Low raltegravir transfer into the breastmilk of a woman living with HIV

A raltegravir-based regimen is among the preferred for pregnant women living with HIV [1,2], making raltegravir a widely used antiretroviral drug in new mothers in high-income countries. European [1] and US [2] guidelines recommend against breastfeeding because of the potential risk of mother-to-child transmission (MTCT). Nevertheless, an increasing number of HIV-infected mothers is breastfeeding their newborns [3], and it is an ongoing debate if the cultural, psychological and social importance of breastfeeding outweighs the MTCT risk in some circumstances [4–8]. Adequate antiretroviral therapy is of particular importance in these women to prevent transmission, but it is widely unknown, which antiretroviral drugs (ARVs) are preferable for these women [5]. Here, we present the first case of raltegravir in a breastfeeding mother.

A 36-year-old HIV-1-infected woman received raltegravir 800 mg once daily (decreased dose because of low body weight) and emtricitabine/tenofovir disoproxil 200/245 mg once daily. Her plasma HIV-RNA has remained <20 copies/ml for more than 6 years. At 41 + 3 weeks of gestation, she delivered a healthy boy (3580 g, 55 cm, APGAR score 9 at 5 min), who received neonatal prophylaxis with oral zidovudine for 14 days [9]. Breastfeeding was chosen, with exclusive breastfeeding until 4 months of age followed by mixed feeding until the age of 9 months. A mild elevation of total bilirubin levels with normal liver function tests was observed at 14, 32, 48, and 90 days of age (6.71 [conjugated 0.61], 4.58, 5.99, and 1.42 mg/dl, respectively). Infant HIV-DNA PCR results were consistently negative up to the age of 8 months.

Maternal blood (at 4 months) and breastmilk samples (4 and 8 months postpartum) were obtained for pharmacokinetic analyses after observed maternal raltegravir intake with food to assess the breastmilk transfer and estimate infant exposure to raltegravir. A single infant blood sample was taken at 4 h after maternal dosing (assumed T<sub>max</sub>) to assess the infant’s exposure. The plasma samples were analyzed using a validated ultra-performance liquid chromatography tandem mass spectrometry assay [lower limit of quantification (LLOQ) 0.01 mg/l] [10]. The method was adapted for analysis of breastmilk samples, which were determined relative to a breastmilk linear calibration curve (0.01–10 mg/l) resulting in circa results of the breastmilk concentration.

An AUC<sub>0–12h</sub> milk-to-plasma (M:P) ratio of 0.46 was calculated from the paired data of 4 months postpartum (noncompartmental analysis using Phoenix 63), indicating low raltegravir transfer into the breastmilk and little accumulation. A similar M:P ratio (range 0.37–0.71) was observed during the sampling interval (Fig. 1a). A similar breastmilk exposure and M : P ratio (0.55) was observed at 8 months postpartum (Fig. 1b). The unexpected delayed T<sub>max</sub> (12 h) at 4 months postpartum could be attributed to a migraine attack the woman suffered from during blood collection and/or the erratic absorption of raltegravir [11,12].

At 4 and 8 months postpartum, the infant’s raltegravir plasma concentrations (~45 min after last breastfeeding) were below the LLOQ (Fig. 1). At 4 months postpartum, the estimated infant dosage of the exclusively breastfed infant was 0.099 mg/kg/day, based on an average infant daily milk intake of 150 ml/kg, weight of 6.7 kg, and an average raltegravir breastmilk concentration of 0.66 mg/l (derived from AUC<sub>0–12h</sub>) [13]. This estimated daily infant dosage corresponded to 0.8% of the approved daily raltegravir dose of 12 mg/kg/day [14].

We showed for the first time that raltegravir can penetrate into breastmilk. The clinical relevance of infant exposure to different ARVs via breastmilk is discussed critically. Therapeutic antiretroviral infant exposure may protect against HIV transmission, whereas low level antiretroviral exposure can result in the development of resistance and false-negative HIV-tests in case of infection [15,16]. The relative raltegravir dose ingested by the tested infant is unlikely to be of therapeutic clinical significance as it seems to be less than 1% of the approved treatment dose and the infant exposure is beneath the protein-adjusted IC<sub>95</sub> of 0.016 mg/l [17].

Raltegravir and bilirubin are both metabolized by UGT1A1 and compete for albumin binding sites [18]. In this case, the UGT1A1 activity of the infant was probably matured at the time of sampling, whereas low UGT1A1 activity in neonates may result in higher raltegravir concentrations [18,19]. The observed hyperbilirubinemia could, therefore, be not only attributed to the raltegravir exposure via breastmilk but also to intrauterine raltegravir exposure as reported in non-breastfed infants after intrauterine integrase inhibitor exposure [20–22]. More longitudinal data, especially in the neonatal period, are needed to establish the applicability of raltegravir in breastfeeding HIV-infected mothers.
The study was approved by the local ethics committee (Charité-Universitätsmedizin Berlin), the mother gave written informed consent.

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Conflicts of interest

There are no conflicts of interest.

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Is a step-down antiretroviral therapy necessary to fight severe acute respiratory syndrome coronavirus 2 in HIV-infected patients?

At present, no evidence exists that people living with HIV (PLWHIV) are at increased risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) compared with the general population or experiencing a worse outcome.

There is also no evidence that PLWHIV receiving a protease inhibitor–based regimen have a lower incidence of coronavirus disease 2019 (COVID-19) compared with PLWHIV receiving other regimens.

At the time of writing, COVID-19 management and outcome have been described in nine PLWHIV, all treated with protease inhibitors [1–3]. The first case has been described in Asia and was a naïve patient who received lopinavir/ritonavir (LPV/r)–containing first-line therapy [1]. A few days later, Blanco et al. [2] reported a case series of five HIV and SARS-CoV-2 coinfected patients in Spain, of whom four were already on antiretroviral therapy (ART) and one was an ART naïve AIDS presenter. Also in this case, they were all treated with protease inhibitors: one patient maintained a darunavir/ritonavir (DRV/r)–based treatment; two replaced dolutegravir with LPV/r; one replaced DRV/r with LPV/r; while the naïve patient started a first-line ART with cobicistat boosted DRV (DRV/c). Finally, also Riva et al. described a case series of PLWHIV in Italy, who were all already treated with DRV/c, and in which the protease inhibitor treatment failed to prevent COVID–19, despite adequate DRV plasma levels. In two of them, the authors replaced DRV/c with LPV/r [3]. All these reported cases were discharged alive from hospital [1–3], but their follow-up is too short to evaluate the efficacy of their new antiretroviral strategies.

The use of LPV/r is not supported by evidence in the current COVID–19 epidemic but is only considered as a potential treatment of SARS, based on previous observations in the first SARS-CoV epidemic in 2003 [4]. DRV is the most recent protease inhibitor, sharing the same mechanism of action with LPV, but is better tolerated and more efficacious for HIV treatment [5]. In the only randomized trial comparing LPV/r with placebo for the treatment of SARS-CoV-2, no benefit was observed in the protease inhibitor arm [6]. Based on these results, do we really have reasons to support the use of protease inhibitors in PLWHIV with COVID–19? Are we forgetting the successes achieved in PLWHIV in recent years overcoming protease inhibitors use? Can we abandon therapies based on modern, better tolerated single-tablet regimens (STR) and go back 15 years to the LPV/r era?