LETTER TO THE EDITOR

Transplacental passage of nevirapine, nelfinavir and lopinavir

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Dear Editor,

Since 1998, the cornerstone of preventing mother-to-child transmission of human immunodeficiency virus (HIV) is the use of highly active antiretroviral therapy (c-ART) in pregnancy and as post-exposure prophylaxis to the neonate. Individual agents differ with respect to their transplacental passage.[1] Our purpose was to examine transplacental passage of nevirapine, lopinavir and nelfinavir by studying the C/M ratio (cord /maternal venous blood concentration), determined by high performance liquid chromatography and the possible influence of the birth weight ratio indicating placental insufficiency rate.

Seventy-nine HIV-infected women out of 263 who delivered between 2003 and 2010 in the Academic Medical Centre, Amsterdam, were included since paired venous mother-cord blood samples were available for them. Data were retrospectively collected from the electronic medical records. Maternal and cord venous samples were drawn simultaneously at delivery and the interval from last c-ART intake registered. All women received intravenous zidovudine during labour. Nine patients were excluded (seven because the post-dose interval was longer than in the average population or unknown and two because swapping of maternal and cord samples was evident).

Nevirapine showed a relatively high median C/M ratio of 0.67, while nelfinavir and lopinavir had lower ratios of 0.14 and 0.24, respectively (*table 1*). *Figure 1* illustrates differences in transplacental passage between the three agents. No association existed between the C/M ratio and the newborn birth weight in any of the antiretroviral drugs.

The C/M ratios in this study were similar to previous reports. The low cord-to-mother ratio for lopinavir and nelfinavir suggests a low transplacental transfer. A reason for this could be that protease inhibitors (PIs) are large molecules with a high protein binding (98%). Moreover, PIs are a substrate for the efflux transport molecule P-glycoprotein, which forms a functional barrier in the human placenta that limits the exposure of the foetus to xenobiotics, to protect it from their potential teratogenic effects.

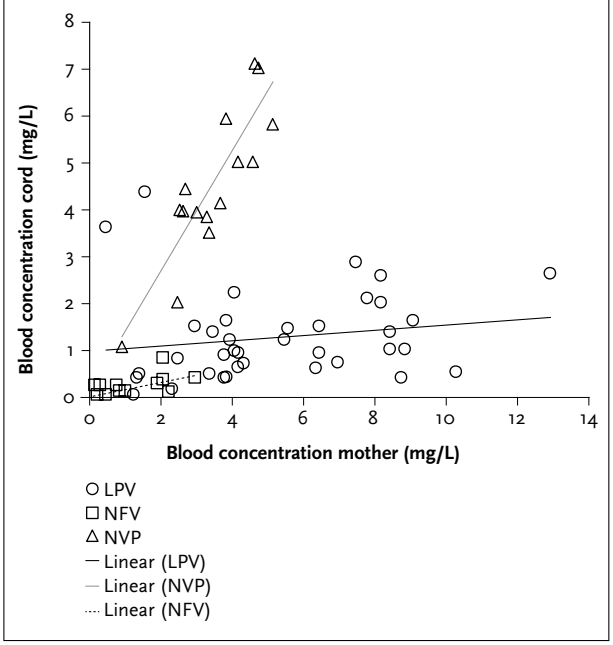
Nevirapine, in contrast, shows a high transplacental passage, which is almost similar to passive diffusion. This could be explained by the lower protein binding (60%), the lower molecular weight of nevirapine and the fact that nevirapine is not a substrate for P-glycoprotein.

Table 1. *Results*

Type of ART (+combivir)	Median post-dose interval (h)	Median maternal concentration (mg/l)	Median population ratio	Median cord concentration (mg/l)	c/m ratio
NVP (n=17)	3.60 (±4.60) (n=14)	4.00 (±1.95)	1.10 (±0.50) (n=9)	3.20 (±1.60)	0.67 (±0.15)
NFV (n=20)	8.40 (±8.00) (n=18)	0.75 (±1.85)	0.80 (±0.4) (n=11)	0.15 (±0.25)	0.14(±0.36)
LPV (n=42)	6.10 (±8.34) (n=36)	4.10 (±5.45)	0.80 (±0.83) (n=26)	0.96 (±1.16)	0.24 (±0.21)

Post-dose intervals, blood concentrations and ratios of nevirapine (NVP), nelfinavir (NFV) and lopinavir (LPV); c/m ratio = the ratio of the venous cord blood/maternal blood concentration.

Figure 1. *Cord and mother blood concentrations of LPV, NFV and NVP*



In a situation where maximum efficacy and minimum toxicity is required, these may be important data for treatment decisions.

Preliminary data were presented at the winter meeting of the Dutch HIV/AIDS Society held in the Netherlands on 23 January 2009. A poster presentation was given at the the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011) in Rome, Italy from 17-20 July 2011.

REFERENCE

1. Gingelmaier A, Kurowski M, Kastner R, Eberle J, Mylonas I, Belohradsky BH, et al. Placental transfer and pharmacokinetics of lopinavir and other protease inhibitors in combination with nevirapine at delivery. AIDS. 2006; 20(13):1737-43.