Drug Safety Evaluation

Safety of oral tenofovir disoproxil fumarate-based HIV pre-exposure prophylaxis use in lactating HIV-uninfected women

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Abstract

**Introduction:** In settings where HIV is prevalent in heterosexual populations, pregnancy and postpartum breastfeeding periods can be associated with substantial HIV acquisition risk. Pre-exposure prophylaxis (PrEP) with daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine is an attractive HIV prevention option for women who are lactating but data are limited on its safety during the lactation period.

**Areas covered:** We provide a concise synthesis and summary of current evidence on the safety of TDF-based PrEP during breastfeeding. We conducted a review, searching Pubmed database and major PrEP conferences for primary studies with TDF-based PrEP exposure during postpartum breastfeeding.

**Expert opinion:** TDF-based oral PrEP is an effective female-controlled HIV prevention option. There is evidence...
ABSTRACT

1. Introduction

In settings where HIV is prevalent in heterosexual populations, women have higher than acceptable HIV risk during pregnancy and lactation, with reported pooled cumulative HIV incidence of 3.8 per 100 woman-years (4.7/100 woman-years during pregnancy and 2.9/100 woman-years during lactation period) in one review [1, 2]. Elevated risk during these periods in many of these settings is because the general HIV risk is higher than acceptable but may also result from infrequent condom use, unknown partner’s HIV status, and biologic changes in women during pregnancy and lactation or changes in their partner’s sexual behavior that increase susceptibility to HIV [3–10].

Pre-exposure prophylaxis (PrEP) using either daily oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF/emtricitabine (TDF/FTC) is an effective HIV prevention option for individuals at substantial risk for HIV including women who are or might become pregnant or are breastfeeding [11–14]. However, clinical trials that established the efficacy of PrEP for HIV prevention excluded

2. Mechanism of action and clinical pharmacology

3. Clinical application of TDF-based PrEP for HIV prevention

4. Safety evaluation

5. Comparison with safety of potential alternative PrEP drugs

6. Conclusions

KEYWORDS: Breastfeeding, pre-exposure prophylaxis, tenofovir disoproxil fumarate, HIV prevention, HIV uninfected women

7. Expert opinion
pregnant and lactating women, and uncertainty about the safety of PrEP during lactation has the potential to limit large-scale PrEP implementation among women in settings and populations where both HIV infection and breastfeeding are common. In this review, we provide a concise synthesis and summary of current data on the clinical safety of using TDF-based PrEP during lactation.

2. Mechanism of action and clinical pharmacology

TDF is a prodrug for tenofovir (Box 1), an acyclic nucleotide analog reverse-transcriptase inhibitor [15]. Tenofovir is a potent competitive inhibitor of HIV and hepatitis B virus (HBV) reverse transcriptase that is additive or synergistic when combined with other antiretroviral agents inhibiting viral replication [15]; for both HIV and HBV, it has a high genetic barrier for the development of viral resistance mutations. It has a long elimination and intracellular half-life (\(\sim 17\) and \(>60\) h, respectively), allowing for once-daily dosing. Tenofovir has poor bioavailability, but after oral administration as TDF, it is rapidly converted into tenofovir which is subsequently metabolized intracellularly to tenofovir diphosphate, its active metabolite [16]. Tenofovir readily crosses into placenta and amniotic fluid but only appears in suboptimal levels in breast milk [17–19]. For breastfeeding women taking oral TDF PrEP, breastmilk will exclusively contain tenofovir in an unconjugated form, and because of its poor oral bioavailability, negligible tenofovir concentrations would be expected to be excreted into breastmilk and subsequently available to the infants through breastfeeding. Studies of pregnant women on TDF for treatment of HIV infection have reported tenofovir umbilical cord levels >70–100% compared to maternal plasma concentration indicating high placental transfer [19–21]. TDF is classified as US Food and Drug Administration Pregnancy Category B meaning that animal reproduction studies fail to demonstrate a risk
to the fetus, and adequate, but well-controlled, studies of pregnant women have not been conducted. FTC, a nucleotide reverse-transcriptase inhibitor, is structurally similar to lamivudine, which has been extensively used and studied for HIV treatment and prevention of mother-to-child HIV transmission as well as for the treatment of HBV infection. FTC has shown to have good placental transfer (>80% of plasma concentration) and readily crosses into the breast milk. Both TDF and FTC are not inducers or substrates for cytochrome P450 enzymes but are primarily eliminated unchanged in urine by a combination of glomerular filtration and active proximal tubular secretion. TDF, alone or with FTC, when used as PrEP is generally safe and well tolerated. Small but nonprogressive decreases in estimated creatinine clearance levels and decreases in bone mineral density can occur in a minority of persons taking TDF as PrEP, but these quickly resolve within weeks of discontinuing PrEP. 

3. Clinical application of TDF-based PrEP for HIV prevention

PrEP has been shown to protect against HIV acquisition by 44–75% in randomized comparisons versus placebo and by >90% in persons adherent to PrEP as prescribed. PrEP is effective in both men and women when taken with sufficient adherence including in groups with substantial HIV risk (e.g. young women, HIV-serodiscordant couples, men who have sex with men, and injection drug users). In 2012, the US FDA approved daily oral FTC/TDF for HIV prevention in persons with heightened risk for HIV in combination with other HIV prevention strategies, and other nations have
subsequently done the same. Normative organizations including the US Centers for Disease Control and Prevention and the World Health Organization (WHO) issued guidelines recommending PrEP be offered as a prevention option to persons at substantial risk for HIV acquisition [29,30]. TDF alone is also effective for HIV prevention and is recommended as an alternative to FTC/TDF by the WHO. PrEP is not for lifelong use but recommended for daily use during periods of substantial HIV risk. Given the extremely low concentration of PrEP medications (i.e. tenofovir and emtricitabine) that the breastfed infant would receive via breast milk, oral PrEP given to the lactating HIV-uninfected mother will not be a direct PrEP to the breastfeeding infant but preventing HIV infection in the mother indirectly prevents HIV infection in her child.

4. Safety evaluation

We conducted a review of literature to identify published reports in English on HIV-uninfected lactating women who received oral PrEP with TDF alone or in combination with FTC during breastfeeding. A search of PubMed electronic database was performed using combination search terms (tenofovir and lactation; tenofovir PrEP and breastfeeding; tenofovir and breast milk; PrEP in breastfeeding; and preexposure prophylaxis and breastfeeding) through March 2017. Manual searches of references from relevant articles and abstracts from relevant conferences between 2010 and 2017 including the Conference on Retroviruses and Opportunistic Infections were also performed. Because of the extensive data on the safety of FTC in treatment and prevention of mother-to-child transmission of HIV, the focus of this review is on the TDF effects on infant growth outcomes when used as PrEP by HIV-uninfected women breastfeeding a child.

Overall, 85 records were identified from the literature search, with 55 unique records retained after removal of
duplicate records. Screening of titles identified only one study that addressed the primary focus of this review [18], use of TDF-based PrEP in lactation. The remaining 54 unique reports were not included in the primary review because they were reviews/policy documents (n = 28), or not relevant to topic of focus (n = 13), or were in animals (n = 2) or vaginal TDF gel study (n = 1), or were either pharmacokinetic (PK) or safety studies of TDF-containing antiretroviral therapy (ART) during pregnancy or lactation (n = 10); however, these articles were how considered as corollary information from HIV-infected populations. An additional seven studies of TDF use in HIV-uninfected women identified through manual search of published articles were reviewed: five from HBV-monoinfected women [31–35] and two PrEP studies of HIV-uninfected women [11,27].

4.1. HIV-uninfected women using TDF-based PrEP during breastfeeding

There are limited data on PrEP in HIV-uninfected women during breastfeeding. In PrEP clinical trials, medication was discontinued for those who became pregnant and was not reinitiated in women who were breastfeeding a child. Only one small pharmacokinetic study reported PrEP use during breastfeeding [18]. This study which included 50 HIV-uninfected mother–infant dyads, half with infants aged <12 weeks and half with infants aged 13–24 weeks, evaluated the transfer of tenofovir and emtricitabine in breast milk and the extent of infant exposure when daily FTC/TDF was used as PrEP by lactating HIV-uninfected women. PrEP was administered to women through daily directly observed therapy for 10 consecutive days and then discontinued thereafter. Non-fasting peak and trough samples of maternal plasma and breast milk were obtained at concentration steady states on days 7 and 10, and a single infant plasma sample was obtained on day 7. In that study, tenofovir was excreted into breast milk in very small quantities, and tenofovir was unquantifiable in 94% of 49 infant samples. Based on the concentration in breast milk,
the doses of tenofovir a breastfeeding infant would be expected ingest daily from breastfeeding were estimated to be the equivalent of <0.01% of the proposed pediatric doses for treatment of infant HIV infection and for prevention of infant postnatal HIV infection. As has been reported for lamivudine [36], emtricitabine levels were somewhat higher in breastmilk and detectable in infant plasma, but the concentrations were still small and represented 200-fold lower (or 0.5%) than those achieved with pediatric therapeutic dosing. No significant adverse events were noted in mothers or infants in that 10-day study.

In addition to these limited data on TDF-based PrEP exposure during lactation, there are encouraging safety data available from infants born to HIV-uninfected women with first trimester TDF exposure in PrEP trials as well as HIV-uninfected women using TDF for prevention of vertical HBV transmission. In the Partners PrEP Study [11], there was no evidence to suggest growth restriction based on z-scores computed from serial weight, height, or head circumference or infant creatinine at age 1 and 3 months [37]. Similarly, no substantial infant adverse growth outcomes have been seen in data from HBV-monoinfected women using TDF during pregnancy or breastfeeding [31–35] although most of these studies discouraged women from breastfeeding while on TDF treatment.

4.2. Corollary information from HIV-infected women using TDF-based HIV treatment and from use of TDF during pregnancy

Although data on TDF PrEP use during breastfeeding are very limited, the safety of TDF and FTC during breastfeeding can be extrapolated from research among HIV-infected women taking antiretroviral therapy for HIV treatment and for prevention of maternal-to-child HIV transmission. TDF and FTC are recommended by global treatment guidelines for use in pregnant women.

Data on use of TDF and FTC in pregnancy and lactation among HIV-infected women for HIV treatment have been
reviewed extensively [38]. Briefly, data have been generally reassuring [38–43]. The Antiretroviral Pregnancy Registry database that includes data from >3000 infants exposed to TDF and FTC in the first trimester in the US sufficient to rule out up to twofold increase in risk of birth defects, has shown no evidence of elevation in risk of congenital anomalies than would be expected in general population [44]. Infant outcome studies have suggested no substantive differences in infant adverse growth outcomes at birth or 12 months between children exposed to TDF versus non-TDF-exposed children [40,41,43,44]. Studies of markers of bone turnover or markers of renal injury in infants have found no substantial difference between TDF and non-TDF-exposed infants [39,40,43]. Recently, the PROMISE study observed lower rates of very preterm birth and neonatal mortality with Zidovudine/FTC/lipinavir–ritonavir (LPV/r) than TDF/FTC/LPV/r regimen, although this may have been related to concurrent TDF and LPV/r use [46]. Taken together, these data provide additional reassurance about the use of TDF and FTC as PrEP during lactation.

5. Comparison with safety of potential alternative PrEP drugs

Currently, fixed-dose, oral co-formulation of FTC/TDF (branded as Truvada®, Gilead Sciences Inc) is the approved regimen for PrEP in the US. The WHO recommends TDF-containing medications as PrEP, which includes TDF combined with FTC as well as potentially TDF alone and TDF combined with lamivudine. However, new PrEP drugs and formulations including other oral agents (maraviroc), intravaginal rings (dapivirine and tenofovir), and longer-acting injectable agents (rilpivirine and cabotegravir) are currently in the pipeline and may provide alternative strategies to daily oral PrEP in the future.
6. Conclusions

Data on infants breastfed by HIV-uninfected women using TDF-based PrEP are limited. However, available information suggests that tenofovir is excreted in breast milk in very small concentrations that are unlikely to be of substantial clinical consequence in breastfeeding infants of HIV-uninfected women using TDF-based PrEP. Extrapolation of data from TDF use in HIV-infected women and uninfected women during pregnancy and lactation are also reassuring in terms of maternal, pregnancy, and infant growth outcomes. Taken together, accumulated data support implementing PrEP in women at substantial HIV risk during lactation, but additional surveillance is still important. Thus, there is need for continued accrual of data on maternal and infant safety, infant growth, and pregnancy outcome information in PrEP research studies and implementation programs, in which women use PrEP throughout pregnancy and lactation.

7. Expert opinion

Women living in regions with high HIV prevalence are at high risk of HIV acquisition in pregnancy and postpartum because they infrequently use condoms, do not know their partner's HIV status, and have biologic changes or changes in their partner's sexual behavior that increase susceptibility to HIV. For young women in Africa, where breastfeeding lasts often beyond the second year in most settings, women spend a significant part of their life either pregnant or breastfeeding a child. Indeed, over 40% of new infant HIV infections worldwide are estimated to be due to maternal HIV acquisition in pregnancy and postpartum [47]. Therefore, urgent implementation of effective HIV prevention options that do not require negotiations for safe sex or interfere with pregnancy or breastfeeding is a priority not only for women's health but also as an indirect protection to her child by preventing maternal HIV during breastfeeding in the
first place.

PrEP with TDF alone or when co-formulated with FTC is a potent prevention option for use during periods of elevated HIV risk including during breastfeeding in high HIV burden settings. A recent PK study in HIV-uninfected mother–infant dyads showing that tenofovir is excreted in breast milk in very small quantities with trivial infant absorption is reassuring – those data strongly suggest that PrEP can be safely used during breastfeeding without exposing an infant to pharmacologically important concentrations of PrEP medication.

Current WHO guidelines permit the use of PrEP during pregnancy and lactation. The benefits of breastfeeding are well documented, associated with infant survival particularly in resources-limited settings [48, 49], as well as cognition and bonding. Women in Africa at substantial risk for infection or at-risk women in other settings should not have to choose whether to breastfeed their child or protect themselves from acquiring HIV. In summary, TDF-based PrEP is a potent female-controlled HIV prevention option, for which the potential risks arguably are outweighed, at the public health level and for at-risk individuals, by its HIV prevention benefits that include indirect protection for infant from vertical HIV transmission as a result of preventing acute maternal infection during lactation.

Declaration of interest

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manuscript apart from those disclosed

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**The only published evidence on use of TDF-based PrEP during breastfeeding.**


• Provides corollary information from mon-HBV-infected women who used TDF during pregnancy and lactation.

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Provides comprehensive review of available evidence of safety of TDF use in pregnancy and lactation.


Provides corollary information from HIV-infected...
women who used TDF during pregnancy and lactation and infant adverse outcomes.


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