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Tenofovir

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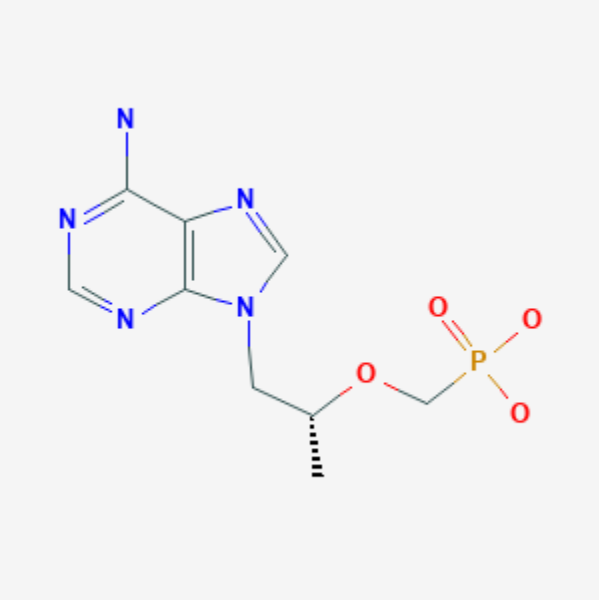

Drug Levels and Effects

Summary of Use during Lactation

Published experience with tenofovir during breastfeeding in HIV-positive mothers and HIV-negative mothers treated for HIV prophylaxis or hepatitis B infection indicates that the exposure of the infant to the drug is trivial.[1] A few infants have been breastfed during maternal tenofovir therapy and no adverse effects have been seen up to 2 years of age. Expert reviews of available data concluded that there is currently no justification for contraindicating the use of tenofovir for hepatitis B during breastfeeding.[2-4] Professional organization guidelines generally allow breastfeeding during tenofovir therapy, although one guideline cautions against it because of a lack of long-term safety data.[5-7] The lack of long-term safety data with long-term, low-level infant exposure should be discussed with the mother.[5] No differences exist in infection rates between breastfed and formula-fed infants born to hepatitis B-infected women, as long as the infant receives hepatitis B immune globulin and hepatitis B vaccine at birth. Mothers with hepatitis B are encouraged to breastfeed their infants

after their infants receive these preventative measures.[8,9] Maternal use of prophylactic vaginal tenofovir (investigational in the U.S.) does not appear to present a great risk to the breastfed infant.[10] Pre-exposure prophylaxis (PrEP) regimens containing tenofovir are considered to be acceptable for use in HIV-negative bursing mothers.[11]

In the United States and other developed countries, HIV-infected mothers should generally not breastfeed their infants. In countries in which no acceptable, feasible, sustainable and safe replacement feeding is available, World Health Organization guidelines recommend that all women with an HIV infection who are pregnant or breastfeeding should be maintained on antiretroviral therapy for at least the duration of risk for mother-to-child transmission. Mothers should exclusively breastfeed their infants for the first 6 months of life; breastfeeding with complementary feeding should continue through at least 12 months of life up to 24 months of life.[12] The first choice regimen for nursing mothers is tenofovir, efavirenz and either lamivudine or emtricitabine. If these drugs are unavailable, alternative regimens include: 1) zidovudine, lamivudine and efavirenz; 2) zidovudine, lamivudine and nevirapine; or 3) tenofovir, nevirapine and either lamivudine or emtricitabine. Exclusively breastfed infants should also receive 6 weeks of prophylaxis with nevirapine.[13,14] Use of tenofovir as an agent for pre-exposure prophylaxis (PrEP) in HIV-uninfected nursing mothers appears to pose little risk to their breastfed infants and might prevent vertical HIV transmission by preventing maternal infection.[15] Treatment of mothers of HIV+ mothers with efavirenz as part of Option B+ therapy does not appear to affect growth of their HIV-negative breastfed infants.

Drug Levels

Tenofovir has very poor bioavailability and is available commercially as the more bioavailable tenofovir disoproxil fumarate which is metabolized intracellularly to the active metabolite tenofovir diphosphate. The bioavailabilities of tenofovir and tenofovir diphosphate from breastmilk are not known, but presumed to be very low.

Maternal Levels. Five exclusively breastfeeding mothers received oral tenofovir 300 mg plus emtricitabine 200 mg and nevirapine 200 mg at the start of labor, then oral tenofovir 300 mg daily and emtricitabine 200 mg for 7 days postpartum. A total of 16 concurrent maternal blood and milk samples were collected on days 1, 2, 3, and 7 postpartum between 10 minutes and 21 hours after the mothers' doses. Median peak and trough tenofovir concentrations in breastmilk were 14.1 mcg/L and 6.8 mcg/L, respectively. The authors estimated that an exclusively breastfed infant would receive about 0.03% of the proposed infant dose for tenofovir and achieve trivial infant serum concentrations that would likely have no adverse consequences.[16]

In a multicenter study in Malawi and Brazil, mothers were given a single dose of either 600 mg or 900 mg of tenofovir during labor. Breastmilk samples were collected from mothers at various times postpartum. Tenofovir was detected (>2.5 mcg/L) in three-fourths of samples collected from 25 mothers during the first 2 days postpartum. Levels ranged from 6.3 to 17.8 mcg/L. At 4 to 6 days postpartum, only one milk sample of 21 had a detectable tenofovir level of 15.7 mcg/L.[17]

Women in Malawi received the option B+ regimen for prevention of mother-to-child transmission of HIV consisting of tenofovir, lamivudine and efavirenz between 6 and 8 pm daily. The tenofovir dose was not stated, but was presumably 300 mg daily. Milk samples collected in the morning from 33 women at month 1 postpartum had a median tenofovir concentration of 5 mcg/L (IQR 0 to 6.1 mcg/L). Milk samples collected in the morning from 47 women at month 12 postpartum had a median tenofovir concentration of 2.5 mcg/L (IQR 0 to 5.5 mcg/L).[18]

Seventeen women received 40 mg vaginal doses of 1% tenofovir gel daily for 6 days, with the first and last doses applied in clinic under observation. Two women reported using four doses at home, eleven women reported five doses, and two reported six doses. Breastmilk samples were collected before and 2, 4, and 6 hours after the first

and last doses. Only 25% of milk samples contained detectable (>1 mcg/L) tenofovir post-dose on day 0, 12.5% at pre-dose on day 6, and 37.5% post-dose on day 6. Breastmilk tenofovir concentrations ranged from 0 to 0.75 mcg/L on day 0 and from 0 to 1.6 mcg/L on day 6.[10]

Fifty HIV-negative women who were nursing their infants were given pre-exposure prophylaxis daily with the combination of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg by directly observed therapy for 10 days. On days 7 and 10 of therapy, peak milk samples were obtained 1 to 2 hours after a dose and trough samples were obtained 23 to 24 hours after the previous dose. The median peak milk tenofovir concentration was 3.2 mcg/L and the trough concentration was 3.3 mcg/L. These values represent an estimated daily dosage of 0.47 to 0.49 mcg/kg, which is less than 0.01% of the proposed infant therapeutic dosage.[19]

Tenofovir was measured in 6 HIV-positive nursing mothers after a 300 mg dose during ongoing therapy. Tenofovir reached a peak breastmilk concentration of 5.9 mcg/L (range 5.5 to 8.0 mcg/L) at an average of 3 hours (range 1 to 7) hours after the dose.[20]

Forty-eight Nigerian and Ugandan women took 300 mg of tenofovir disoproxil fumarate once

daily as part of a combination therapy for HIV. Expressed milk samples were taken before the dose and at several times in the 12 hours after the morning dose (n = 30) or at 12, 16 and 20 hours after a dose given the previous evening (n = 18). The median peak breastmilk concentration from dried breastmilk spots was 5.98 mcg/L (IQR 0 to 8.05 mcg/L) at a median of 4 hours after the dose (IQR 1 to 6 hours).[21]

Eleven mothers taking tenofovir disoproxil fumarate for chronic hepatitis B. The dosage of the drug and timing of milk samples were not specified in the abstract. Median milk levels were 669 mcg/L (IQR 4.88 to 7.03 mcg/L).[22]

A meta-analysis of 4 previous studies[16,18,19,21] calculated that breastfed infants would receive ony 0.03% of the recommend dose of tenofovir.[1]

Infant Levels. Five infants were exclusively breastfed by 4 mothers who took tenofovir 245 mg (presumably 300 mg of tenofovir disoproxil fumarate) daily. At an average of 1.8 months of age, infant serum tenofovir concentrations were measured. Tenofovir was undetectable (<0.005 mg/L) in the serum of 4 of the infants, and 0.0055 mg/L in the serum of one infant.[23]

In a study of women and their infants receiving antiretroviral therapy for HIV infection, mothers who received a tenofovir-containing regimen were compared to those who did not. The risk of infant death was reduced by 57% among infants who were breastfed and exposed to tenofovir compared to those who were not breasted. No alterations in growth and development were seen among breastfed infants in 2 years of follow-up.[24]

Blood samples were taken from 25 breastfed infants of mothers who were receiving option B+ regimen for prevention of mother-to-child transmission of HIV consisting of tenofovir, lamivudine and efavirenz between 6 and 8 pm daily. The tenofovir dose was not stated, but was presumably 300 mg daily. The median morning infant plasma concentration of tenofovir at 6 months of age was 24 mcg/L (IQR 0 to 51.6 mcg/L). The median morning infant plasma concentration of tenofovir at 12 months of age was 0 mcg/L.[18]

Seventeen women received 40 mg vaginal doses of 1% tenofovir gel daily for 6 days, with the first and last doses applied in clinic under observation. Two women reported four doses at home, eleven women reported inserting five doses, and two reported six doses. Infant blood was collected 6 hours after the maternal dose, which ranged from 1 to 4 hours after breastfeeding. Six infants (37.5%) had detectable tenofovir levels after the maternal dose on day 0, and 12 (75%) of infants post-dose on day 6. In infants with detectable tenofovir serum concentrations, day 6 levels were higher (median 2.4 mcg/L) than on day 0 concentrations (median 0). No difference was seen in the anti-HIV activity of breastmilk between day 0 and day 6.[10]

Fifty HIV-negative women who were nursing their infants were given pre-exposure prophylaxis daily with the combination of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg by directly observed therapy for 10 days. A single infant blood sample was obtained after the mother's 7th dose. Of 49 infant blood samples collected, 46 had an undetectable (<0.31 mcg/L) concentration of tenofovir. The 3 with detectable levels contained 0.9, 0.9 and 17.4 mcg/L of tenofovir.[19]

Tenofovir 300 mg daily was given to 6 HIV-positive nursing mothers. None of the breastfed infants had detectable tenofovir serum levels.[20]

Forty-eight Nigerian and Ugandan women took 300 mg of tenofovir disoproxil fumarate once

daily either in the morning or evening as part of a combination therapy for HIV. Their exclusively breastfed infants were fed on demand and had blood samples taken at 2 and 8 hours after the dose. Dried blood spots were analyzed and no infants had a measurable (>4.2 mcg/L) tenofovir blood concentration.[21]

Eleven infants breastfed (extent not stated) of mothers taking tenofovir disoproxil fumarate for chronic hepatitis B had undetectable (<4 mcg/L) tenofovir in their plasma. Timing of the samples was not stated.[22]

Effects in Breastfed Infants

Two newborn infants whose mothers were treated with tenofovir 245 mg (presumably 300 mg of tenofovir disoproxil fumarate) daily were exclusively breastfed for 3 months. At 4 months of age, neither showed any adverse outcomes on standard developmental parameters.[23]

Five women with hepatitis B infection were treated with tenofovir disoproxil fumarate 300 mg daily beginning in the third trimester of pregnancy and continuing postpartum. Although instructed not to breastfeed, 5 mothers breastfed (extent not stated) their newborn infants. No short-term adverse reactions were seen and the infants' HBsAg was negative between 28 and 36 weeks of age.[25]

Fourteen mothers were treated with tenofovir (dosage unspecified) during pregnancy (12 beginning in the first trimester) for hepatitis B. Three of the mothers breastfed while taking tenofovir. No adverse outcomes were noted in their breastfed infants up to 1 year of age.[26]

In a study of 17 nursing mothers who receive 40 mg of 1% vaginal tenofovir daily for 6 days, 4 of 17 infants had one or more adverse effects. There were a total of 8 adverse reactions. Seven were mild, and one had diarrhea that was thought to be related to tenofovir exposure.[10]

In a study of 50 infants breastfed by HIV-negative women who were given pre-exposure prophylaxis daily with the combination of tenofovir disoproxil fumarate 300 mg and emtricitabine 200 mg by directly observed therapy for 10 days, 2 infants reportedly had diarrhea lasting 2 to 3 days. No other side effects were reported.[19]

A study of 136 breastfed infants of mothers who took tenofovir, efavirenz and lamivudine during pregnancy and postpartum (Option B+) in Malawi measured bone markers at 1, 6 and 12 months of age. Markers included bone-specific alkaline phosphatase and C-terminal telopeptide of type I collagen. Although tenofovir is known to affect bone density and bone mineral density in adults, no effects were seen on infants' bone markers in the study.[27]

In a long-term study of tenofovir for chronic hepatitis B, 3 women reportedly breastfed their infants (extent not stated). None of the infants had any adverse effects up to 1 year of age.[28]

A prospective cohort study compared the growth and development of infants of HIV-negative mothers and infants of HIV-positive mothers taking tenofovir and efavirenz as part of Option B+ HIV treatment. Infants were followed up to 12 months of age. No differences in the groups was found in any growth parameters.[29]

A study of pregnant women with hepatitis B infection in China enrolled 143 women. Tenofovir disoproxil fumarate 300 mg daily was given starting at 22 to 33 weeks of pregnancy and continued postpartum. Thirty-one mothers breastfed (extent not stated) their infants who received standard hepatitis B prophylaxis. At 28 weeks postpartum, infant physical and neurologic development was within national standards and none had developed hepatitis B infection. Mild side effects of cough and fever were reported in >5% of infants. Less frequent reactions included skin rash, diarrhea, vomiting, jaundice and pneumonia. All adverse effects were judged not to be related to the drug by the authors.[30]

Effects on Lactation and Breastmilk

Relevant published information was not found as of the revision date.

Alternate Drugs to Consider

(Hepatitis B) Interferon Alfa, Lamivudine

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Substance Identification

Substance Name

Tenofovir

CAS Registry Number

147127-20-6

Drug Class

Breast Feeding

Lactation

Anti-Infective Agents

Anti-HIV Agents

Antiviral Agents

Anti-Retroviral Agents

Reverse Transcriptase Inhibitors