Plasma and breast milk pharmacokinetics of tenofovir alafenamide in mothers with chronic hepatitis B infection

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Summary

Background: Antenatal antiviral therapy (AVT) is effective in preventing mother-to-child transmission (MTCT) in chronic hepatitis B (CHB); tenofovir disoproxil fumarate (TDF) is the preferred agent. Tenofovir alafenamide (TAF) is a prodrug of tenofovir (TFV) similar to TDF, with improved bone and renal safety. There are no data on TAF breast milk pharmacokinetics and exposure to breastfeeding infants in CHB.

Aim: To assess the pharmacokinetics of TAF/TFV in breastfeeding women with CHB on TAF monotherapy.

Methods: Pregnant women with CHB requiring AVT commenced TAF 25 mg daily at third trimester or postpartum. Sample collection occurred while breastfeeding and taking TAF for minimum 4 weeks. Maternal blood, breast milk and infant urine samples were collected. Drug concentrations were measured by LCMS/MS analyses using validated methods. Non-compartmental analyses were performed to quantify the pharmacokinetic parameters.

Results: Eight women provided samples. In breast milk and plasma, median TAF half-life was 0.81 and 0.94 h, respectively, and $C_{\text{max}}$ 1.69 and 120.5 ng/ml, respectively. Median maternal breast milk to plasma (M/P) ratio of TAF was 0.029; for and TFV it was 2.809. The relative infant dose of TAF was 0.005% of maternal dose, well below safety threshold of 5–10%. TFV was detectable in three out of seven infant urine samples with median steady-state concentration of 5 ng/ml being 300–2500 times less than reported adult steady-state urine concentrations in those taking TAF and TDF, respectively.

Conclusions: In this first pharmacokinetic study of TAF monotherapy in breastfeeding women with CHB, concentrations of TAF and TFV were low in breast milk with negligible infant exposure, supporting the use of TAF to prevent MTCT.
1 INTRODUCTION

Approximately 257 million people live with chronic Hepatitis B (CHB) infection, most of whom were infected from mother-to-child transmission (MTCT).\(^1\,^2\) The risk of CHB-associated chronic liver disease, hepatocellular carcinoma and liver-related death is substantial, especially in those infected at birth.\(^3\) Current World Health Organisation (WHO) guidelines recommend all infants of hepatitis B surface antigen (HBsAg)-positive mothers, receive hepatitis B immunoglobulin and first dose of hepatitis B (HBV) vaccine within 24 h of birth to prevent MTCT; however, these measures may fail to prevent MTCT in almost 10% of mothers with high viral loads.\(^2\,^4\)-\(^6\) Antenatal antiviral therapy (AVT) significantly decreases MTCT in this group.\(^1\,^7\)

Tenofovir disoproxil fumarate (TDF) is the preferred agent, owing to its high antiviral potency, high barrier to viral resistance and superior safety profile, and is recommended by WHO in this setting.\(^2\,^4\,^8\)

Indications for commencing AVT for prevention of MTCT differ between regional guidelines.\(^8\) WHO has recommended antenatal AVT commencement with TDF for women with CHB infection when HBV DNA \(>200,000\text{IU/ml}\) (5.3 log\(10\text{IU/ml}\)). This should be commenced at the beginning of the third trimester (28–30 weeks of gestation) to suppress maternal viraemia and prevent transmission during the third trimester and at birth. Breastfeeding is encouraged as breastfed infants are at no higher risk of transmission compared to those that are formula-fed.\(^2\) Exposure to clinically significant doses of TDF or its active moiety, tenofovir (TFV) via breast milk is thought to be low based on pharmacokinetic studies of women who took TDF while breastfeeding with median breast milk/maternal plasma ratios between 0.03 and 0.07 and median ingested TFV in infants being 0.03% of the recommended infant dose.\(^9\) TDF is rapidly converted to tenofovir which is expressed in breast milk at low concentrations (<3% serum levels). Any TFV consumed via breast milk will have very low bioavailability in the foetus due to its charged anionic state.\(^10\)

Like TDF, tenofovir alafenamide (TAF) (Vemlidy\(^\text{®}\), Gilead Sciences Pty Ltd) is a nucleotide reverse transcriptase inhibitor pro-drug that produces the same intracellularly active metabolite, TFV. TAF is available as an alternative to TDF in human immunodeficiency virus (HIV) and CHB.\(^11\,^12\) Unlike TDF which rapidly converts to TFV in plasma, TAF remains stable within plasma and only converts to TFV intracellularly at peripheral blood mononuclear cells (PBMCs) and hepatocytes.\(^13\,^14\) In pharmacokinetic studies, 25 mg TAF has demonstrated 86%–91% lower serum concentration of TFV, and 6.5 times higher intracellular concentration of active metabolite TFV di-phosphate (TFV-DP) compared to 300 mg TDF.\(^12\,^15\)-\(^17\)

Due to higher systemic exposure to TFV, long-term use of TDF has been associated with decreased bone mineral density and impaired renal function.\(^16\,^18\,^19\) For TAF, 25 mg has equivalent viral suppression and less bone and kidney-related adverse effects compared to 300 mg TDF.\(^20\,^21\) TAF is effective in viral suppression and prevention of MTCT in highly viraemic mothers with no safety concerns for mothers or infants at 24–48 weeks follow-up.\(^11\) There are no data on TAF pharmacokinetics in breast milk and the exposure to breastfeeding infants in women with CHB.\(^22\)

The aim of this study was to determine the pharmacokinetics of TAF in breastfeeding women with CHB particularly steady-state serum, breast milk and infant urine drug concentrations.

2 METHODS

This was a phase IV, open label, single arm, multi-centre pilot study, evaluating the pharmacokinetics of TAF and its metabolite TFV, in breastfeeding women with CHB infection. The study was performed in compliance with current Good Clinical Practice (GCP) and was conducted at three public hospitals: Liverpool Hospital, NSW Australia; Auckland City Hospital and Middlemore Hospital in Auckland New Zealand. The study was registered on the Australian New Zealand Clinical Trials Registry and followed national regulatory authority guidelines with sites in each country obtaining local regulatory ethics approvals. Subjects provided written informed consent prior to study participation.

Pregnant women with CHB requiring AVT during their third trimester for prevention of MTCT or alternative CHB-related indication, including mothers continuing antiviral therapy with TAF or TDF that was initiated prior to pregnancy, were included. Those co-infected with HIV or Hepatitis C and other systemic diseases were excluded (Table 1). Mothers were required to predominantly breastfeed (supplementation with small amounts of formula was accepted). Patients on other AVT within the previous 6 months, except TDF, those with significant drug interactions or TDF were excluded. Subjects had to have normal liver function tests (serum alanine aminotransferase), normal renal function (creatinine clearance), and no significant laboratory abnormalities. Women who were pregnant at study inception or had a positive pregnancy test at any study visit were excluded. Women with severe mental illness, with a history of suicide attempts, or with a history of substance or alcohol abuse were also excluded.

TABLE 1 Inclusion and exclusion criteria

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Pregnant women (age 18 years or older) with HBV aged ≥18                           | Nucleos(t)ide analogue therapy (except TDF) within 6 months                      |
| Indicates to take AVT during third trimester of pregnancy and post-partum for either: | Significant co-morbidities including advanced liver disease, HIV or HCV co-infection, or other systemic disease |
| ○ Prevention of MTCT of HBV OR                                                     | Any concomitant regular medications except iron or folate as routinely recommended for pregnancy |
| ○ Treatment of active chronic hepatitis B (including mothers continuing AVT with TDF initiated prior to pregnancy) |                                                                                   |
| Willing to take TAF (Vemlidy\(^\text{®}\)) as antiviral therapy for at least 4 weeks |                                                                                   |
| prior to sample collection day, commencing within 5 months post-partum             |                                                                                   |
| Willing to participate in PK study within 6 months post-partum                     |                                                                                   |
| Intending to breastfeed infants while on TAF (can be supplemented with small amounts of formula) |                                                                                   |
co-morbidities or other concomitant regular medications except iron or folate supplementation were excluded (Table 1). Participants could either commence TAF during pregnancy and continue to post-partum period or take TDF (Viread®/Teva) during pregnancy then switch to TAF 25mg daily post-partum. A sample collection day was scheduled after minimum 4 weeks of TAF therapy.

Consenting participants underwent screening of clinical and laboratory parameters to confirm eligibility. Fortnightly, phone calls to enrolled patients were made to assess adherence, tolerability and side effects while on treatment. Patients were required to present to an on-site ambulatory unit for sample collection once within 6 months post-partum. Maternal blood, breast milk and infant urine samples were collected and stored.

Maternal blood and breast milk sampling were taken at the following time points: pre-dose, 0.5 h post-dose, 1–1.5 h post-dose, 2.5–3.5 h post-dose, 5–6 h post-dose, 8 h post-dose and 24 h post-dose. Breast milk collection was via a breast pump and infant urine samples were collected as described below. Samples collected were processed and prepared for shipping to the University of North Carolina at Chapel Hill Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core, Chapel Hill, North Carolina, USA.

Primary outcomes assessed were median (interquartile range, IQR) pharmacokinetic parameters of TAF and TFV in plasma and breast milk at steady-state dosing. When drug concentrations were below the predetermined lower level of quantification (LLOQ) of 0.05 ng/ml after Cmax, we calculated that value to be LLOQ/2 in our analysis. Non-compartmental analyses were performed (Phoenix WinNonlin version 8.2, Certara) to quantify pharmacokinetic parameters including area under curve (AUC), half-life (t1/2), peak serum concentration (Cmax) and time to peak serum concentration (Tmax). Linear regression correlations were used to compare drug levels in breast milk and plasma. Statistical analysis was performed using GraphPad Prism® (GraphPad Software, Inc.).

Infant drug exposure was assessed by determining infant urine TFV concentration from samples collected via urine bag attached at hour 0 and urine was collected through hour 8. Below limit of quantification (BLQ) was also assigned as LLOQ/2 if the concentration was below LLOQ of 10 ng/ml. Secondary measures of infant drug exposure through maternal breast milk were milk to plasma (M/P) ratios and Relative Infant Dose (RID). Calculated AUCfinal ratios were used to determine M/P ratios of TFV and TAF and C ss ave (AUC/dosage interval) was utilised to calculate RID. Daily infant breast milk consumption was assumed to be 150 ml/kg/day for these calculations. 23–25

3 | RESULTS

3.1 | Patient characteristics

There were 12 women enrolled in the study, three withdrew, two were not able to predominantly breastfeed, one was not able to continue as she was recruited just prior to COVID-19 restrictions which prevented patient presenting to ambulatory unit for sample collection and further recruitment, one was lost to follow-up. Of the included eight patients, median (range) age was 34.5 years (26.8–39.7), median (range) duration of TAF treatment at the time of sample collection was 6.6 weeks (5.0–11.1) and median (range) time post-partum 11.3 weeks (6–15.4) (Table 2). Baseline blood tests (prior to commencement of TAF) demonstrated median (range) viral load was 2692 IU/ml (<20–7720) and liver function tests within normal limits. Seven patients already on AVT with TDF commenced TAF post-partum. One patient commenced TDF then switched to TAF antepartum and her viral load was <20 at baseline (Table 2). Five women were born in South-East Asia, two in Tonga and one in New Zealand.

3.2 | Plasma and breast milk concentrations

The eight women provided total of 48 breast milk and plasma samples of which, only one breast milk sample was not able to be analysed due to insufficient sample volume. In breast milk and plasma, Cmax for TAF was reached at 0.5 h (Table 3), and at that time median
(IQR) concentrations were 1.7 ng/ml (0.22–5.65) and 120.5 ng/ml (41.60–308.50), respectively (Figure 1). By 6–8 h post-dose, median (IQR) TAF concentrations were BLQ for all but one woman, in breast milk and plasma (Figure 1). The $t_{1/2}$ was 0.8 h (0.8–3.3) and 0.9 h (0.7–1.1) in breast milk and plasma, respectively. The median TAF concentrations ranged from 0.06 to 11.6 ng/ml in breast milk and 0.06 to 481 ng/ml in plasma (Figure 2).

In contrast to TAF, TFV concentrations were relatively steady in breast milk and plasma at all time points (Figure 1) with median (IQR) $C_{max}$ 53.1 ng/ml (29.6–57.8) and 16.7 ng/ml (11.3–19.9), respectively, reached at $T_{max}$ of 5.5 h (3.0–8.0) and 1.3 h (0.7–2.6), respectively (Table 3). In breast milk and plasma, the median TFV concentrations at 0.5, 3, 8 and 24 h ranged from 7.1 to 58.7 ng/ml and 3.2–23.6 ng/ml, respectively (Figure 2). Average TFV concentrations over the 24 h in breast milk and plasma ($C_{ss\ ave}$) were 33.3 ng/ml (IQR 18.9–42.3) and 8.6 (IQR 6.1–12.7), respectively.

### 3.3 Milk to plasma ratio and relative infant dose

Median (IQR) AUC$_{ss\ ave}$ values for TAF were 2.9 ng·h/ml (2.4–3.4) and 149.9 ng·h/ml (70.9–214.3) and TFV were 584.7 ng·h/ml (453.7–1015.8) and 207.4 ng·h/ml (146.4–305.6) in breast milk and plasma, respectively. M/P ratios were calculated from AUC$_{ss\ ave}$ values of TAF and TFV based on concentrations that were not BLQ (Table 4). The median (IQR) M/P ratio of TAF was 0.03 (0.02–0.04) and TFV was 2.81 (2.04–3.98) demonstrating TAF is diluted in breast milk but TFV is concentrated in breast milk compared to plasma.

Nevertheless, the $C_{ss\ ave}$ for TAF was very low at 0.125ng/ml (IQR 0.103–0.141), as TAF concentrations were BLQ for the largest part of the dosing duration. Based on the $C_{ss\ ave}$, the infant daily exposure of TAF was calculated to be 18.75ng/kg/day. Median maternal weight was 64.9 kg and TAF dose 25 mg/day; therefore, the RID of TAF was calculated to be 0.005% of maternal dose of the drug.

### 3.4 Infant urine concentrations

TFV was detectable in three out of seven infant urine samples and the remaining four samples were BLQ. The three detectable infant urine concentrations of TFV were 12, 24 and 25 ng/ml (Figure 3) with median (IQR) maternal breast milk AUC$_{ss\ ave}$ 3.6, 6.9 and 2.3 ng·h/ml, respectively (Table 5). The median infant urine TFV concentration at steady state was 5 ng/ml. Infants with the highest urine TFV concentrations were not breastfed by mothers with the highest TAF plasma and breast milk AUC$_{ss\ ave}$ (Table 5).

### 4 DISCUSSION

This is the first study to evaluate steady-state breast milk pharmacokinetics of TAF and examine infant drug exposure using urine TFV concentrations. Our sample size was anticipated to be sufficient to detect quantifiable concentrations of TAF and TFV in human milk based on regulatory guidelines and findings from previous studies. We observed very low transfer of TAF into breast milk resulting in very low calculated infant exposure. The RID of TAF is 0.005% of maternal dose of the drug, which is well within the accepted safety threshold RID of 5%–10%. This is also lower than the RID of TDF reported in literature at 0.01%–0.04%. The median M/P ratio of TAF is 0.029 and this is comparable to the M/P ratio reported of TDF ranging 0.03–0.07. In contrast, the median M/P ratio of TFV is 2.8. Despite this concentrating of TFV, the overall concentration of plasma TFV remains low and infant drug exposure is estimated to be minimal. Furthermore, as TFV is a diatomic at physiologic pH with poor absorption, membrane permeability and oral bioavailability, only a negligible amount would be expected to reach infant plasma circulation.

To indirectly quantify infant drug exposure, we measured urine TFV concentrations. Measuring urine concentrations has been used to indicate TDF or TAF adherence in other studies and was a less invasive method for assessing exposure in infants. We found very low concentrations of TFV in infant urine with a median steady-state concentration of 5 ng/ml. We compared our findings to steady-state adult urine TFV concentrations reported in adults taking TDF and TAF, which were 12,504 and 1480ng/ml, respectively. This is 2500 and 296 times greater, respectively, than our infant urine steady-state concentrations, indicating negligible infant exposure to TFV. Furthermore, there was no correlation between higher infant urine TFV concentrations and corresponding maternal plasma or breast milk concentrations of TAF.

As reported in the general population, TAF is eliminated from plasma very quickly as reflected by mostly BLQ concentrations within 8h in breast milk and plasma. Our breast milk half-life of 0.81 h (0.8–3.3) is comparable to the reported plasma half-life of TAF. We also observed very little TAF in mature breast milk, demonstrated by median (IQR) AUC$_{ss\ ave}$ of 2.89 ng·h/ml (2.41–3.37) which is much lower than the median (IQR) plasma AUC$_{ss\ ave}$ of TAF at 149.92ng·h/ml (70.94–214.30). The median plasma half-life of

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**Table 3** Median (IQR) pharmacokinetic data of TAF and TFV in plasma and breast milk

|          | Half-life (hours) | $C_{max}$ (ng/ml) | $T_{max}$ (hours) | AUC$_{ss\ ave}$ ng·h/ml |
|----------|------------------|-------------------|------------------|-------------------------|
| Plasma TFV | 40.5 (18.5–65.1) | 16.7 (11.3–19.9) | 1.3 (0.7–2.6)    | 207.4 (146.4–305.6)     |
| Plasma TAF | 0.9 (0.7–1.1)    | 120.5 (41.6–308.50)| 0.5 (0.5–1.1)    | 149.9 (70.9–214.3)      |
| Breast milk TFV | 27.7 (20.0–35.4) | 53.1 (29.6–57.8) | 5.5 (3.0–8.0)    | 584.7 (453.7–1015.8)    |
| Breast milk TAF | 0.8 (0.8–3.3)    | 1.7 (0.22–5.65)  | 0.5 (0.5–1.3)    | 2.9 (2.4–3.4)           |

[Correction added on June 02, 2022, after first online publication: Table 3 has been updated]
TAF was 0.94 h and this is similar to other studies with plasma half-life 0.26–0.5 h.35–37 Median plasma $C_{\text{max}}$ and $T_{\text{max}}$ of TAF at 166.5 (84.48–354.75) and 0.5 (0.5–1.06), respectively, is also supported by other studies.36,37 As expected, plasma TFV concentrations were small with median $C_{\text{max}}$ 16.7 ng/ml. Breast milk TFV concentrations were higher with median $C_{\text{max}}$ 53.1 ng/ml and the half-life was shorter compared to plasma half-life. In comparative studies reporting pharmacokinetics of breastfeeding women on TDF, the plasma $C_{\text{max}}$ of TFV is almost six times lower in our study of TAF administration,9,10,16,31,38 whereas in breast milk, TFV concentrations are higher in women taking TAF compared to published breast milk values of women taking TDF.9,28,39 Nevertheless, the low infant urine concentrations, with four of seven samples BLQ, suggest this remains clinically inconsequential for infant exposure.28

The lack of a TDF group in our study and variability in collection times between studies precludes direct comparisons with published literature. However, investigations of TAF and TDF in
semen demonstrate a similar pattern of relatively higher TFV concentrations in seminal plasma with TAF administration compared to TDF administration. The mechanism of these observations has not been conclusively elucidated. Drug transporters such as P-glycoprotein and breast cancer resistance protein play critical roles in the blood-testis and blood-mammary tissue barriers; TFV is not a substrate of these efflux transporters, but TAF is a substrate of both. TAF that is not converted to TFV may be transported back to blood, while biotransformed TFV in the semen or breast milk may remain trapped in those fluids.

Pharmacokinetic and physiochemical differences between TAF and TDF also provide several hypotheses for the mechanism of increased TFV concentrations in physiologic sanctuaries with TAF administration. Both are pro-drugs of TFV, and TFV is phosphorylated to the active metabolite TFV-DP in cells. TDF is predominantly converted to TFV by gut and plasma esterases in plasma then transferred to breast milk via passive or facilitated diffusion down a concentration gradient. TAF is stable in plasma and undergoes hydrolysis in hepatocytes and immune cells by cathepsin A to TFV. TAF is fat soluble and may therefore be distributed in mammary alveoli more readily compared to TDF. TFV is a dianion at physiological pH with poor membrane permeability which likely accounts for comparatively lower breast milk concentrations in breastfeeding populations taking TDF due to its hydrolysis in plasma. Further mechanistic studies to determine the causes and pathways of TFV accumulation in breast milk with TAF administration are warranted.

Plasma pharmacokinetics of TAF have been previously reported, with one other study evaluating breast milk concentrations of TFV in women taking TAF. Yang et al determined breast milk concentrations of TFV in HBeAg-positive women taking TAF or TDF at third trimester and up to 30 days post-partum. Day three post-partum breast milk Cmax of TFV in women taking TAF was 101.2 ng/ml which is almost two times greater than we observed. Perhaps the nature of day 3 colostrum when alveolar epithelium is more porous enables greater diffusion of TFV into breast milk. In our study of mothers tested at median 11.3 weeks post-partum, milk flow and drug absorption by mammary tissue are established. The study by Yang et al was a method validation study for the quantification of TFV in breast milk (using ultra-performance liquid chromatography–tandem mass spectrometry), without comparative plasma and breast milk analysis of parent drug TAF, with TFV metabolite over dosage period so we are unable to make further comparison with our data.

Most guidelines recommend commencing AVT at the beginning of third trimester. Optimal timing to stop AVT after birth is not well established. Mothers may continue AVT to manage post-partum flares and the impact of breastfeeding on infant exposure required a definitive study rather than educated guesswork based on what was known, to allow informed decision-making. Short-term TDF use (median 8.57 weeks) does not impact long-term infant bone health. Maternal bone health also needs consideration and as most mothers may stay on AVT for a longer period, the risk of osteopenia while breastfeeding on TDF, is an important consideration. As TAF has lower bone-related side effects in adults compared to TDF in the long term, this may be a better option and should be confirmed by evaluating clinical outcomes in breastfeeding mothers.

### TABLE 4 Milk to plasma ratios of each patient using AUC<sub>all</sub>

|   | M/P TAF | M/P TFV |
|---|---------|---------|
| 1 | 0.13    | 2.06    |
| 2 | 0.04    | 6.58    |
| 3 | 0.01    | 1.37    |
| 4 | 0.03    | 1.96    |
| 5 | 0.02    | 3.34    |
| 6 | 0.03    | 3.72    |
| 7 | 0.04    | 2.28    |
| 8 | 0.02    | 4.76    |
| Median (IQR) | 0.029 (0.016–0.039) | 2.81 (2.03–3.98) |

### TABLE 5 Infant urine concentrations of TFV with corresponding median maternal TAF AUC<sub>all</sub> in plasma and breast milk

| Urine TFV concentration (ng/ml) | Maternal plasma AUC<sub>all</sub> (ng·h/ml) | Maternal breastmilk AUC<sub>all</sub> (ng·h/ml) |
|--------------------------------|-------------------------------------------|---------------------------------------------|
| 1 5<sup>a</sup>               | 18.6                                      | 2.5                                         |
| 2 5<sup>a</sup>               | 75.8                                      | 2.9                                         |
| 3 5<sup>a</sup>               | 331.6                                     | 1.9                                         |
| 4 12                          | 116.0                                     | 3.6                                         |
| 5 5<sup>a</sup>               | 200.8                                     | 3.3                                         |
| 6 24                          | 254.7                                     | 6.9                                         |
| 7 25                          | 56.4                                      | 2.3                                         |
| 8 –                            | 183.8                                     | 2.8                                         |

<sup>a</sup>Concentrations below LLOQ of 10 ng/mL were assigned as LLOQ/2.
receiving TAF for CHB and their infants. Our data are reassuring that infant exposure to TFV in established breastfeeding is likely low, suggesting little impact on infant outcomes when maternal AVT continues at length post-partum.

5 | LIMITATIONS

Due to challenges of mothers with newborn infants presenting for plasma and breast milk sampling, it was not feasible to ensure they all presented at the same time post-partum. Hence, duration of prior treatment on day of sample collection varied. Furthermore, recruitment was halted at the onset of the COVID-19 pandemic to reduce risks to women and infants and this prevented including a larger sample size.

This study is primarily ‘lactating women only’ design meaning that infant exposure is extrapolated and infant PK was not directly studied. However, we used infant urine TFV concentrations to estimate infant exposure, rather than pursue a ‘mother-infant pair’ design as analysing infant plasma concentrations of TAF and TFV was not feasible.

6 | CONCLUSION

This is the first human pharmacokinetic study of TAF monotherapy in breastfeeding women with CHB. The concentrations of TAF and TFV in breast milk are reassuringly low and we found no evidence of significant infant exposure. These results support the use of TAF to prevent MTCT in pregnant and breastfeeding women.

AUTHORSHIP

Guarantor of the article: Miriam T. Levy.

AUTHOR CONTRIBUTIONS

Tahrima Kayes: Software (supporting); visualization (supporting); writing – original draft (lead); writing – review and editing (lead).

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Angela DM Kashuba: Conceptualization (equal); formal analysis (equal); investigation (equal); resources (equal); supervision (equal); writing – review and editing (supporting).

Miriam T Levy: Conceptualization (lead); formal analysis (equal); investigation (equal); resources (equal); supervision (equal); writing – review and editing (supporting). All authors approved the final version of the manuscript.

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