



Review

Guides concerning tenofovir exposure via breastfeeding: A comparison of drug dosages by developmental stage



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ABSTRACT

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, and after being administered orally, it converts to tenofovir in the blood. With the increasing use of TDF in women for treatment and prevention of mother-to-child transmission (MTCT) of both human immunodeficiency virus (HIV) and hepatitis B virus (HBV), or the pre-exposure prophylaxis (PrEP) for HIV, many nursing mothers have to understand the risk of exposure to tenofovir via breastmilk and make the decision about breastfeeding while on TDF treatment. Despite the safety record of TDF in pregnancy, some guidelines recommend against its use during breastfeeding. In this paper, we compared the dosage levels of tenofovir exposure in fetuses, breastfed infants, and children receiving tenofovir treatment. We found that breastfed infants were exposed to only 0.5%–16% of the tenofovir dosage that fetuses experienced via placental transfer, and 0.01–0.04% of the recommended weight-adjusted therapeutic dose. The assessment of toxicity risk from the dose perspective is an important and natural way of addressing safety concerns about exposure to tenofovir via breastfeeding. Based on the safety data from fetuses and children with tenofovir exposure, and the comparatively negligible exposure dosage from breastfeeding, our study supports mothers on TDF treatment should be encouraged to breastfeed.

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Introduction

Breastfeeding has important benefits for both infants and their mothers. The World Health Organization (WHO) recommends that breastfeeding should be started from one hour after birth up for to two years or beyond (WHO, 2019). However, breastfeeding may increase the risk of vertical transmission from the mother-to-child transmission (MTCT) of HIV (WHO, 2016b). In places such as the United States and Europe, HIV infected mothers are advised to avoid breastfeeding (Centers for Disease Control and Prevention, 2019; EACS, 2018; de Ruiter et al., 2014), but in resource-limited settings clean water and affordable replacement feeding are not accessible. WHO recommends antiretroviral treatment during the breastfeeding period under the current global “test and treat” strategy to further reduce the risk of MTCT (WHO, 2016b).

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, and it was designed to overcome tenofovir's poor membrane permeability and oral bioavailability. After being administered orally, TDF is quickly absorbed from the gut and is converted into tenofovir, the pharmacologically active drug. Because only TFV is present in breast milk and it has poor absorption, blood exposure to TFV by an infant would be extremely low. TDF is being widely used, including preventing MTCT of HIV infection (WHO, 2016a) and hepatitis B virus (HBV) infection (European Association for the Study of the Liver, 2017; WHO, 2015; Sarin et al., 2016; Terrault et al., 2018), and also as the backbone of HIV pre-exposure prophylaxis (PrEP) (Fonner et al., 2016). Data from HIV treatment practices showed tenofovir use in pregnancy and breastfeeding is safe and effective to HIV infected mothers and their exposed infants (Nachega et al., 2017). Also, in the context of HIV PrEP, the safety data of TDF-based regimen during pregnancy and the lactation period among HIV negative women were also satisfactory (Mofenson et al., 2017). Now it has been recommended by the WHO as part of a comprehensive HIV prevention package during the antenatal and postnatal period for mothers and infants (WHO, 2016a).

Currently, there are an estimated 257 million people chronically infected with HBV worldwide, which is associated with significant mortality related to cirrhosis, liver failure, and hepatocellular carcinoma (Maini and Bertolotti, 2017). MTCT is also the main transmission route of HBV infection, many guidelines recommend TDF-based therapy for pregnant women with high HBV viral loads to further reduce HBV MTCT in addition to vaccination and passive immunoprophylaxis for infants (European Association for the Study of the Liver, 2017; WHO, 2015; Sarin et al., 2016; Terrault et al., 2018). In contrast to HIV, breastfeeding does not pose any additional risk of HBV MTCT (Hill et al., 2002). However, there are inconsistent recommendations on whether HBV-infected mothers who are on TDF treatment should breastfeed or not. In the US and European guidelines (European Association for the Study of the Liver, 2017; Terrault et al., 2018), breastfeeding is not discouraged while the mother is on TDF treatment. But in the TDF drug labels and WHO guidelines (WHO, 2016a), as well as the clinical practice guidelines of Asian Pacific (Sarin et al., 2016) and the guideline established by Chinese Society of Hepatology in China (Hou et al., 2017), there were no clear instructions about breastfeeding by HBV infected mothers who are on TDF treatment. The reasons behind the inconsistency of those guidelines may include the gap in the long-term safety data about tenofovir exposure through breastfeeding, although tenofovir excretion to breast milk is known to be low.

To help address safety concerns of tenofovir exposure during the lactation period, we conducted this review and

analysis to: (1) to summarize the long term (one year after birth) safety data including bone development among infants who had maternal TDF exposure; (2) estimate the daily tenofovir exposure dose through breast milk, and compare this low dosage with tenofovir exposure in children with the recommended therapeutic dose to contextualize the exposure via breast milk and in fetuses with maternal TDF treatment. The purpose of this review is to provide developmental stage-based dosages and safety data to assist clinicians and others in their discussion about breastfeeding with nursing mothers who receive TDF treatment.

Methods

Data sources and search strategy

We performed a systematic search of the literature in the following databases (from inception to March 2019): PubMed, World Health Organization (WHO) Global Index Medicus, trials in progress (International Clinical Trials Registry Platform), and Web of Science. Keywords we used including tenofovir disoproxil fumarate (or TDF), Hepatitis B virus (or HBV), human immunodeficiency virus (or HIV), pregnancy, breastfeeding, pediatric(s), and children. Only studies or reports in humans and published in English were included in this review.

Quantification of tenofovir exposure

Tenofovir exposure via breast milk

We estimated daily tenofovir dose exposure from breast milk and calculated the relative infant dose of tenofovir. The daily dose and the relative infant dose were used in a previous study to contextualize the clinical significance of the measured drug concentration among breastfed infants (Mugwanya et al., 2016). The drug dose received from breast milk per day was the tenofovir concentration in breast milk multiplied by the daily volume of breast milk consumption, which was calculated as 150 mL/kg/day (Hirt et al., 2009). The relative infant dose was calculated as the percentage of the daily dose from breast milk divided by the weight-adjusted recommended infant dose. By using PK methods, one study estimated that infants should receive 6 mg/kg/day of tenofovir for preventing HIV transmission, which corresponded to 11–13 mg/kg/day of TDF for oral administration (Hirt et al., 2009).

Trans-placental exposure to tenofovir

Cord-to-maternal concentration ratio is often used as an index of relative drug exposure. However, a population pharmacokinetics study found that the median cord-to-maternal ratio of tenofovir concentration at delivery was 71%, and ranged from 8% to 101% (Hirt et al., 2009). The researchers believed that a more representative measure of placental transfer could be the ratio between neonatal and maternal tenofovir area under the curve (AUC) for 24 h since this ratio was relatively constant at 60%, when the delay between TDF administration and delivery was more than four hours (Hirt et al., 2009). In our review, we recalculated the fetus exposure to tenofovir by multiplying the maternal tenofovir concentration with the ratio of neonatal-to-maternal concentration of 60%.

Comparison of tenofovir dosage by developmental stage

We assessed the toxicity risk from breastfeeding from the dose perspective and compared tenofovir exposure by developmental stage: (1) Estimating relative infant dose from breastfeeding and the weight-adjusted therapeutic oral doses, and (2) Comparing tenofovir exposure in breastfed infants with that in fetuses from maternal TDF treatment.

Findings

Safety data among infants who had maternal TDF exposure

Many studies including reports from the Antiretroviral Pregnancy Registry have shown that there was no increased risk of congenital or other severe anomalies related to TDF used in pregnancy with the standard maternal dose of 300 mg/day. Additionally, the safety of TDF use in pregnancy was confirmed by a systematic review and meta-analysis in 2017 (Nachega et al., 2017). However, an animal study in macaques raised concerns about the potential adverse effect of TDF on infant bone mineral density, but the dose of TDF to the Rhesus monkey was 30 mg/kg/day, which was much higher than that administered to pregnant human beings (Castillo et al., 2002). A study by Siberry et al also reported maternal TDF use was associated with the statistically significant lower neonatal bone matter at the mean age of 15 days (Siberry et al., 2015). For a longer duration, however, Salvadori et al and Kourtis et al reported there were no significant effects of maternal TDF use on bone growth in infants at 6 months and one year of age (Kourtis et al., 2018; Salvadori et al., 2019). Despite possible safety signals at very high doses, it seems that the standard maternal dose of TDF exposure has not been linked to a significant effect on infants' bone growth over time.

Dosage of tenofovir exposure through breastfeeding

As seen in Table 1, three studies measured blood tenofovir concentration in infants when the mothers received 300 mg oral TDF per day for their HIV treatment. In a population pharmacokinetics (PK) study among 47 HIV infected mothers receiving long term treatment containing 300 mg oral TDF in Malawi, the median (interquartile range, IQR) tenofovir blood concentrations of the infants were 24 ng/ml (0–51.6) and 0 ng/ml (0–30) at the age of 6 and 12 months (Palombi et al., 2016); infants' tenofovir blood concentration from maternal PrEP treatment was also low: Tenofovir was only detected in three out of 50 infants (up to 24 weeks of age) exposed to maternal oral PrEP at the ages of 11 weeks, 13 weeks and 17 weeks. The tenofovir concentration in these infants' blood was 0.9, 0.9, and 17.4 ng/ml, respectively (Mugwanya et al., 2016). Another PK study among 48 HIV positive women treated with 300 mg TDF reported no infant had a measurable tenofovir concentration (Waite et al., 2018).

Tenofovir concentration in breast milk has been relatively well studied (Table 1). In the study including 16 breastmilk samples from five Ivorian mothers infected with HIV and treated with a

TDF-containing regimen of 300 mg per day since labor until seven days postpartum, the maximum concentration of tenofovir in breast milk was 14.1 ng/ml (IQR 11.60–16.25) (Benaboud et al., 2011). Palombi et al observed the concentration of tenofovir in breast milk was 5.0 ng/ml (IQR 0–6.1) at one month after birth and 2.5 ng/ml (IQR 0–5.5) at twelve months after birth (Palombi et al., 2016). Mugwanya et al found that the maximum concentration of tenofovir in breastmilk was 3.2 ng/ml (IQR 2.3–4.7) (Mugwanya et al., 2016). Waite et al reported maximum concentration was 6.0 ng/ml (IQR 0–8.1) at 101 days (range 81–146) and 143 days (range 80–125) after delivery (Waite et al., 2018).

Breastfed infants compared to children on tenofovir treatment

We estimated the infant daily tenofovir dose from breastmilk, and based on this, we calculated the relative infant dose. The daily tenofovir dose ingested from breastmilk is estimated at 0.4–2.1 µg/kg/day (see Table 1), which represented 0.01–0.04% of the proposed pediatric therapeutic daily dose of 6 mg/kg/day. The result was consistent with the report from a previous study that oral tenofovir dose in breastfeeding was only 0.03% of the oral tenofovir proposed dose for infants (Benaboud et al., 2011). The relative infant dose calculated in our study, and the poor absorption of tenofovir via breastfeeding resulted in an extremely low dose exposure by breastfed infants.

Breastfed infants compared to fetuses with maternal TDF treatment

Table 2 lists studies with the measurement of maternal blood tenofovir concentrations when the maternal dose of TDF was 300 mg, 600 mg or 900 mg (Best et al., 2015; Colbers et al., 2013; Hirt et al., 2009; Flynn et al., 2011). For mothers who took TDF at a dose of 300 mg per day for either HIV prevention or HIV treatment, the maternal plasma maximum tenofovir concentration during pregnancy ranged from 245–280 ng/ml (Best et al., 2015; Colbers et al., 2013). Therefore, breastfed infants experienced much lower drug exposure from breastmilk than the fetuses in utero (Figure 1). Our calculation indicated that the blood concentration of tenofovir in breastfed infants represented 0.5%–16% of those in exposed the fetuses.

Our study has some limitations. First, the approach we used to calculate the drug dose from breast milk was based on the drug concentration in the milk multiplied by 150 mL/kg per day, but there were differences between studies: some studies only estimated the drug concentration at a single time point (Palombi et al and Mugwanya et al), whereas others calculated the AUC for

Table 1
Dosage of tenofovir exposure in breastfed infants when nursing mothers were on TDF treatment.

Citation year (References)	Infants' blood TFV concentration (ng/mL) (Number of samples)	Median concentration of tenofovir in breast milk (ng/mL)	Infant daily dose of tenofovir in breast milk (µg/kg/day)*	Relative infant dose %
Palombi et al. (2016)	Median (IQR): 24 (0.0–51.6) (n = 33)	5.0	0.8	0.01%
	Median (IQR): 0.0 (0.0–30) (n = 47)	2.5	0.4	0.01%
Mugwanya et al. (2016)	0.9 (n = 1) 0.9 (n = 1) 17.4 (n = 1)	C _{max} 3.2	0.5	0.01%
Waite et al. (2018)	BLQ	C _{max} 6.0	0.9	0.02%
Benaboud et al. (2011)	NA	C _{max} 14.1	2.1	0.04%

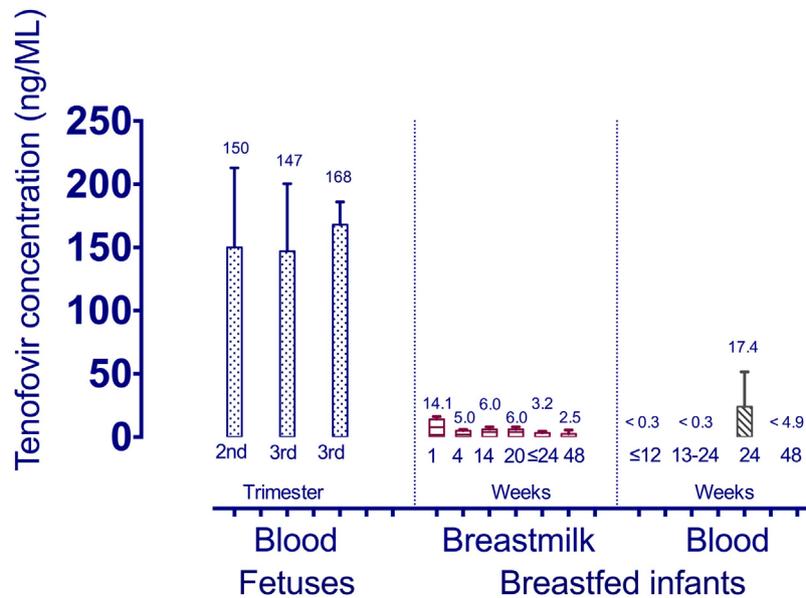
Abbreviations: TDF, tenofovir disoproxil fumarate; TFV, tenofovir; IQR, interquartile range; C_{max}, maximum concentration; BLQ: Below the Limit of Quantitation.

*The daily amount of breast milk consumed by an infant was assumed to be 150 mL/kg/day; relative infant dose represents the daily amount of tenofovir dose an infant would ingest from breast milk as a percentage of the proposed pediatric therapeutic daily dose (6 mg/kg/day).

Table 2

The estimated blood tenofovir concentration in fetuses when mothers receiving TDF doses ranging from 300 mg to 900 mg per day.

Citations year (References)	Study types	Maternal dose (mg/day)	Median C _{max} of maternal blood TFV concentration (ng/mL)	Estimated blood TFV concentration in fetuses, at 60% of maternal levels (ng/mL)
Best et al. (2015)	PK study	300	250 245	150 147
Colbers et al. (2013)	Open-label multicenter phase IV study	300	280	168
Hirt et al. (2009)	PK study	600	310	186
Flynn et al. (2011)	PK study	600	234	140.4
		900	456	273.6

Abbreviations: TDF, tenofovir disoproxil fumarate; C_{max}, maximum concentration; PK, pharmacokinetic.**Figure 1.** Tenofovir concentration in two developmental stages. Median tenofovir concentration in the blood from fetuses and breastfed infants whose mothers were on TDF treatment, and in breastmilk from TDF-exposed mothers. Abbreviations: 2nd, second; 3rd, third.

breast milk exposure. Second, it is not feasible to quantify the volume of breast milk intake, so we assumed 150 ml/kg/day as the breast milk intake, and the intake level may vary in different populations. Third, we use 6 mg/kg/day of TFV to estimated relative infant dose, which corresponded to 11–13 mg/kg/day of TDF for oral administration. However, when Mirochnick et al administered TDF directly to neonates, they found the oral effective dose of TDF was 6 mg/kg/day (Mirochnick et al., 2014). In our study, since the infants' bioavailability, absorption rate and volume of distribution have not been established yet, we could not apply the estimated tenofovir dosage from breast milk to oral TDF dosage directly, hence we used 6 mg/kg/day tenofovir rather than TDF. As a result, we ended up comparing the exposure of infants through the placenta (where the drug is already in the circulation in its active form) vs through the breast milk (where the drug is delivered to the infant's GI tract in a non-bioavailable form) and so our estimate should represent the upper bound rather than the true exposure level from breastfeeding (Hirt et al., 2009). Fourth, there were substantial differences in study design between the included studies. In the Palombi et al study, the samples were not obtained from mother/child pairs, so those infants who had tenofovir measured may not be the infants of the mothers who had their blood and breast milk concentration measured, which might make the infant blood concentration at 24 weeks to be a skewed data point. Lastly, the limits of detection were varied from 1 to 4.9 ng/ml

in milk and 0.31 to 16.6 ng/ml in blood. This may also generate differences in the median concentration of TFV in breast milk and in blood.

Conclusion

To achieve the goal of elimination viral hepatitis by 2030, the 3rd step is the preventive treatment to reduce Mother to child transmission which includes antiretroviral treatments. Continuation of treatment from birth to 3 months after delivery may be necessary (European Association for the Study of the Liver, 2017; Terrault et al., 2018; Sarin et al., 2016). Therefore, the number of women who are facing a breastfeeding decision is increasing, especially those living in low-middle income countries. In our study, most of the data were from HIV-infected mothers and their infants, in part because nowadays individuals with HIV infection are advised to take lifelong antiretroviral drugs regardless of pregnancy. HIV and HBV share a similar transmission route and TDF is recommended to treat both infections. Besides, the TDF exposure to infants born to HIV infected mothers is generally longer than those born to HBV infected women. It is likely that what we learn from infant exposure in the context of HIV can be applied to infant exposure because of HBV infection. From the toxicology perspective, safety concerns about exposure to tenofovir via breastfeeding are baseless in light of the extremely low

exposure through breastfeeding. Considering the known benefits of breastfeeding, the comparatively low drug exposure, and TDF's safety profiles during pregnancy and in children, we recommend that women who receive TDF treatment due to either HBV or HIV should be encouraged to breastfeed.

Conflict of interest

We declare no conflict of interest.

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Ethical approval

No ethical approval was sought.

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