AIDS

Pharmacokinetics of maraviroc in plasma and breastmilk in a treatment-experienced perinatally HIV-1 infected women

--Manuscript Draft--

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Submission to AIDS

Title of paper: Pharmacokinetics of maraviroc in plasma and breastmilk in a treatment-experienced perinatally HIV-1 infected women

Date submitted: August 09, 2019

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Dear Sir / Madam,

On behalf of my co-authors and myself, I submit the enclosed manuscript for consideration for publication as a Correspondence letter in AIDS. We present the first case of maraviroc pharmacokinetics in a breastfeeding HIV-1-infected woman. Our data show that maraviroc penetrates very well into human breastmilk, with a milk-to-plasma ratio of 0.61.

This case has not been published in this or a substantially similar form, nor accepted for publication elsewhere, nor is it under consideration by another publication.

Sincerely,

Cornelia Feiterna-Sperling, M. D.

AIDS: Author's paper submission checklist

Title of paper:	► Pharmacokinetics of maraviroc in plasma and breastmilk in a treatment-experienced perinatally HIV-1 infected women
Names of authors:	►Cornelia Feiterna-Sperling, Renate Krüger, Alieu Amara, Saye Khoo, Catriona Waitt

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► C.W. is funded by a Wellcome Trust Clinical Postdoctoral Fellowship WT104422MA. S.K. has received funding from ViiV Healthcare, Gilead Sciences, Merck and Janssen for support of the Liverpool HIV drug interactions resource. C.F., R.K., A.A., and C.W. have no conflict of interest to declare

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► C.F. and C.W. are the primary authors who conceived and designed the study. R.K. was directly involved in the design. S.K. developed the assay methodology and measured the drug concentrations. A.A. organized the PK analysis. All authors contributed to interpreting the results and the editing of the manuscript. All authors have read and approved the text as submitted to AIDS.

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Pharmacokinetics of maraviroc in plasma and breastmilk in a treatment-experienced perinatally HIV-1 infected women

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Running head: Maraviroc transfer into breastmilk

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Maraviroc (MVC), a C-C chemokine receptor type 5 (CCR5) antagonist, was approved as part of combination antiretroviral therapy (cART) in 2007, for use in treatment-experienced adults infected with CCR5-tropic HIV-1 [1]. Whilst with current treatment strategies such as maternal cART, low rates of mother-to-child transmission (MTCT) have been reported, in high-income countries, breastfeeding is not recommended because of the potential MTCT risk. However, since 2017, European [2] and US [3] guidelines have acknowledged that some HIV-infected women may wish to breastfeed, and should be given appropriate support in this decision. Whilst data exist describing the transfer of NRTI, NNRTI and PI to breastfed infants [4-5], the pharmacokinetics and safety of MVC in lactating women and their breastfed infants have not been reported. Here, we present the first case of MVC in a breastfeeding mother.

A 36-year-old perinatally HIV-1-infected woman received MVC (150 mg twice daily), lamivudine (150 mg twice daily) and lopinavir/ritonavir (400/100 mg twice daily). Her plasma HIV-RNA has remained undetectable with a CD4 count above 500 cells/µL on this regimen for over a decade.

In 2018, at 38+4 weeks of gestation, she was delivered of a healthy girl (2710 g, 49 cm, head circumference 35 cm, APGAR score 10 at 5 minutes). Standard neonatal chemoprophylaxis with oral zidovudine (4 mg/kg twice daily) for fourteen days was given according to German-Austrian guidelines [6]. Although not recommended, breastfeeding was chosen. Exclusive breastfeeding continued until six months of age, with complete weaning by seven months. Clinical and laboratory assessment at two, four and eight weeks, and three, six, nine, and 12 months after birth revealed normal development. Full blood cell count, renal and liver parameters remained within normal range. HIV-DNA PCR results were consistently negative, and at twelve months of age, an HIV antibody test was

negative.

At five months postpartum, a twelve-hour pharmacokinetic sampling of maternal plasma and breastmilk was performed to assess the breastmilk transfer and estimate infant exposure to MVC. After approval by the local ethics committee of the Charité University Medicine Berlin, the mother gave informed consent. Paired maternal plasma and breastmilk samples were obtained pre-dose (0 h), and 1, 2, 4, 6, 8, and 12 h following observed dosing. Thirteen days later, one single plasma sample from the still exclusively breast-fed infant was obtained during a routine follow-up visit. Samples were frozen at -30°C until shipment on dry ice to the laboratory (University of Liverpool, UK) for analysis. Plasma concentrations of MVC were determined by validated liquid chromatography tandem mass spectrometry method as previously described [7], with a modification for breastmilk. Briefly, the standards and quality control (QC) samples were prepared by spiking known concentration of drugs (TRC, Ontario, Canada) into breastmilk (donated by consenting volunteers through the UK Northwest Milkbank with ethics approval) to obtain a calibration curve (range 2.5 to 2500 ng/mL). MVC stable isotope was used as internal control to minimize matrix effect.

Inter- and intra-day precision measured at the QC levels were 5.60% (3.71 – 6.72) and 3.04% (2.00 – 4.40), respectively (Mean, range). Inter- and intra-day accuracy were 0.84% (-7.02 – 6.99) and 3.30% (-2.78 – 10.61), respectively. Mean recovery at all QC levels was 98.68% (SD, 5.69).

The plasma MVC pharmacokinetic profile in the mother (Fig. 1) was comparable to published data of postpartum women [8], with full results reported in the figure legend. MVC was undetectable in the single infant sample.

A significant breastmilk transfer of MVC was demonstrated, with a milk-to-plasma (M:P) ratio of 0.61, consistent with studies in lactating rats which indicated that MVC is extensively secreted into rat milk [9]. MVC is licensed for children (two years and older) weighing at least 10 kg, at a starting dose of 50 mg. Assuming an infant milk intake of 150 ml/kg/day, we estimate a daily MVC ingestion of less than 2 mg in this 6.5 kg infant. Concerns relating to breastmilk exposure of antiretroviral drugs relate to both infant toxicity and the potential for HIV drug resistance to develop, should MTCT occur in the presence of low drug concentrations. Although MVC was not detected in the infant, it should be noted that the lower limit of quantification of the assay (2.5 ng/mL) is above the IC90 (0.57 ng/mL) [10]; low, but clinically relevant infant concentrations were possible. Data from a single case must be interpreted with caution and more data regarding MVC in breastfeeding mother-infant pairs are needed.

In conclusion, there is significant penetration of MVC into breastmilk with a M:P ratio of 0.61, but MVC was undetectable in the breastfed infant.

Conflicts of Interest and Source of Funding:

C.W. is funded by a Wellcome Trust Clinical Postdoctoral Fellowship WT104422MA. S.K. has received funding from ViiV Healthcare, Gilead Sciences, Merck and Janssen for support of the Liverpool HIV drug interactions resource. C.F., R.K., A.A., and C.W. have no conflict of interest to declare.

References

1. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, et al. **Maraviroc for previously treated patients with R5 HIV-1 infection**. *N Engl J Med* 2008; **359**:1429-1441.
2. EACS. European AIDS Clinical Society Guidelines, Version 9.0 October 2017. http://www.eacsociety.org/files/guidelines_9.0-english.pdf. [Accessed 13 July 2019]
3. DHHS. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 19 October 2017. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf [Accessed 13 July 2019]
4. Waitt C, Low N, Van de Perre P, Lyons F, Loutfy M, Aebi-Popp K. **Does U=U for breastfeeding mothers and infants? Breastfeeding by mothers on effective treatment for HIV infection in high-income settings**. *Lancet HIV* 2018; **5**:e531-e536.
5. Waitt CJ, Garner P, Bonnett LJ, Khoo SH, Else LJ. **Is infant exposure to antiretroviral drugs during breastfeeding quantitatively important? A systematic review and meta-analysis of pharmacokinetic studies**. *J Antimicrob Chemother* 2015; **70**:1928-1941.
6. DAIG. Deutsch Österreichische Leitlinie zur HIV-Therapie in der Schwangerschaft und bei HIV-exponierten Neugeborenen. March 2017. https://daignet.de/site-content/hiv-therapie/leitlinien-1/Deutsch_OsterreichischeLeitliniezurHIV_TherapieinderSchwangerschaftundbeiHIV_exponiertenNeugeborenenStandMarz2017.pdf. [Accessed 13 July 2019]
7. Else L, Watson V, Tjia J, Hughes A, Siccardi M, Khoo S, et al. **Validation of a rapid and sensitive high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay for the simultaneous determination of existing and new antiretroviral compounds**. *J Chromatogr B Analyt Technol Biomed Life Sci* 2010; **878**:1455-1465.
8. Colbers A, Best B, Schalkwijk S, Wang J, Stek A, Hidalgo Tenorio C, et al. **Maraviroc Pharmacokinetics in HIV-1-Infected Pregnant Women**. *Clin Infect Dis* 2015; **61**:1582-1589.
9. FDA. Highlights of prescribing information: Selzentry (maraviroc). https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022128s002lbl.pdf. November 2009. [Accessed 02 December 2018]
10. eMC. Celsentri film-coated tablets, summary of product characteristics. 12 October 2018. https://www.medicines.org.uk/emc/product/6159/smpc. [Accessed 13 July 2019]

Figure1

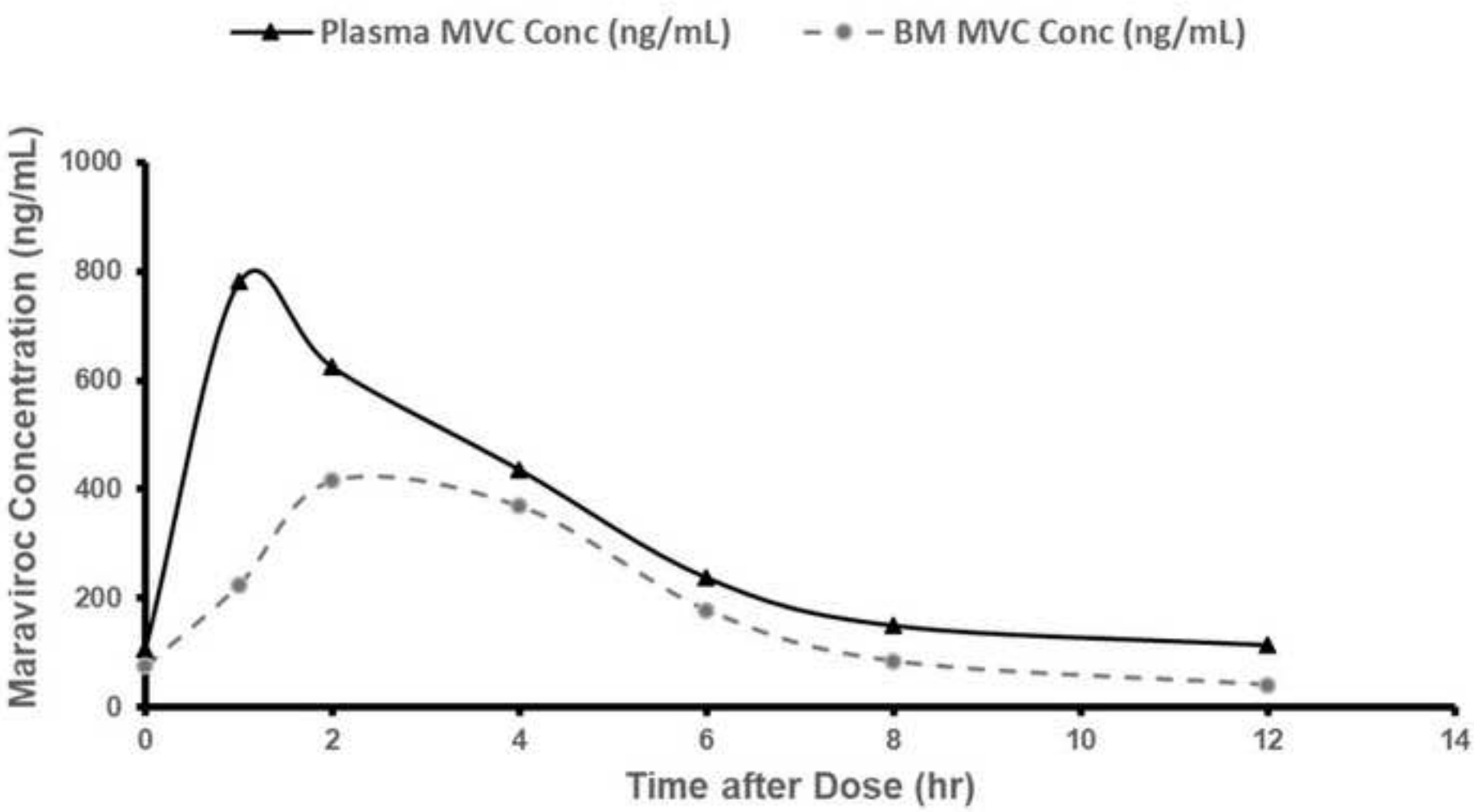

Fig. 1. Maraviroc maternal plasma and breastmilk concentration time-profiles at five months postpartum. Maraviroc concentrations in plasma and breastmilk measured by validated liquid chromatography tandem mass spectrometry as described in the case report. The $AUC_{0\text{-}12\ h}$ for maraviroc in plasma was 3790 h*ng/mL with a C_{max} of 780 ng/mL reached after 1 hour. The breastmilk $AUC_{0\text{-}12\ h}$ was 2317 h*ng/mL with a C_{max} of 415 ng/mL reached after 2 hours. The milk-to-plasma (M:P) ratio of $AUC_{0\text{-}12\ h}$ was 0.61.