

Transplacental passage of tenofovir (TDF) and other antiretrovirals (ARVs) at delivery.

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Background Knowledge of magnitude of the ARVs transfer across the placenta is essential for management of efficacy and safety of HAART in pregnancy. NRTIs showed to cross the placenta by simple diffusion and to concentrate in amniotic fluid. TDF has been found to cross the placenta in animal models, while human placental transfer has not yet been investigated. Therefore, aim of our study was to evaluate placental transfer of TDF and other ARVs in the clinical setting.

Methods In a substudy of TARGET (observational, multicenter Italian study of HAART in pregnancy), we obtained paired samples of maternal and cordal blood at delivery of 30 HIV-positive women taking HAART. Samples were simultaneously collected from a peripheral maternal vein and from the umbilical vein. Drugs administered were TDF (cases, $n=5$), zidovudine (AZT, $n=30$), lamivudine (3TC, $n=27$), abacavir (ABV, $n=3$), nevirapine (NVP, $n=14$), nelfinavir (NFV, $n=8$), lopinavir/ritonavir (LPV/RTV, $n=2$) and amprenavir/ritonavir (APV/RTV, $n=1$). Plasma concentration of all ARVs administered were measured by a validated HPLC method. Placental transfer was determined as a ratio of cordal-to-maternal drug concentrations.

Results Median cordal vs maternal plasma concentrations and median (range) ratios (R) of cordal-to-maternal drug plasma concentration were the following: TDF 48 vs 47.5 ng/ml, R 0.99 (0.94-1.05); AZT 955 vs 664 ng/ml, R 1.85 (0.17-3.66); 3TC 206 vs 147 ng/ml, R 1.41 (0.5-2.18); ABV 216 vs 144 ng/ml, R 1.50 (1.05-2.24); NVP 2611 vs 3653 ng/ml, R 0.79 (0.60-0.91); NFV 69 vs 468 ng/ml, R 0.14 (0-0.27); LPV 358 vs 6396 ng/ml, R 0.06 (0-0.11); APV 2534 vs 6839 ng/ml, R 0.37 (only 1 case), RTV 14 vs 292 ng/ml, R 0 (0-0.003).

Conclusions. To the best of our knowledge, this is the first clinical report of TDF passage across placenta. This drug appeared to have an efficient transplacental passage, showing equivalent concentration in cordal and maternal blood at delivery. However, as opposite to NRTIs that confirmed median ratio values above 1, TDF ratios were always around 1 in all patients, suggesting simple diffusion without drug concentration in fetal blood. An high transfer was confirmed also for NVP, while PIs showed to poorly cross the placenta, as previously reported. These data warrant further clinical evaluation towards a better understanding of pharmacology of ARVs in the fetal compartment.

BACKGROUND

The synergistic effects of ARV treatment during pregnancy, elective caesarean section, and newborn prophylaxis and bottle feeding have reduced the risk of vertical transmission of HIV infection to less than 2%.

Although the use of ARVs during pregnancy has consequently become a standard of care, available data for estimating *in utero* drug exposure are not exhaustive. On one hand, in fact, NRTIs have been shown to cross the placenta by simple diffusion and to concentrate in amniotic fluid. On the other hand, TDF, a widely used NtRTI, has been found to cross the placenta in animal models but human placental transfer has not yet been investigated. Moreover, published studies concerning transplacental passage of other classes of ARVs, such as NNRTIs and PIs, are limited. Therefore, aim of our study was to evaluate the extent of placental transfer of TDF and other ARVs in the clinical setting.

PATIENTS AND METHODS

TARGET is an ongoing observational, multicenter Italian study of HAART in pregnancy.

In a PK substudy of TARGET, 30 HIV-positive pregnant women administered with HAART according to standard clinical protocols were enrolled after giving their written informed consent.

Paired samples of maternal and cordal blood at caesarean delivery were obtained. Samples were simultaneously collected from a peripheral maternal vein and from the umbilical vein.

Drugs administered at delivery were TDF (cases, $n=5$), zidovudine (AZT, $n=30$), lamivudine (3TC, $n=27$), abacavir (ABV, $n=3$), nevirapine (NVP, $n=14$), nelfinavir (NFV, $n=8$), lopinavir/ritonavir (LPV/RTV, $n=2$) and amprenavir/ritonavir (APV/RTV, $n=1$). Regimens administered at delivery were AZT/3TC/NVP ($n=14$), AZT/3TC/NFV ($n=6$), AZT/3TC ($n=2$), AZT/3TC/ABV ($n=2$), TDF/AZT/NFV ($n=2$), TDF/AZT/3TC/ABV ($n=1$), TDF/AZT/3TC/LPV/RTV ($n=1$), TDF/AZT/APV/RTV ($n=1$) and AZT/3TC/LPV/RTV ($n=1$).

Plasma concentration of all ARVs administered were measured by a validated HPLC method. When applicable (maternal concentration above limit of detection of HPLC method), placental transfer was calculated as a ratio of cordal-to-maternal drug concentrations,

CONCLUSIONS

- This is the first clinical report of TDF passage across human placenta. This drug appeared to have an efficient transplacental passage, showing equivalent concentration in cordal and maternal blood at delivery.

- As opposite to NRTIs, such as AZT, 3TC, and ABV, that confirmed previous findings of median ratio values above 1, TDF cordal-to-maternal ratios resulted exactly 1 in all the paired samples, suggesting simple diffusion without drug concentration in fetal blood.

- A marked, although not complete, placental transfer was confirmed for NVP, while PIs NFV, LPV, APV and boosting RTV showed to poorly cross the placenta, as previously reported.

- Our data showed an adequate plasma exposure and, consequently, a full antiviral activity of TDF in fetal compartment. This finding support further clinical evaluation of efficacy and toxicity of this drug as a component of HAART in pregnancy.

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RESULTS

Population characteristics at baseline of pregnancy

Age (years)	30 [28-34]
Height (cm)	164 [160-168]
Weight (kg)	63 [57-72]
Risk factor, n (%)	
<i>Heterosexual</i>	26 (86)
<i>Drug abuse</i>	4 (14)
CDC status, n (%)	
A	28 (93)
C	2 (7)
HBSAg-positive, n (%)	2 (7)
HCV-positive, n (%)	6 (20)
Previous pregnancy, n (%)	25 (83)
Previous childbirth, n (%)	16 (53)
HIV-RNA(cps/ml), median [range]	145 [-50-2087]
HIV-RNA < 50 copies/ml, n (%)	11 (36)
T CD4+ cells/mm ³ , median [range]	491 [370-593]
On HAART, n (%)	14 (46)
Discontinuation of HAART, n (%)	4 (13)

Immunovirological characteristics at delivery

HIV-RNA <50 copies/ml, n (%)	25 (83)
HIV-RNA <400 copies/ml, n (%)	28 (93)
CD4 cells/mm ³ , median [range]	437 [309-641]
HIV-infected newborns	0

Pharmacokinetic analysis at delivery

DRUG (n)	CORDAL BLOOD* median [range]	MATERNAL BLOOD* median [range]	RATIO C : M median [range]
TDF (5)	48 [21-83]	47.5 [15-79]	0.99 [0.94-1.05]
AZT (30)	955 [0-1889]	664 [0-5182]	1.85 [0.17-3.66]
3TC (27)	206 [0-584]	147 [0-966]	1.41 [0.5-2.18]
ABV (3)	216 [175-348]	144 [30-323]	1.50 [1.05-2.24]
NVP (14)	2611 [606-9018]	3653 [660-10380]	0.79 [0.6-0.91]
NFV (8)	69 [0-481]	468 [20-1773]	0.14 [0-0.27]
LPV (2)	358 [0-690]	6396 [6518-6274]	0.06 [0-0.11]
APV (1)	2534 [NA]	6839 [NA]	0.37[NA]
RTV (3)	14 [0-33]	292 [20-406]	0 [0-0.003]

*Values are expressed in ng/ml