcastle Ottawa Scale score <5).[3,14]

Key outcomes assessed included the following: MTCT rates and safety in TAF-treated, TDF-treated, and control groups; infant safety outcomes; infant physical development at birth and beyond postpartum Month 6; maternal outcomes, including ALT level changes; and maternal AEs and obstetric complications.[3]

In the 31 studies included, of the 4468 pregnant women with CHB, 280 participants were TAF treated, 2588 were TDF treated, and 1600 were untreated or received placebo (control group). The cohort of TAF-treated participants included data from 4 studies in which participants received TAF 25 mg or TDF 300 mg once daily. In 3 of the studies, participants began treatment pregnancy by gestational Week 24.[3]

Results[3]

Among studies that compared MTCT rates between TAF- and TDF-treated participants, similar rates of effectiveness were observed, with a pooled RR of 1.09 (95% CI: 0.16–7.61). In a network meta-analysis (TAF or TDF treatment and infant immunoprophylaxis), comparable efficacy was observed (RR, 0.1 [95% CI: 0.07–0.16]; *P*=0.68). In a pairwise analysis, TAF and TDF were equally effective in MTCT prevention.

Safety

Overall, pregnancy complications were reported in 18 studies, including 48/244 cases (19.7%) in the TAF-treated group; the frequency of complications was comparable between the TAF- and TDF-treated groups (TDF, 378/1493 [25.3%]; RR, 0.93 [95% CI: 0.66–1.31]). One case of CK elevation occurred in the TAF studies, and the rates of postpartum hemorrhage were comparable between the TAF and TDF treatment groups (RR, 0.61 [95% CI: 0.08–4.56]).[3,14]

Across the 4 studies that evaluated TAF treatment, there was no association between TAF and negative fetal or infant outcomes. No Grade 3 or 4 AEs or fetal deaths were reported. The RRs (95% CI) for TDF vs TAF for prematurity and fetal death were 0.88 (0.32–2.38) and 1.9 (0.51–6.99), respectively. Safety outcomes including Apgar score at 1 minute, and physical growth parameters were similar between TAF-treated and TDF-treated groups. No TAF studies reported BMD scores in infants.[3]

Prospective, Randomized Study in China: Perinatal Prophylaxis With 8 vs 12 Weeks of TAF[10]

Study design and demographics

A prospective, open-label, multicenter, randomized controlled study was conducted to compare the safety and efficacy of 12 weeks of TAF with those of a shorter course of TAF (8 weeks) for the prevention of MTCT in pregnant women with CHB. Women aged 20 to 40 years with a gestational age >30 weeks and HBV DNA VLs between 5.3 and 9 $\log_{10}$ IU/mL and normal levels of ALT (ie, <40 U/L) and TB (ie, <17.1 mcmol/L) were eligible for inclusion. Key exclusion criteria were as follows: prior treatment to reduce ALT and TB levels, prior treatment for CHB (except prophylaxis of HBV MTCT during a previous

pregnancy that occurred >6 months to the current pregnancy); comorbid HCV, HDV, HEV, or HIV; prior or current HCC, cirrhosis, or other systemic disorders; or Hgb level <80 g/L.

Participants were randomly assigned in a 1:1 ratio to receive TAF 25 mg once daily starting the first day of gestational Week 33 for an expected 8 weeks (ie, discontinuing at delivery; Group 1) or 12 weeks (ie, halting at postpartum Week 4; Group 2). Adherence was evaluated via pill counts; participants were followed through postpartum Month 6. All infants received HBV immunoprophylaxis. The primary endpoint was maternal and infant safety; specifics are presented below. Secondary endpoints included maternal virologic responses throughout the study and infant HBV MTCT at postpartum Month 7.

Table 2. Baseline Demographics and Disease Characteristics (ITT[a]; Zeng et al)[10]

Key Demographics and Characteristics	Group 1: 8 Weeks of TAF (n=119)	Group 2: 12 Weeks of TAF (n=120)
Age, mean (SD), years	28.8 (3.5)	29.2 (4.2)
Primipara, n (%)	73 (61.3)	76 (63.3)
HBV DNA, mean (SD), $\log_{10}$ IU/mL	7.9 (0.6)	7.9 (0.6)
HBsAg, mean (SD), IU/mL	45,269 (20,515.9)	44,776.5 (18,847.2)
ALT, mean (SD), U/L	16.9 (7.1)	16 (6.8)
SCr, mean (SD), mcmol/L	44.6 (8.3)	45.8 (10)
eGFR, mean (SD), mL/min/1.73 m^2	128.2 (8)	127.1 (8.2)

[a]Defined as all enrolled participants, except those who withdrew consent prior to the assigned treatment started.

At delivery, 115 and 116 mothers had data available in Groups 1 and 2, respectively (4 LTFU due to COVID-19 lockdown in each group), and 115 and 116 infants, respectively, were born to those mothers. After delivery, 110 and 112 mother-infant pairs in Groups 1 and 2, respectively, completed the study (another 4 and 5 pairs were LTFU due to COVID-19 lockdown). At delivery, the mean (SD) durations of TAF exposure were 6.2 (1) weeks and 10.5 (1.1) weeks in Groups 1 and 2, respectively.

Results

Overall, mean HBV DNA VL decreased significantly from 7.86 $\log_{10}$ IU/mL at baseline to 4.05 $\log_{10}$ IU/mL at delivery (P<0.001), and 97% of participants (224/231) had a VL <5.3 $\log_{10}$ IU/mL at delivery. Additionally, significant decreases from baseline to delivery in mean HBsAg (4.6 to 4.55 IU/mL, respectively) and HBeAg (386 to 360.17 PEIU/mL) levels were recorded (each, P<0.001).

In the ITT and PP populations (n=222; excluded infants born to women who withdrew consent, were LTFU, or discontinued TAF due to any reason), the MTCT rates of infants at 7 months were 7.1% (17/239) and 0% (0/222) of participants, respectively. In the PP population, infants were anti-HBs+ in both groups. There was no significant difference between groups for any of the efficacy outcomes at Month 6 postpartum. Efficacy outcomes by group are shown in Table 3.

Table 3. Efficacy Outcomes (Zeng et al)[10]

Outcomes	Group 1: 8 Weeks of TAF		Group 2: 12 Weeks of TAF	
	Delivery (n=115)	Postpartum Month 6 (n=110[a])	Delivery (n=116)	Postpartum Month 6 (n=112[a])
HBV DNA, mean (SD), $\log_{10}$ IU/mL	4 (0.8)	7.8 (0.8)	4.1 (0.5)	7.9 (0.5)
<5.3 $\log_{10}$ IU/mL	111 (96.5)	0	113 (97.4)	0

Outcomes	Group 1: 8 Weeks of TAF		Group 2: 12 Weeks of TAF	
	Delivery (n=115)	Postpartum Month 6 (n=110[a])	Delivery (n=116)	Postpartum Month 6 (n=112[a])
HBsAg, mean (SD), log_{10} IU/mL	4.5 (0.2)	4.6 (0.2)	4.6 (0.2)	4.6 (0.2)
HBeAg, mean (SD), PEIU/mL	362.8 (105.4)	387.1 (111)	357.6 (108.4)	384.8 (117.2)
ALT, mean (SD), U/L	19.6 (36.4)	23.2 (18.8)	17.3 (7.6)	23.7 (24.5)
>200 U/L, n (%)	1 (0.9)[b]	0	0	0

[a]Two participants in each group restarted TAF due to ALT elevations.
[b]One participant had an ALT level of 399 U/L at delivery and was diagnosed with liver injury due to concomitant treatment with a Chinese herbal supplement. Their ALT level gradually normalized after discontinuation of the supplement.

Safety

Compliance was 100% via self-report, confirmed by pill counts. No participants discontinued treatment due to AEs. Overall, in Groups 1 and 2, the most common AEs and complications were nausea (11.8% vs 10.8%, respectively) and PROM (9.2% and 8.3%); no Grade 3 or 4 AEs were reported (Table 4). Similar rates of mild ALT elevations occurred in each group at delivery and postpartum Months 3 and 6; no ALT flares occurred through postpartum Month 6. Though approximately 90% of participants maintained elevations in total cholesterol and triglycerides at delivery, levels returned to normal after delivery in most women; overall lipid profiles were similar between groups through postpartum Month 6. Overall, in terms of renal function, no significant changes from baseline to delivery in SCr or β2MG levels were noted; 1 participant in Group 1 had a mild increase in β2MG levels at postpartum Month 6.

Preterm delivery occurred in 3% of cases (7/231), and no infants had congenital defects or malformations or an Apgar score <8 at 1 minute (Table 4). In the PP population, the most common abnormal condition was prolonged neonatal jaundice: Group 1, 14.6% (16/110); Group 2, 16.1% (18/112; *P*=0.752); each case spontaneously resolved or was cured with phototherapy by postpartum Month 2.

Table 4. Maternal and Infant Safety Outcomes (Zeng et al)[10]

Maternal Safety Parameters, n (%)		Group 1: 8 Weeks of TAF (n=119)	Group 2: 12 Weeks of TAF (n=120)
Any AE		33 (27.7)	32 (26.7)
Grade 1 or 2 AEs that occurred in >5% of participants	Nausea	14 (11.8)	13 (10.8)
	Anorexia	13 (10.9)	13 (10.8)
	Fatigue	11 (9.2)	12 (10)
Any obstetrical complication		14 (11.8)	13 (10.8)
Complications that occurred in >5% of participants	PROM	11 (9.2)	10 (8.3)
Grade 1 or 2 ALT elevation[a] at any time		18 (15.1)	22 (18.3)
Grade 3 ALT elevation[a] at any time		1 (0.8)[b]	0
Hgb <110 g/dL at delivery		34 (29.6)	33 (28.4)

Maternal Safety Parameters, n (%)	Group 1: 8 Weeks of TAF (n=119)	Group 2: 12 Weeks of TAF (n=120)
Infant Safety Parameters	**Group 1: 8 Weeks of TAF (n=115)**	**Group 2: 12 Weeks of TAF (n=116)**
Gestational age at birth, mean (SD), weeks	39.2 (1)	39.2 (1)
<37 weeks, n (%)	3 (2.6)	4 (3.4)
Cesarean section delivery, n (%)	55 (47.8)	59 (50.9)
Weight, mean (SD), kg	3.41 (0.34)	3.45 (0.34)
Height, mean (SD), cm	50.25 (1.43)	50.25 (1.43)
Head circumference, mean (SD), cm	34.53 (0.84)	34.5 (0.79)
Apgar score at 1 minute, mean (SD)	9.6 (0.6)	9.5 (0.6)
Breastfed, n (%)	64 (55.7)	66 (56.9)

[a]Grade 1 or 2 elevation was defined as an ALT level of 1.1–5 × ULN; Grade 3 elevation was defined as an ALT level of 5–20 × ULN. No Grade 4 ALT laboratory abnormalities occurred in either group.
[b]One participant had an ALT level of 399 U/L at delivery and was diagnosed with liver injury due to concomitant treatment with a Chinese herbal supplement. Their ALT level gradually normalized after discontinuation of the supplement.

Phase 4 Multicenter Cohort Study in China

Study design

A phase 4, single-arm, prospective, multicenter clinical study was conducted in China to assess the safety and efficacy of TAF in preventing MTCT of HBV among pregnant women with CHB who were HBeAg+ and had high levels of HBV DNA (>200,000 IU/mL). Women aged 20 to 35 years and who were 24 to 26 weeks pregnant received TAF 25 mg once daily from 27 to 29 weeks of gestation until delivery,[15] and participants were followed until 6 months postpartum. Infants received combined immunoprophylaxis and were followed through HBV vaccination.[4] Primary outcome measures included the rate of MTCT of HBV from the time of enrollment through the last infant post-HBV vaccination serological test. Secondary outcome measures included the rate of infant birth defects. The study started in April 2021 and was estimated to conclude in December 2023 with approximately 330 participants.[15]

Interim results[4]

The interim analysis included up to 28 weeks of postpartum data from those enrolled up to June 2022, including 134 pregnant participants, 105 of whom gave birth to 108 infants. At delivery, 89% of mothers (89/100) achieved HBV DNA <200,000 IU/mL, and 2% (2/102) had undetectable levels. During treatment, the median (IQR) decreases in serum HBV DNA and HBsAg levels were 4 (3–4) $\log_{10}$ IU/mL and 11,319 (-5909 to +28,534) IU/mL, respectively. All 33 infants who completed the postvaccination serological evaluation tested negative for HBsAg.

At 6 months postpartum, 65.4% of mothers (51/78) had ALT levels >ULN, compared with 2.1% of mothers (2/95) who had ALT levels >ULN during pregnancy. No infants had malformations or congenital defects, and body weight, height, and head circumferences were within normal limits.

Prospective, Multicenter Study in China: TAF in Participants With High HBV DNA VLs[8]

Study design and demographics

A multicenter, prospective study was conducted to assess the safety and effectiveness of TAF initiated during the second trimester for the prevention of MTCT of HBV in 89 pregnant participants with CHB and a high VL. Women aged 20 to 35 years with an HBV DNA VL ≥1 × 10^6 IU/mL who were HBsAg+ and HBeAg+ were eligible for inclusion. Exclusion criteria included comorbid HIV, HCV, or major systemic disease, antiviral treatment at the time of enrollment, congenital fetal abnormalities, or a history of spontaneous abortion.
All participants were treated with TAF 25 mg once daily beginning between gestational Weeks 24 and 28 and continuing until postpartum Week 4. All infants received HBV immunoprophylaxis. The primary endpoint was the rate of MTCT (defined as HBsAg+ or HBV DNA >20 IU/mL) at postpartum Month 7. Other outcomes were mother and infant safety.

The mean (SD) TAF treatment duration prior to delivery was 14.3 (1.2) weeks, and treatment began at a mean (SD) gestational age of 25 (1) weeks. Ninety-one infants (male, n=41 [45.1%]; cesarean delivery, n=37 [40.7%]) were born at a mean (SD) gestational age of 39.21 (1.16) weeks, and all mother-infant pairs were followed to postpartum Month 7. Most infants (62.6%, 57/91) were fed with formula, and 17 infants (18.7%) each were fed with breast milk or breast milk and formula.

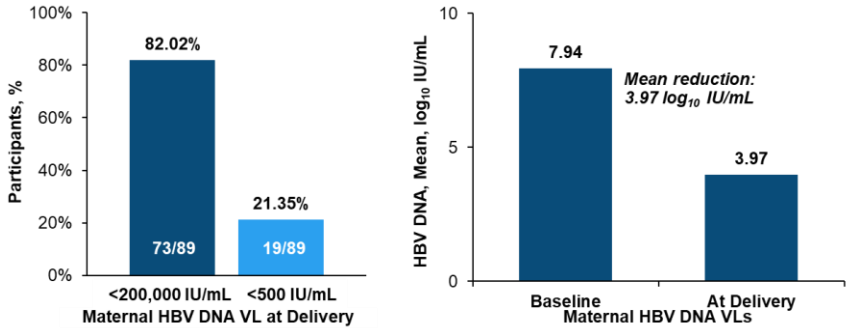
Table 5. Baseline Demographics and Disease Characteristics (Han et al)[8]

Key Demographics and Characteristics	TAF-Treated Mothers (N=89)
Age, mean (SD), years	28.82 (3.61)
Primipara, n (%)	56 (62.9)
Family history of HBV, n (%)	46 (51.7)
Initiated TAF between gestational Weeks 24 and 25, n (%)	64 (71.9)
HBV DNA VL, mean (SD), log_{10} IU/mL	7.94 (0.6)
HBsAg titer, mean (SD), mIU/mL	30,837.31 (14,170.54)
ALT/AST level, mean (SD), U/L	14.29 (8.09)/18.71 (4.76)

Results

TAF therapy led to maternal HBV DNA VLs <2 × 10^5 IU/mL in 82% of participants at delivery, with a mean (SD) reduction in HBV DNA of 3.97 (1.2) log_{10} IU/mL (Figure 1).

Figure 1. Maternal HBV DNA (Han et al)[8]



Of the 35 infants with HBeAg and HBsAg serology available at birth, all infants were HBeAg+; 3 of these infants (8.6%) were HBsAg+ at birth, and none had detectable HBV DNA at birth. The MTCT rate (HBsAg+) in 91 infants at 7 months of age was 0%, which included the 3 infants who were HBsAg+ at birth.

Safety

All AEs were mild and did not result in discontinuation of TAF; no serious AEs were reported in the mothers. Maternal complications and AEs are shown in Table 6.

Table 6. Maternal Complications and AEs (Han et al)[8]

Maternal Complications and AEs, n (%)		TAF-Treated Mothers (N=89)
Complications	PROM	9 (10.11)
	Postpartum hemorrhage	7 (7.87)
	Preterm labor	4 (4.49)
	Gestational DM	3 (3.37)
	Gestational HTN	2 (2.25)
AEs that occurred in >1 participant	Fatigue	5 (5.62)
	Constipation	4 (4.49)
	Insomnia	3 (3.37)
	Nausea	2 (2.25)

Mean (SD) SCr levels increased from 45.97 (5.6) mcmol/L at baseline to 52.23 (8.5) mcmol/L at delivery (*P*<0.05); however, SCr levels remained within normal limits at delivery. Mean (SD) serum phosphorus levels remained stable from baseline to delivery: 1.2 (0.1) mmol/L and 1.21 (0.13) mmol/L, respectively (*P*>0.05). During treatment and pregnancy, no ALT flares were noted. After delivery, 9 participants had mild ALT increases (range, 1.09–1.52 × ULN). Of these participants, 7 did not have an intervention with ALT levels returning to normal in 4 to 8 weeks, and 2 received glutathione with ALT levels returning to normal levels.

No congenital defects or malformations were reported in the infants. Infant measurements at delivery and at postpartum Month 7 are shown in Table 7. After delivery, mean (SD) Apgar scores were the following: at 1 minute, 9.95 (0.23); at 5 minutes, 9.97 (0.16).

Table 7. Infant Measurements at Delivery and at Postpartum Month 7 (Han et al)[8]

Infant Measurements, Mean (SD)	Delivery			Postpartum Month 7	
	Overall	Boys	Girls	Boys	Girls
Weight, kg	3.37 (0.43)	3.49 (0.41)	3.28 (0.43)	8.53 (0.48)	8.14 (0.51)
Height, cm	49.97 (0.92)	50.07 (0.26)[a]	49.9 (1.21)	69.06 (1.95)	68.24 (2.08)
Head circumference, cm	34.72 (0.65)	34.77 (0.44)[a]	34.69 (0.79)[a]	43.47 (1.01)	42.65 (1.46)

[a]*P*<0.05 for comparison with national standards.

PreMIT: Prospective Taiwanese Study of TAF vs TDF[9]

Study design and demographics

A multicenter, prospective cohort study was conducted to assess the safety and effectiveness of TAF compared with TDF for the prevention of MTCT of HBV in pregnant women. Women aged 20 to 45 years with HBV DNA 6 $\log_{10}$ IU/mL who were HBsAg+ and HBeAg+, had ALT levels <40 U/L, did not have HIV or HCV, and did not receive antiviral treatment during pregnancy were eligible for enrollment in this study. Exclusion criteria

included systemic disease, fetal anomalies, cirrhosis, and malignant liver tumors. The TAF group comprised mothers treated with TAF 25 mg once daily from the third trimester to 2 weeks after the delivery date between 2019 and 2021 (n=78). Outcomes for TAF-treated mothers and their children were compared with outcomes for those who were treated with TDF 300 mg once daily from the third trimester to 2 weeks postpartum between 2016 and 2018 (TDF P2W group, n=53). All infants received passive/active HBV immunoprophylaxis.

Maternal outcomes included evaluations of prepartum and postpartum HBV DNA and ALT levels through postpartum Month 6; infant outcomes included HBsAg status testing at birth and postpartum Months 6 and 12. Safety outcomes were evaluated in mothers and infants. Additional outcomes were compared with those of an earlier cohort of TDF-treated mothers who received TDF 300 mg once daily from the third trimester to 4 weeks postpartum between 2011 and 2015 (TDF P4W group, n=101) or no antivirals (control group). In the TAF and TDF P2W groups, 27.5% and 26%, respectively, were exclusively breastfed; 22.5% and 32% of infants were fed with breast milk and formula.

Table 8. Baseline Demographics, Disease and Treatment Characteristics, and Maternal and Infant Disposition (Chen et al)[9]

Key Demographics and Characteristics	TAF Group (n=78)	TDF P2W Group (n=53)
Age, mean (SD), years	35.84 (4.57)	34.56 (3.65)
Prepartum treatment duration, mean (SD), weeks	12.6 (2.1)	11 (1.3)
Duration >4 weeks/>8 weeks, n (%)	77 (98.7)/70 (89.7)	53 (100)/45 (84.9)
CK, mean (SD), U/L	52.74 (40.21)	68.62 (79.95)
SCr, mean (SD), mg/dL	0.47 (0.1)	0.45 (0.08)
Participant Disposition	**TAF Group (n=78)**	**TDF P2W Group (n=53)**
Completed postpartum Month 6 follow-up, n	77	53
Infants born/completed postpartum Month 12 follow-up, n	81/78	55/55

Results

The mean decreases in HBV DNA levels from baseline to delivery were similar between TAF- and TDF-treated mothers, although HBV DNA VLs were significantly lower at postpartum Month 6 in the TAF group than in the TDF P2W group (*P*<0.0001; Table 9). In addition, no differences were observed between groups in the proportion of participants who achieved HBV DNA levels <6 log_{10} IU/mL at delivery (Table 9). Significantly more TAF-treated than TDF-treated participants continued or restarted antiviral treatment by postpartum Month 6: 11.54% vs 1.89%, respectively (*P*=0.04).

Table 9. Maternal Efficacy Results (Chen et al)[9]

Maternal Efficacy Parameters		TAF Group (n=78)	TDF P2W Group (n=53)	*P*-Value
HBV DNA VL, mean (SD), log_{10} IU/mL	Baseline	7.87 (0.59)	8.3 (0.36)	<0.0001
	Delivery	3.99 (1.07)	4.47 (0.86)	0.0086
	Postpartum Month 6	6.98 (2.14)	8.3 (0.7)	<0.0001
HBV DNA VL <6 log_{10} IU/mL at delivery, n (%)		74 (94.87)	51 (96.23)	0.6839
Reduction from baseline in HBV DNA VL, mean (SD), log_{10} IU/mL	At delivery	-3.87 (0.85)	-3.83 (0.83)	0.7883
	Postpartum Month 6	-0.89 (1.96)	0 (0.68)	0.0045
HBeAg+/HBeAg- at postpartum Month 6, n (%)		76 (98.7)/1 (1.3)	53 (100)/0	1

Maternal Efficacy Parameters		TAF Group (n=78)	TDF P2W Group (n=53)	*P*-Value
ALT, mean (SD), U/L	Baseline	24.03 (30.7)	16.74 (9.36)	0.0521
	Delivery	19.56 (20.15)	18.28 (9.67)	0.6285
	Postpartum Month 6	33.84 (29.61)	28.04 (16.24)	0.2616
ALT level >2 × ULN, n (%)	At least once	20 (25.64)	9 (16.98)	0.3658
	Lasting ≥3 months	7 (8.97)	1 (1.89)	0.1234
ALT level >5 × ULN, n (%)	At least once	9 (11.54)	3 (5.66)	0.3412
	Lasting ≥3 months	1 (1.28)	0	1

Note: Data were missing from 1 participant at 6 months in the TAF group, and in no participants in the TDF P2W group.

The rates of delivery at a gestational age ≥37 weeks (*P*=0.6704) and body weight at birth (*P*=0.4282) were similar between groups (Table 10). One infant in the TAF group was HBsAg+ at Months 6 and 12; the infant's mother had a decrease in HBV DNA from 8.23 $\log_{10}$ IU/mL at baseline to 4.92 $\log_{10}$ IU/mL at delivery. Similarly, 1 infant in the TDF group was HBsAg+ at Months 6 and 12 (*P*=1 for each between-groups comparison per time point); this infant's mother also had a decrease in HBV DNA from 8.34 $\log_{10}$ IU/mL at baseline to 4.1 $\log_{10}$ IU/mL at delivery. In a univariate logistic regression analysis of risk factors associated with infant HBsAg+ status at postpartum Month 6 (overall, n=237; TAF group, n=75; TDF P2W or P4W groups, n=162), treatment type (TAF vs TDF) was not identified as a risk factor (odds ratio, 0.72 [95% CI: 0.07–7]; *P*=0.7743).

Table 10. Infant Efficacy Results (Chen et al)[9]

Infant Efficacy Parameters		TAF Group (n=81)	TDF P2W Group (n=55)	*P*-Value
Gestational age, ≥37 weeks/<37 weeks, n (%)		67 (82.72)/14 (17.28)	47 (85.45)/8 (14.55)	0.6704
Type of delivery, vaginal/cesarean, n (%)		54 (66.67)/27 (33.33)	34 (61.82)/21 (38.18)	0.5615
Emergent cesarean delivery, n (%)		2 (2.47)	0	0.5147
Body weight at birth, mean (SD), g		2987.36 (482.56)	3051.58 (431.26)	0.4282
HBsAg+, n (%)	Delivery	6 (7.41)	8 (14.55)	0.1788
	Postpartum Month 6	1 (1.33)	1 (1.82)	1
	Postpartum Month 12	1 (1.28)	1 (1.82)	1
Anti-HBs+ at postpartum Month 12, n (%)		73 (94.81)	52 (94.55)	1
Anti-HBs titer at postpartum Month 12, mean (SD), mIU/mL		647.2 (378)	497.36 (390.54)	0.0285

Note: Of the 78 infants with 12 months of follow-up in the TAF group, 6 infants missed the postpartum Month 6 visit, and 3 missed the postpartum Month 12 visit; 1 did not have a sufficient sample for anti-HBs analysis. Due to the COVID-19 pandemic, 7 infants did not have data at Month 6 or 12, and 1 infant missed both of those assessments; all of these infants were HBsAg- at birth.

Safety

One mother in the TAF group had an AE of nausea, and another had an AE of dry eyes. In the TDF group, AEs of mild gastrointestinal symptoms (n=3) and skin itching (n=1) occurred. No participants discontinued treatment due to intolerance. All AEs resolved without intervention.

ALT levels tended to peak 2 to 4 months postpartum and were similar between groups at delivery and at postpartum Month 6 (Table 9). No participants experienced decompensation. In a model that evaluated ALT levels in 332 participants from the TAF, TDF (P2W and P4W), and control groups, 87.2% of participants had generally stable ALT levels prepartum and postpartum. Additionally, 8% had moderate postpartum flares, 2.4% had marked postpartum flares, and 2.4% had flares during the third trimester; study investigators concluded these participants were candidates for antiviral treatment extension.

No major congenital abnormalities were noted in either group, and infant weights and heights (through Month 12) and laboratory values (eg, AST, ALT, Cr, and calcium levels) were generally similar between groups.

Prospective, Multicenter Study in Southwest China[5]

Study design and demographics

An ongoing, prospective, multicenter study in Southwest China is evaluating the effectiveness of TAF in preventing MTCT in pregnant women with CHB (HBsAg+, HBeAg+, and HBV DNA >200,000 IU/mL). All mothers initiated TAF between gestational Weeks 24 and 29 and continued treatment until postpartum Weeks 4 to 6; all infants received HBV immunoprophylaxis within 12 hours of birth and HBV vaccination. The primary endpoint was the MTCT rate, which was determined by HBsAg positivity at birth and at 7 to 9 months of age in the infants.

Of the 128 women who enrolled, 69 mothers and infants completed 7 to 9 months of postpartum follow-up. The mean (IQR) age of the pregnant women was 29 (27–32) years; the mean (IQR) ALT and AST levels were 18 (14.3–34.8) IU/L and 21.5 (18.65–37.8) IU/mL, respectively. Thirty women (43.48%) had a family history of HBV; the mean (SD) HBV DNA level at treatment initiation was 7.22 (1.2) $\log_{10}$ IU/mL (52 women had an HBV DNA level $\geq 2 \times 10^7$ IU/mL).

Interim results

Mean (SD) HBV DNA levels in mothers decreased significantly from baseline to delivery: 7.22 (1.2) vs 3.76 (0.91) $\log_{10}$ IU/mL, respectively (P=0.0001). Most mothers (95.7%; 66/69) had HBV DNA levels <200,000 IU/mL, and 46.4% (32/69) had HBV DNA levels <500 IU/mL at delivery. Additionally, before and after TAF treatment, maternal ALT and AST levels were maintained at normal levels. The MTCT rate at 7 to 9 months postpartum was 0%, and the body weight, height, and head circumferences of the infants were comparable with national standards. No congenital abnormalities or growth retardation was observed. Treatment with TAF was well tolerated, and the most common AEs in mothers were fatigue (3%) and weakness (1%). No participants discontinued treatment due to an AE.

Retrospective, Real-World Study[6]

Study design and demographics

A retrospective, multicenter, single-arm, real-world study was conducted in China to investigate the efficacy and safety of TAF in preventing MTCT of HBV infection. Data were collected up to postpartum Weeks 24 to 28. Pregnant women aged >20 years who were HBeAg+, had HBV DNA levels >200,000 IU/mL during pregnancy, and were treated with TAF therapy from the second or third trimester until delivery were eligible for inclusion. Exclusion criteria included comorbid viral hepatitis (other than HBV) or HIV, evidence of HCC or cirrhosis, fetal deformity (evidenced by ultrasound), or use of other HBV antiviral therapy. The primary outcomes were the rate of congenital defects or physical malformation in infants and the rate of MTCT of HBV (HBsAg+ or detectable HBV DNA). Secondary outcomes included rates of maternal HBV DNA levels <200,000 IU/mL at delivery and safety outcomes. All infants received passive/active HBV immunoprophylaxis. A total of 57.5% of infants (42/73) were fed with breast milk only.

Table 11. Baseline Demographics and Characteristics of Mothers (Ding et al)[6]

Key Demographics and Characteristics	Overall (N=71)
Age, mean (SD), years	30.3 (2.2)
HBV DNA, mean (SD), log_{10} IU/mL	7.78 (0.72)
HBeAg+, n (%)	71 (100)
HBsAg titer, mean (SD), S/CO	28,937.74 (23,413.77)

Results

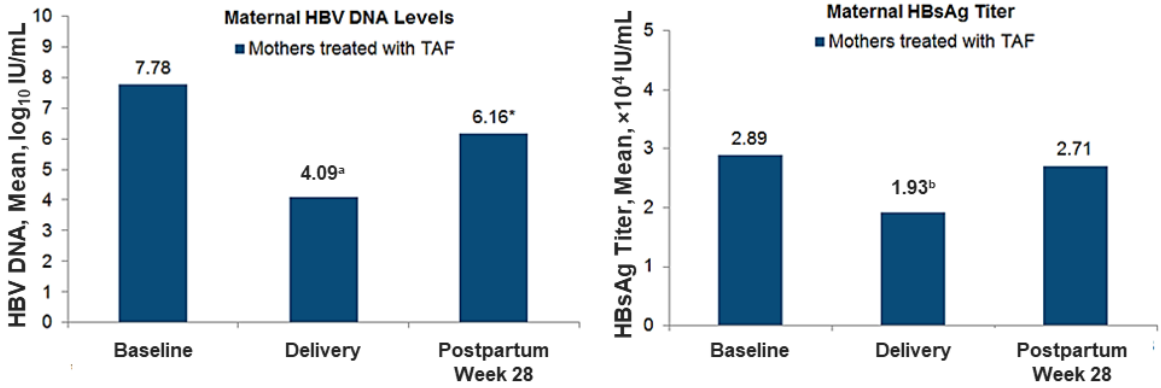
There were no cases of MTCT of HBV infection; all infants were HBsAg- and had undetectable HBV DNA at birth and at 24 to 28 weeks (Table 12). Significant improvements from baseline to delivery were observed in maternal HBV DNA levels and HBsAg titers (Figure 2). At delivery, 86% of mothers (61/71) had HBV DNA levels of <200,000 IU/mL; 1 mother had HBeAg loss.

A total of 78.9% of mothers (56/71) discontinued TAF treatment immediately after delivery, and 93% (66/71) discontinued treatment at postpartum Weeks 24 to 28. Before delivery, the adherence rate to TAF was 77.5% (16/71 mothers missed 1–7 days of TAF treatment during pregnancy).

Table 12. Summary of AEs, Complications, and Pregnancy Outcomes (Ding et al)[6]

Pregnancy Outcomes	Infants (n=73)
Gestational age, mean (SD), weeks	38.22 (2.94)
Cesarean delivery, n (%)	26 (35.62)
HBsAg+ at birth,[a] n/N (%)	0/52 (0)
HBeAg+ at birth,[a] n/N (%)	40/52 (76.92)
Detectable HBV DNA at birth,[a] n (%)	0

Figure 2. Effects of TAF Treatment on HBV DNA Levels and HBsAg Titers (Ding et al)[6]



[a]*P*<0.001 vs baseline. [b]*P*=0.005 vs baseline.

Safety

The most commonly reported AEs in mothers and infants were postpartum ALT flares (15.5%) and eczema (8.2%), respectively (Table 13). No severe AEs were reported. No cases of congenital defects or physical malformations were reported. The body weight, height, and head circumference values of infants with TAF exposure were comparable to or exceeded the Chinese national standards for physical development. Significant changes in maternal Cr and eGFR levels were also observed (Table 14).

Table 13. Summary of Maternal and Infant AEs, Maternal Complications, and Infant Outcomes (Ding et al)[6]

AEs and Maternal and Infant Outcomes		Overall (N=71)
Maternal AEs (n=71), n (%)	Postpartum ALT flares	11 (15.49)
	Nausea	2 (2.82)
	Upset stomach	2 (2.82)
	Vomiting	2 (2.82)
	Birth canal hematoma	1 (1.41)
	Constipation	1 (1.41)
	Maternal fall	1 (1.41)
	Palpitations	1 (1.41)
	Pyrexia	1 (1.41)
	On-treatment ALT flares	0
Maternal complications (n=71), n (%)	Gestational DM	2 (2.82)
	PROM	1 (1.41)
	Preterm labor	1 (1.41)
Infant AEs (n=73), n (%)	Eczema	6 (8.22)
	Diarrhea	5 (6.85)
	Constipation	4 (5.48)
	Vomiting	4 (5.48)
	Skin rash	1 (1.37)
Infant outcomes (n=73)	Male, n (%)	30 (41.1)
	Weight, mean (SD), kg	3.32 (0.41)
	Height, mean (SD), cm	50.55 (2.03)
	Head circumference, mean (SD), cm	33.55 (1.03)
	Apgar score at 1 minute, mean (SD)	9.7 (1.11)

Table 14. Changes in Maternal Cr Levels and eGFR (Ding et al)[6]

Parameters	Mothers Treated With TAF		
	Baseline	Delivery	Postpartum Week 28
Cr levels, mean (SD), mcmol/L	52.88 (9.49)	56.25 (9.72)	57.48 (8.54)
P-value vs baseline	–	0.04	0.003
eGFR, mean (SD), mL/min/1.73 m^2	122.04 (10.56)	118.58 (11.6)	117.37 (10.67)
P-value vs baseline	–	0.07	0.01

Retrospective Study of TAF vs TDF in MTCT Prevention in High-Viremia Mothers[7]

Study design

A retrospective study assessed the safety and efficacy of TAF (n=61) vs TDF (n=73) initiated between gestational Week 24 and approximately Week 28 for the prevention of MTCT of HBV in TN pregnant women. Women (mean age, ~30 years) with HBV DNA ≥2 × 10^5 IU/mL who had normal liver function and had not received antiviral therapy prior to pregnancy were included in the study. Primary outcomes included the decrease in VLs and rate of MTCT (defined as the proportion of infants who had serum HBV DNA levels >20 IU/mL or were HBsAg+). Secondary outcomes included the change in serum ALP level in mothers and the BMD Z-score of infants. A PS analysis was conducted, and 51 pairs of patients were matched.

Results of the PS-matched cohort

The mean treatment duration ± SD was 12.74±4.86 weeks in the TAF group and 12.52±4.54 weeks in the TDF group (*P*=0.819). The maternal HBV DNA decline from treatment initiation to predelivery was similar in both the TAF and TDF groups (*P*=0.216). The MTCT rates were 0% in both the TAF- (0/39 infants) and TDF-treated (0/29 infants) patients in the PP analysis (*P*>0.05). No significant differences in the BMD Z-scores of infants were observed between groups (*P*=0.797). A significant difference in serum ALP expression was observed between patients treated with TDF and patients treated with TAF (*P*=0.049). Results for patients who received TAF or TDF are summarized in Table 15. A safety analysis was not conducted.

Table 15. Effects of TAF or TDF in Mothers With High Viremia and Infants (Zhu et al)[7a]

Parameters, Mean (SD)		TAF (n=51)	TDF (n=51)	*P*-Value
Mothers	HBV DNA levels before treatment initiation, log_{10} IU/mL	8.07 (8.1)	8.06 (8.13)	0.982
	Reduction in HBV DNA, log_{10} IU/mL	3.7 (0.91)	3.43 (1.2)	0.216
	ALP level, U/L	144.67 (45.71)	162.06 (42.3)	0.049
Infants	Z-score for BMD	0.66 (0.41)	0.69 (0.46)	0.797

[a]n=51 pairs of patients matched by PS analysis.

Retrospective Chinese Study: TAF vs TDF Treatment Outcomes Stratified by Level of Viremia[11]

Study design and demographics

A retrospective study was conducted in China to compare the effectiveness and safety of TAF (n=46) vs TDF (n=50) in preventing MTCT in pregnant women who delivered at or attended several Chinese medical centers. Pregnant women aged 20 to 40 years who had an HBV DNA level ≥2 × 10^5 IU/mL, were HBeAg+, were TN, and had ALT levels ≤40 U/L in the year before pregnancy were eligible for inclusion. Within each treatment group, participants were stratified according to their HBV DNA levels: High-G (≥8 log_{10} IU/mL), Middle-G (7 to <8 log_{10} IU/mL), and Low-G (<7 log_{10} IU/mL).

Study outcomes in mothers included viral suppression rates, predelivery, rates of abnormal ALT levels, cesarean delivery, and AEs; infant outcomes included the MTCT rate (defined as HBsAg+ at postpartum Months 7–12) and growth and development. Patients began taking TAF 25 mg or TDF 300 mg once daily between pregnancy Weeks 24 and 28 and continued until delivery. All infants received passive/active HBV immunoprophylaxis.

Table 16. Baseline Demographics and Disease Characteristics (Tao et al)[11]

Key Demographics and Characteristics	TAF Group (n=46)	TDF Group (n=50)
Age, mean ± SD, years	30.41±4.16	29.14±3.95
Gestational age at enrollment, mean ± SD, weeks	24.21±1.71	24.3±1.59
HBV DNA, median (IQR), log_{10} IU/mL	8.23 (6.75–8.23)	7.67 (7.08–8.36)
HBsAg, median (IQR), log_{10}10 IU/mL	4.46 (4.11–4.72)	4.5 (3.98–4.72)
HBeAg, median (IQR), S/CO	3.16 (2.98–3.23)	3.13 (3.06–3.2)
ALT, median (IQR), U/L	19.9 (15.43–35.5)	24.5 (18–36)
CrCl, median (IQR), mcmol/L	47 (43.25–49)	47 (43–49)
Serum phosphorus, median (IQR), mmol/L	1.19 (1.1–1.27)	1.2 (1.13–1.3)

Results

Prior to delivery, there was no significant difference between the TAF and TDF groups in the proportion of patients with an HBV DNA level <4 log_{10} IU/mL: 84.78% vs 74%, respectively (*P*=0.194; Table 17). Median (IQR) HBV DNA levels decreased from baseline to predelivery by 4.51 (4.11–4.96) log_{10} IU/mL in the TAF group and 4.09 (3.76–4.7) log_{10} IU/mL in the TDF group (*P*=0.04); significantly more patients in the TAF group than in the TDF group had a reduction from baseline to predelivery in HBV DNA by ≥4 log_{10} IU/mL (78.26% vs 58%, respectively; *P*=0.034). In terms of stratified group, among patients in the High-G group (≥8 log_{10} IU/mL), those in the TAF group had significantly greater decreases in HBV DNA from baseline to predelivery than those in the TDF group (Table 17). The Middle-G and Low-G TAF groups had numerically greater but non-significant decreases from baseline to delivery in HBV DNA compared to their corresponding TDF groups.

Table 17. Overall Maternal HBV DNA Levels Predelivery and Stratified HBV DNA Levels at Baseline and Predelivery (Tao et al)[11]

HBV DNA Levels			TAF Group (n=46)	TDF Group (n=50)	*P*-Value
Overall (predelivery)	Median (IQR), log_{10} IU/mL		3.37 (2.47–3.77)	3.61 (2.99–4.07)	0.075
	HBV DNA level <10^4 IU/mL, n (%)		39 (84.78)	37 (74)	0.194
	HBsAg, median (IQR), log_{10} IU/mL		4.43 (3.92–4.69)	4.32 (3.9–4.54)	0.385
	HBeAg, median (IQR), S/CO		3.09 (2.72–3.21)	3.1 (2.98–3.17)	0.728
Stratified groups by HBV DNA level	High-G (≥8 log_{10} IU/mL), median, log_{10} IU/mL	n	29	19	–
		Baseline	8.23	8.54	–
		Predelivery	3.73	4.14	0.045
	Middle-G (7 to <8 log_{10} IU/mL), median, log_{10} IU/mL	n	4	21	–
		Baseline	7.81	7.51	–
		Predelivery	2.95	3.48	0.266
	Low-G (<7 log_{10} IU/mL), median, log_{10} IU/mL	n	13	10	–
		Baseline	5.8	6.52	–
		Predelivery	1.3	2.76	0.061

The HBsAg+ rate at birth was 2.17% (n=1) and 4% (n=2) in the TAF and TDF groups, respectively. At postpartum Months 7 to 12, no infants in either group were HBsAg+; therefore, both treatments resulted in a 0% MTCT rate.

Safety

Median (IQR) serum phosphorus levels were significantly different between groups predelivery: TAF, 1.23 (1.16–1.35) mmol/L; TDF, 1.17 (1.07–1.29) mmol/L (*P*=0.04). Predelivery ALT elevations occurred in 21.74% and 22% of patients in the TAF and TDF groups, respectively; most events were mild or moderate in severity (Table 18). Indices of infant growth were similar between the two groups (Table 18); no neonatal deaths or congenital abnormalities occurred.

Table 18. Maternal and Infant Safety Outcomes (Tao et al)[11]

Key Maternal Outcomes	TAF Group (n=46)	TDF Group (n=50)
Gestational age at delivery, mean ± SD, weeks	39.56±1.07	39.21±1.15
Type of delivery, vaginal/cesarean, n (%)	36 (78.26)/10 (21.74)	37 (74)/13 (26)
Gestational DM/HTN, n (%)	5 (10.87)/1 (2.17)	6 (12)/1 (2)
Oligohydramnios, n (%)	7 (15.22)	4 (8)
Postpartum hemorrhage,[a] n (%)	6 (13.04)	6 (12)

Key Maternal Outcomes	TAF Group (n=46)	TDF Group (n=50)
PROM, n (%)	3 (6.52)	6 (12)
Predelivery ALT, median (IQR), U/L	16.9 (12–23.1)	17 (13–25.75)
Abnormal ALT level during pregnancy, mild or moderate/severe,[b] n (%)	8 (17.39)/2 (4.35)	10 (20)/1 (2)
CrCl, median (IQR), mcmol/L	52 (48–56)	51.5 (48–57)
Key Infant Outcomes	**TAF Group (n=46)**	**TDF Group (n=50)**
Birth weight, mean ± SD, kg	3.33±0.39	3.23±0.43
Low birth weight/macrosomia, n (%)	0/2 (4.35)	2 (4)/1 (2)
Apgar score, median (IQR)	10 (9–10)	10 (9–10)
Apgar score ≤7 (neonatal asphyxia), n (%)	2 (4.35)	3 (6)

[a]Defined as blood loss ≥500 mL after vaginal delivery or ≥1000 mL after caesarean delivery.
[b]Mildly abnormal ALT level was defined as an ALT level of 40 to <80 U/L; moderately abnormal level was defined as ALT level of 80 to <200 U/L; and severely abnormal level was defined as ALT level ≥200 U/L.
[c]Low birth weight was defined as <2.5 kg, and macrosomia was defined as birth weight ≥4 kg.

Retrospective, Single-Center Study in China: TAF Initiated Pre-Conception[12]

Study design and demographics

A retrospective, single-center study evaluated the effectiveness and safety of treatment with TAF 25 mg in 27 pregnant women with CHB. Patients were followed until postpartum Month 7. The primary endpoint was maternal and infant safety; the secondary endpoint was the HBsAg+ rate at postpartum Month 7 in infants. All infants received immunoprophylaxis. The median age of patients was 32 years, and most (77.78%) began TAF treatment prior to conception.

Results

At the first visit (median gestational age, 26 weeks), 65.38% of patients (17/26) were HBeAg+, 57.14% (12/21) achieved virologic response (defined as HBV DNA $<5 \times 10^2$ IU/mL), and 92.31% (24/26) achieved ALT normalization (defined as an ALT level <40 U/L). At a median of 2 months postpartum, 76.9% of patients (10/13) achieved virologic response, and 78.57% (11/14) achieved ALT normalization. No infants were HBsAg+ at postpartum Month 7.

No patients had abnormalities in eGFR values or urinary retinol-binding protein or β2MG levels during pregnancy. One patient underwent an abortion for nonmedical reasons. No infants had birth defects or malformations, and all had growth parameters (eg, head circumference, height, and weight) within normal limits.

PK Data: TAF Use in Pregnancy and Lactation

TAF PK in Breastfeeding Women With CHB

Study design and demographics[13]

A phase 4, open-label, multicenter, single-arm study evaluated the PK of TAF and TFV in women with CHB who were breastfeeding and infant exposure. Treatment with TAF 25 mg once daily was initiated during the third trimester or postpartum. Samples were collected

within 6 months postpartum once mothers had received ≥4 weeks of TAF from the following number of participants: maternal blood, n=8; breast milk, n=8; and infant urine, n=7. Maternal plasma and breast milk samples were collected predose and several times through 24 hours postdose; infant urine samples were collected via urine bag at Hour 0 through Hour 8. Primary outcomes included TAF and TFV PK parameters in maternal plasma and breast milk. Infant drug exposure was assessed via TFV concentrations in urine, maternal breast milk to plasma ratio, and the RID.

In mothers, the median (range) of demographics at baseline was as follows: age, 34.5 (26.8–39.7) years; weight, 64.9 (44.9–130.8) kg; HBV VL, 2692 (<20–7720) IU/mL; duration of TAF at sample collection, 6.6 (5–11.1) weeks; and timing of sample collection, 11.3 (6–15.4) weeks postpartum. In infants, the median (range) weight at the time of sample collection was 3.49 (2.5–5.45) kg.

Results

Within 6 to 8 hours after a dose, TAF levels were below the LoQ in breast milk and maternal plasma in 7 of the 8 mothers (Figure 3),[13] and the TAF $t_{1/2}$ was 0.8 hours in breast milk and 0.9 hours in maternal plasma (Table 19).[16] TFV levels remained generally stable after a dose in both breast milk and maternal plasma, but higher levels were observed in breast milk than in maternal plasma.[13]

Figure 3. PKs of TAF and TFV in Maternal Plasma and Breast Milk (Kayes et al)[13]

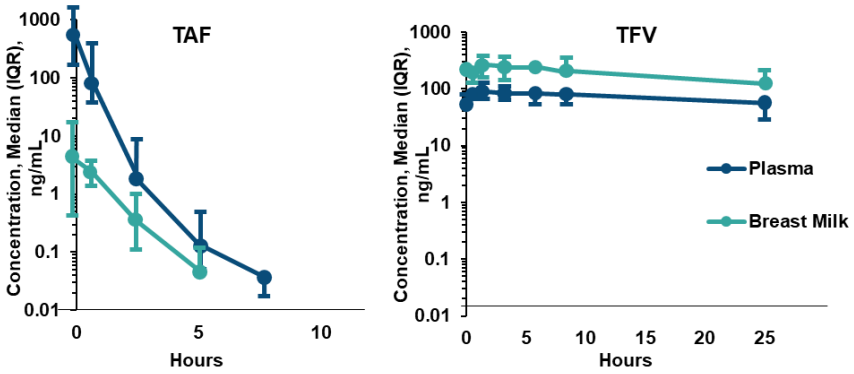


Table 19. PK Values (Non-Compartmental Analysis) of TAF and TFV in Maternal Plasma and Breast Milk (Kayes et al)[16]

PK Parameters, Median (IQR)	Maternal Plasma		Breast Milk	
	TAF	TFV	TAF	TFV
$t_{1/2}$, h	0.9 (0.7–1.1)	40.5 (18.5–65.1)	0.8 (0.8–2.2)	26.4 (18.5–33)
C_{max}, ng/mL	166.5 (84.5–354.8)	16.7 (11.3–19.9)	2.3 (0.9–11.6)	49.2 (30–58.5)
T_{max}, h	0.5 (0.5–1.1)	1.3 (0.7–2.6)	0.5 (0.5–1.3)	4.3 (3–8)
AUC_{all}, ng·h/mL	149.9 (70.9–214.3)	207.4 (146.4–305.6)	2.9 (2.4–3.4)	602.6 (517–1015.6)

Abbreviations: AUC_{all}=area under the concentration-time curve for all time points; C_{max}=peak concentration; T_{max}=time needed to achieve peak concentration.

The median (IQR) breast milk to plasma ratio of TFV was greater than that of TAF: TFV, 2.81 (2.04–3.98) and TAF, 0.03 (0.026–0.04); indicating that TFV was more concentrated in breast milk than plasma and TAF was diluted in breast milk. The RID of TAF (18.75 ng/kg/day) was calculated to be 0.005% of the maternal dose and was below the accepted standard of safe exposure (<10%). Three infant urine samples had TFV levels above the LoQ: 12, 24, and 25 ng/mL. There was no clear correlation between TFV levels in infant urine and maternal plasma and breast milk levels.[13] The median urine TFV level at

steady state in infants (5 ng/mL) was lower than the median levels of TFV in another study that was conducted in adults (1480 ng/mL).[13,17]

No safety data were provided.[13]

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Abbreviations

β2MG=β-2 microglobulin
AE=adverse event
ALP=alkaline phosphate
APR=Antiretroviral Pregnancy Registry
ARV=antiretroviral
BMD=bone mineral density
CHB=chronic hepatitis B
CK=creatine kinase
DM=diabetes mellitus
HAV=hepatitis A virus
HBeAg=hepatitis B envelope antigen
HBs=hepatitis B surface
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
HEV=hepatitis E virus
HTN=hypertension
LoQ=level of quantification
LTFU=lost to follow-up
MTCT=mother-to-child transmission
P2W/P4W=stopping medication 2/4 weeks postpartum
PEIU/mL=Paul Ehrlich Institute units per mL
PK=pharmacokinetic(s)
PP=per protocol
PROM=premature rupture of membranes
PS=propensity score
RID=relative infant dose
RR=risk ratio
S/CO=signal to cut-off ratio
$t_{1/2}$=half-life
TAF=tenofovir alafenamide
TB=total bilirubin
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TN=treatment naïve
ULN=upper limit of normal
VL=viral load

Product Label

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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