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Transfer of antiretroviral drugs into breastmilk: a prospective study from the Swiss Mother and Child HIV Cohort Study

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Introduction: In 2018, Switzerland changed its guidelines to support women living with HIV wishing to breastfeed. The exposure of antiretroviral drugs (ARVs) in breastmilk and the ingested daily dose by the breastfed infant are understudied, notably for newer ARVs. This study aimed to quantify ARV concentrations in maternal plasma and breastmilk to determine the milk/plasma ratio, to estimate daily infant ARV dose from breastfeeding and to measure ARV concentrations in infants.

Methods: All women wishing to breastfeed were included, regardless of their ARV treatment. Breastmilk and maternal plasma samples were mostly collected at mid-dosing interval.

Results: Twenty-one mother/child pairs were enrolled; of those several were on newer ARVs including 10 raltegravir, 1 bictegravir, 2 rilpivirine, 2 darunavir/ritonavir and 3 tenofovir alafenamide. No vertical HIV transmission was detected (one infant still breastfed). The median milk/plasma ratios were 0.96/0.39 for raltegravir once/twice daily, 0.01 for bictegravir, 1.08 for rilpivirine, 0.12 for darunavir/ritonavir and 4.09 for tenofovir alafenamide. The median estimated infant daily dose (mg/kg) from breastfeeding was 0.02/0.25 for raltegravir once/twice daily, 0.01 for bictegravir, 0.02 for rilpivirine, 0.05 for darunavir/ritonavir and 0.007 for tenofovir alafenamide, resulting in relative infant dose <10% exposure index for all ARVs.

Conclusions: ARVs were transferred to a variable extent in breastmilk. Nevertheless, the estimated daily ARV dose from breastfeeding remained low. Differential ARV exposure was observed in breastfed infants with some ARVs being below/above their effective concentrations raising the concern of resistance development if HIV infection occurs. More data on this potential risk are warranted to better support breastfeeding.

Introduction

Until recently, guidelines in high-income settings advised women living with HIV not to breastfeed and to give formula milk to their babies. Due to the important health advantages of breastfeeding for the newborn and the mother and the recent evidence of very low mother-to-child transmission through breastmilk,[1] the benefits and risks of this approach are balanced and more women

with HIV decide to breastfeed, even in high-resource settings.[2] Switzerland changed its guidelines in 2018 to suggest a shared decision-making process and support women living with HIV who wish to breastfeed.[3]

The main concerns about the transfer of maternal antiretroviral drugs (ARV) via breastmilk to the newborn are the potential for development of HIV resistance in infants in case of HIV infection and the potential toxicity of long-term ARV exposure via breastfeeding.

To date, nearly all reports about ARV transfer in breastmilk came from low-income and middle-income countries. First generation ARVs were shown to transfer in breastmilk to a various extent with low, moderate and high levels for PI, NNRTI and NRTI, respectively.[4] However, there are little data about the infant exposure to newer ARVs via breastfeeding. The aim of our study was to measure ARV concentrations in the breastmilk and the maternal plasma to evaluate their transfer and estimate the daily infant ARV dose from breastfeeding. In addition, ARV concentrations were measured in the plasma of the breastfed infant.

Methods

The present project was nested in the Swiss Mother and Child HIV Cohort Study (MoCHiV). MoCHiV prospectively collects coded data on HIV-infected pregnant women and their children. The mothers are also followed in the adult cohort [Swiss HIV Cohort Study (SHCS)]. MoCHiV and SHCS were approved by the local ethical committees of the participating centres and written informed consent was obtained from all participants.

All women living with HIV who gave birth and wishing to breastfeed underwent interdisciplinary counselling. Breastfeeding was deemed possible if the following criteria were fulfilled: good adherence to treatment, suppressed HIV plasma viral load (i.e. <50 RNA copies/mL) ideally throughout pregnancy and accepting a strict follow-up in the postpartum period. Routine clinical care included monthly visits during breastfeeding as recommended by the Swiss guidelines.[3]

All infants were tested at 1 and 6 months of age by PCR and, in addition, 3 months after weaning. Finally, all children underwent a serology test at 18–24 months of age.

Maternal plasma and milk samples (collected manually) were obtained at a single point during the follow-up visits (1, 3 and 6 months after birth). There was no protocol-specified sampling schedule relative to dose intake but the dosing times [i.e. time of maternal drug intake (self-reported) and time of blood and breastmilk sampling] were documented in order to interpret drug levels. When possible, a drug measurement was performed in the infant (i.e. venous blood sample) at the 1 month follow-up visit.

ARV quantification was carried out by LC coupled to tandem MS according to multiplex methods developed and validated in the Laboratory of Clinical Pharmacology in Lausanne.[5–8] Stable isotopically labelled analogues of drugs were used as internal standards. The drug quantification in the breastmilk was performed using matrix-matched calibrations prepared with blank breastmilk.

ARV concentrations in the breastmilk were compared with the simultaneous concentrations in the maternal plasma to determine their transfer in breastmilk (milk/plasma ratios were determined based on single point measurement). The milk drug concentrations were also used to calculate the estimated infant daily drug dose received from breastfeeding, and the corresponding relative infant dose using the equations detailed in the Supplementary material, available as Supplementary data at *JAC* Online.

Results

Between 9 January 2019 and 7 February 2021, 41 women registered in MoCHiV delivered a child, and 25 decided to breastfeed, of which 21 accepted to be included in this pharmacokinetic study. No change was made to their ARV treatment during the breastfeeding period. Women prescribed multivitamins while on integrase strand inhibitors (INSTIs) were provided recommendations on how to take multivitamins in order to avoid drug interactions (i.e. chelation), which could result in lower absorption of the INSTI. Table 1 summarizes the demographic characteristics and the ARV treatments. Several women were on newer ARVs including raltegravir (10 women), bictegravir (1), rilpivirine (2), darunavir/ritonavir (2) and tenofovir alafenamide (3). None of the breastfed neonates received HIV post-exposure prophylaxis, in line with Swiss recommendations.[9] Among the 21 included women, 1 was still breastfeeding when we analysed the study results. There was no HIV transmission in the 20 children who completed breastfeeding including the child who was still breastfeeding (HIV negative when tested at 18 months of age).

Table 1. Demographics of 21 women

Age, median (IQR), years	35 (29–38)
Time since HIV diagnosis, median (IQR), years	9 (3.7–13.5)
Time since start ART, median (IQR), years	7.5 (3.6–10.3)
Ethnicity (%)	white 33.3; black 57.1; Hispanic 4.8; Asian 4.8
Parity >1, *n* (%)	11 (64.7)
Heterosexual HIV acquisition, *n* (%)	18 (85.7)
Hepatitis B coinfection, *n* (%)	7 (33.3)
Hepatitis C coinfection, *n* (%)	0 (0)
CD4 at delivery, median (IQR)	795 (669–930)
HIV RNA suppressed, *n* (%)	21 (100)
ART at delivery, *n* (%), containing:	
raltegravir	10 (47.6)
dolutegravir	3 (14.3)
bictegravir	1 (4.8)
efavirenz	1 (4.8)
nevirapine	2 (9.5)
rilpivirine	2 (9.5)
darunavir/ritonavir	2 (9.5)
emtricitabine/tenofovir disoproxil fumarate	13 (61.9)
emtricitabine/tenofovir alafenamide	3 (14.3)
abacavir/lamivudine	5 (23.8)

ARV concentrations, measured mostly at mid-dosing interval in maternal plasma, milk and infants (drug measurements done in 16 infants), are presented in Table 2.

The median milk/plasma ratios of the newer ARVs are 0.96/0.39 for raltegravir once/twice daily, 0.01 for bictegravir, 1.08 for rilpivirine, 0.12 for darunavir/ritonavir and 4.09 for tenofovir alafenamide. These data indicate that rilpivirine transfers well in the breastmilk similarly to the other NNRTIs efavirenz and nevirapine. INSTIs transfer to a variable extent, with bictegravir and dolutegravir having a low transfer whereas raltegravir has a moderate-high transfer. Unlike other ARVs, bictegravir and dolutegravir concentrations in the infant are higher than the concentrations in the breastmilk. The PI darunavir shows very little transfer into breastmilk and no detectable concentrations in the infant. Finally, tenofovir derived from tenofovir alafenamide

Table 2. ARV concentrations in the mother, milk and infant

Drug (dose)/ number of dosages in the mother and breastmilk	Median (IQR) time from drug intake, h	Median (IQR) plasma drug concentration in mother, ng/mL. [reference concentration][a]	Median (IQR) drug concentrations in milk, ng/mL	Milk/plasma concentration ratio[b]	Median (IQR) estimated infant daily dose from breastmilk, mg/kg[c]	Relative infant dose, %[c]	Infant drug concentration, ng/mL (time interval from mother drug intake, h)
Efavirenz (600 mg once daily) *n* = 3	18.5 (18.0–18.8)	2947 (2856–3038) [≈2400][10]	2701 (2139–3228)	0.86 (0.70–1.11)	0.41 (0.32–0.48)	1.35 (1.07–1.61)	267 (17)
Nevirapine (400 mg once daily) *n* = 5	14.5 (13.6–18.1)	3893 (2927–4108) [≈4000][11]	2721 (1905–2806)	0.70 (0.68–0.75)	0.41 (0.29–0.42)	3.40 (2.38–3.51)	960 (12); 227 (21)
Rilpivirine (25 mg once daily) *n* = 2	15.5 (15.3–15.8)	113 (120–126) [≈100][12]	123 (107–140)	1.08 (1.1–1.1)	0.02 (0.02–0.02)		4 (16)
Bictegravir (50 mg once daily) *n* = 3	8.5 (5.5–11.5)	5177 (3576–6010) [≈5000][5]	57 (44–67)	0.01 (0.01–0.01)	0.01 (0.01–0.01)		103 (19)
Dolutegravir (50 mg once daily) *n* = 6	15 (13.0–19.7)	2627 (2360–3244) [≈2000][12]	107 (83–142)	0.04 (0.03–0.05)	0.02 (0.01–0.02)	1.00 (0.78–1.33)	279 (15); 100 (13)
Raltegravir (400 mg twice daily) *n* = 3	3.6 (3.1–5.7)	4250 (2520–5111) [≈4000][13]	1635 (973–2142)	0.39 (0.39–0.42)	0.25 (0.15–0.32)	4.09 (2.43–5.35)	21 (2)
Raltegravir (1200 mg once daily) *n* = 14	13.7 (10.4–15.9)	160 (82–274) [≈200][14]	111 (69–566)	0.96 (0.44–2.68)	0.02 (0.01–0.08)	0.28 (0.17–1.42)	0 (11); 0 (16); 0 (15); 14 (19); 0 (18); 0 (15)
Darunavir/r (800/100 mg once daily) *n* = 4	15.4 (11.6–16.5)	2419 (2135–3503) [≈2600][15]	316 (284–325)	0.12 (0.10–0.14)	0.05 (0.04–0.05)	0.12 (0.11–0.12)	0 (16)
Abacavir (600 mg once daily) *n* = 11	12.8 (10.3–13.6)	50 (44–126) [≈50][16]	91 (45–123)	1.03 (0.78–1.66)	0.01 (0.01–0.02)	0.34 (0.17–0.46)	1 (11); 1 (18); 9 (13); 49 (12)

Emtricitabine (200 mg once daily) $n=29$	15.5 (13.1–17.5)	201 (126–249) [≈200][17]	803 (475–1118)	3.92 (2.34–5.55)	0.12 (0.07–0.17)	4.02 (2.38–5.59)	44 (2); 21 (15); 5 (21); 14 (16); 18 (15); 27 (19); 0 (19); 26 (20); 0 (15); 49 (16); 24 (16)
Lamivudine (300 mg once daily) $n=11$	12.8 (10.3–13.6)	371 (194–543) [≈200][16]	1313 (787–1628)	3.74 (2.77–4.73)	0.20 (0.12–0.24)	4.92 (2.95–6.10)	15 (11); 4 (18); 20 (13); 91 (12)
TAF[d] (25 mg once daily) $n=5$	8.5 (5.0–15.0)	13 (11–14) [≈10][18]	45 (37–54)	4.09 (3.38–4.92)	0.007 (0.006–0.008)		0 (19)
TDF[d] (300 mg once daily) $n=24$	16 (14.3–17.9)	61 (53.3–97.0) [≈10][19]	5 (4–10)	0.08 (0.06–0.10)	0.001 (0.001–0.002)	0.01 (0.01–0.02)	0 (2); 0 (15); 0 (21); 0 (16); 0 (15); 0 (19); 0 (20); 0 (15); 0 (16); 0 (16)

TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

[a]Expected ARV concentration considering the time interval from drug intake based on reference studies evaluating full pharmacokinetic profiles or population pharmacokinetic analyses of the corresponding ARV in non-pregnant individuals.

[b]Detailed milk/plasma ratios at Months 1, 3 and 6 are presented in the Supplementary material.

[c]The median estimated infant daily dose and the relative infant dose were calculated as detailed in the Supplementary data. These values were calculated considering the situation of a fully breastfed infant; however, it should be noted that a significant proportion of infants in the study were partially breastfed and also received formula milk.

[d]Prodrugs of tenofovir, measured levels refer to tenofovir.

transfers well in the breastmilk, reaching generally higher concentrations compared with the maternal plasma, similarly to other NRTIs other than tenofovir disoproxil fumarate. However, despite high levels in the breastmilk, NRTI levels are very low or undetectable in the infant.

The median estimated infant daily dose (mg/kg) from breastfeeding is 0.02/0.25 for raltegravir once/twice daily, 0.01 for bictegravir, 0.02 for rilpivirine, 0.05 for darunavir/ritonavir and 0.007 for tenofovir alafenamide. The resulting relative infant dose is below the exposure index of 10% that has been proposed as a safety threshold for infant exposure to maternal drugs from breastmilk.[20]

Discussion

We showed that rilpivirine and tenofovir derived from tenofovir alafenamide transfer well in the breastmilk, similarly to other NNRTIs and NRTIs (except tenofovir derived from tenofovir disoproxil fumarate). Conversely, darunavir/ritonavir, like other PIs, has a low transfer. Finally, INSTIs transfer to a variable extent. Bictegravir and dolutegravir (highly protein bound) have a low transfer whereas raltegravir (protein binding: 80%) has a moderate to high transfer. The differences in drug transfer are partially explained by the physicochemical properties of the drug (i.e. molecular weight, lipophilicity, ionization and protein binding), which affect passive diffusion. Another influencing factor relates to the interaction of ARVs with drug transporters expressed on the mammary epithelium, and which may limit their transfer in the milk.[21] For instance, the breast cancer resistance protein (BCRP) was shown to be localized on the apical side of lactating mammary glands and to be up-regulated during lactation.[22] Substrates of this transporter are expected to be actively pumped into the breastmilk whereas inhibitors of this transporter (e.g. PIs) are less likely to transfer in the breastmilk.[22,23] The milk/plasma ratios obtained in our study are consistent with previous data reporting a good transfer for efavirenz and nevirapine,[4,23,24] accumulation of abacavir, lamivudine, emtricitabine and tenofovir derived from tenofovir alafenamide in the breastmilk,[4,23,25,26] but minimal transfer for tenofovir derived from tenofovir disoproxil fumarate.[25,26] The difference between tenofovir alafenamide and tenofovir disoproxil fumarate could be explained by the fact that tenofovir disoproxil fumarate is rapidly converted to tenofovir in the maternal plasma. Tenofovir is present as a dianion at physiological pH and has poor membrane permeability.[26] Conversely, tenofovir alafenamide is stable in plasma and more liposoluble and therefore can distribute more in the mammary alveoli, where it is subsequently converted to tenofovir.[26] Another potential explanation may relate to the fact that tenofovir alafenamide is a substrate of BCRP and therefore is actively pumped into the milk.[27] Conversely, tenofovir disoproxil fumarate is rapidly converted to tenofovir, which is not a substrate of BCRP.[28]

Regarding the newer ARV concentrations in the infant, we found very low or undetectable levels for rilpivirine, raltegravir, darunavir/ritonavir and tenofovir derived from tenofovir alafenamide, whereas the bictegravir level was 103 ng/mL, a value below the EC95 (see Supplementary material). The infant concentrations of other ARVs were consistent with previous data showing differential exposure with very low or undetectable levels for lamivudine,[4,23] emtricitabine, tenofovir derived from tenofovir disoproxil fumarate[25] and raltegravir,[29] whereas efavirenz, nevirapine and dolutegravir were shown to be detectable in infants.[4,30,31] We observed that dolutegravir levels in the infant are comparable or higher than levels measured in the breastmilk, as also reported previously.[30,31] This observation relates to the fact that dolutegravir is mainly metabolized by UGT1A1, a drug-metabolizing enzyme whose immaturity, particularly in preterm infants, can result in slow elimination of the drug.[30,31]

Our results indicate that the daily infant ARV dose from breastfeeding is low for all evaluated ARVs and within the safety threshold (i.e. exposure index <10%) as observed by others.[4,24,25] The clinical relevance of subtherapeutic ARV concentrations in the breastmilk is unknown but raises concerns about the potential development of resistances in the rare event of vertical transmission. Another potential concern relates to the differential drug exposure in the infant, with some ARVs being below or above their MICs, leading to monotherapy exposure and the related risk of acquiring resistant HIV strains. Of interest, two large studies showed that infants who had acquired HIV had high rates of multiclass drug resistance, with similar maternal patterns.[32,33]

The strength of this study is the variety of evaluated ARVs. The study has several limitations such as the short follow-up period and the limited number of enrolled breastfeeding women resulting in a small amount of data for several ARVs. Furthermore, the study included only single point measurements with no protocol-specified sampling schedule relative to the dose, and the time of dose intake was self-reported. However, despite these limitations the ARV concentrations measured in our study were aligned with the expected maternal concentrations and milk/plasma ratios reported previously for some ARVs.

In summary, our data show that ARVs transfer into breastmilk and in the breastfed infant to different extents. Thus, breastfeeding women should be counselled to strictly adhere to their ARV treatment to prevent vertical HIV transmission and the development of resistances, which may be favoured by the fact that not all ARVs achieve effective inhibitory concentrations in the breastfed infant. This study is small so more data are needed to evaluate the risk of acquiring resistances. In addition, future work will need to expand pharmacokinetic data during breastfeeding as well as follow-up data for the breastfed infants.

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Supplementary data

Supplementary material is available as Supplementary data at *JAC* Online.

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