Transplacental passage of etravirine and maraviroc in a multidrug-experienced HIV-infected woman failing on darunavir-based HAART in late pregnancy

A. Calcagno1*, L. Trentini1, L. Marinaro1, C. Montrucchio1, A. D’Avolio1, V. Ghisetti2, G. Di Perri1 and S. Bonora1

1Unit of Infectious Diseases, Department of Medical Sciences, University of Torino at Amedeo di Savoia Hospital, ASLTO2, C.so Svizzera 164, Torino, Italy; 2Laboratory of Virology and Microbiology, Amedeo di Savoia Hospital, ASLTO2, C.so Svizzera 164, Torino, Italy

*Corresponding author. Clinica Universitaria di Malattie Infettive, Ospedale Amedeo di Savoia, C.so Svizzera 164, 10159 Torino, Italy. Tel: +390114393856; Fax: +390114393942; E-mail: andrea.calcagno@unito.it

Keywords: pharmacokinetics, antiretrovirals, ws glQ, virological failure, cord blood concentrations

Sir,

Although highly active antiretroviral treatment (HAART) in HIV-infected pregnant women has been shown to be effective in reducing mother-to-child-transmission (MTCT), some therapeutic issues remain a concern. Changes in drug pharmacokinetics (PK) in the second and third trimesters could cause reductions in plasma exposure of several antiretrovirals,1 while for most recent compounds few data are available. Boosted darunavir is widely used in multidrug-experienced pregnant patients, but information in this setting is limited to heterogeneous case reports showing lower trough concentrations (1168–1908 ng/mL) as compared with non-pregnant patients.2–6 The use of inhibitory quotients (IQs) has been proposed to individualize the exposure of drugs in relation to the harboured viruses; our group showed that the darunavir weighted score genotypic IQ (ws glQ) was the most accurate predictor of virological response in treatment-experienced patients.7 Therefore the use of darunavir ws glQ could help clinicians to manage multidrug-experienced pregnant women.

We describe the case of a young woman infected with HIV and hepatitis C virus whose therapeutic history includes suboptimal adherence to several antiretrovirals and virological failures on regimens containing efavirenz, indinavir and saquinavir. HIV polymerase revealed resistance-associated mutations both in the reverse transcriptase (D67N, T69N, K70R, A98G, M184V, K103N and K219Q) and the protease (M46I, I84V and L90M) gene. After successfully receiving tenofovir/emtricitabine and darunavir/ritonavir (800/100 mg once daily) she discontinued every treatment. Two years later she agreed to reinitiate tenofovir/emtricitabine and darunavir/ritonavir (800/100 mg once daily) she discontinued every treatment. Two years later she agreed to reinitiate tenofovir/emtricitabine and darunavir/ritonavir; at this time she presented with 539 CD4+ T lymphocytes/mm3 (15%, 0.27 CD8/CD4 ratio), 55,500 HIV RNA copies/mL and an R5 tropic virus. Three months later (at 10 weeks of gestational age) her pregnancy test was positive and her darunavir/ritonavir dosage was increased to 600/100 mg twice daily. After a net decrease in viral load (252 copies/mL at 16 weeks and 115 copies/mL at 20 weeks) she consented to delivery, which was uneventful. At birth the infant had a CD4+ cell count of 475 cells/mm3 (27%), 14,800 copies/mL HIV RNA and an R5 phenotype. At 4 months of age CD4+ cell count and HIV RNA were 1,470 cells/mm3 (29%), and 41 copies/mL HIV RNA, respectively. In conclusion, plasma concentrations of darunavir may drop during pregnancy, but this is not always associated with virological failure. Boosted darunavir remains an effective option for multidrug-experienced women in late pregnancy.

![Figure 1.](https://example.com/figure1.png)
20 weeks) it rebounded at 28 weeks (507 and 735 copies/mL at two different controls). Raltegravir had previously been poorly tolerated due to creatine phosphokinase elevations, therefore etravirine (200 mg twice daily) and maraviroc (150 mg twice daily) were added (at 29 weeks), leading to a sustained HIV RNA decrease (178 copies/mL at 32 weeks and <20 copies/mL at delivery, at 38 weeks). The baby, born through elective caesarean section, did not show abnormalities and received zidovudine prophylaxis for 6 weeks; at 1 and 6 months of age his HIV-1 DNA PCR test was negative and no laboratory abnormalities were noted. Lower than expected darunavir trough concentrations both in the second (two samples, 2041 and 2192 ng/mL) and third trimester (two samples, 1768 and 1719 ng/mL) were noted; self-reported adherence was >95%. Figure 1 shows the time profile of HIV RNA, darunavir trough concentrations and darunavir ws gIQ. Maternal plasma and cord blood drug concentrations were measured at delivery (and 13 h after drug intake) through validated HPLC-MS and HPLC-UV (for maraviroc) methods. Plasma concentrations (ng/mL) and cord-to-plasma ratios were: darunavir, 1399, 212 and 0.15; ritonavir, 153, 49 and 0.32; tenofovir, 47, 53 and 1.13; emtricitabine, 151, 250 and 1.66; maraviroc, 186, 69 and 0.37; and etravirine, 421, 218 and 0.51.

The expected PK changes in the third trimester affect darunavir exposure, but their clinical impact is unknown in patients harbouring multidrug-resistant viruses; furthermore, unbound plasma concentrations seem unchanged. A case report suggested that a third trimester increase in darunavir/ritonavir dosage to 900/100 mg twice daily could not counterbalance this effect. Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance the effect. Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.3 Our patient is the first case showing that a modified dosage to 900/100 mg twice daily could not counterbalance this effect.

In conclusion, the management of HAART in multidrug-experienced HIV-infected pregnant women should be individualized by tailoring drug dosages according to PK modification; the safety and efficacy of the most recent compounds need to be assessed in order to rely on the full armamentarium of antiretroviral drugs.

**Funding**

This study was carried out as part of our routine work.

**Transparency declarations**

A. C., G. D. P. and S. B. have received speaker honoraria from Janssen-Cilag and ViVi, the manufacturers of darunavir, etravirine and maraviroc. All other authors: none to declare.

**References**