

11th International Workshop on Clinical Pharmacology of HIV Therapy

7-9 April 2010 - Sorrento, Italy

Placental transfer of antiretroviral drugs in HIV-infected women : a retrospective study from 2002 to 2009



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Background

- The rate of mother-to-child transmission (MTCT) of HIV-1 is as low as 0.5% in non breast feeding mothers who delivered at term while receiving HAART with a plasma HIV-RNA < 500 c/mL in the French ANRS perinatal cohort (*Tubiana R et al, CID, 2010*)
- Therapeutic Drug Monitoring of antiretroviral drugs (ARV) in HIV-infected pregnant women is used to detect adherence difficulties or intolerance or pharmacokinetic modifications (*French National Guidelines 2008*)
- The degree of fetal exposure theoretically depends largely on the amount of placental transfer of drugs

Objectives

- To evaluate the *in vivo* placental transfer of ARV used to prevent MTCT, based on the determination of concentrations in the different compartments of the maternal-foetal unit
- To look for the impact of usual determinants of membrane transfer (Protein Binding, LogP and Molecular Weight) on the results obtained in this study
- To compare the *in vivo* results obtained in the present study with those from the *ex vivo model* of double perfusion of human placental cotyledon reported in the literature (when available)

Material et Methods (1)

- HIV-infected women were selected based on the availability of blood (maternal and cord) and amniotic concentrations performed at delivery
- Determinations of steady-state plasma concentrations of ARV were performed using validated HPLC coupled with UV-PDA or fluorimetric detection with respective LOQ:
 - 5 ng/mL for TFV, IDV and APV
 - 10 ng/mL for ZDV and Glucuronide (G-ZDV), ABC, 3TC, ddI and EFV
 - 20 ng/mL for SQV
 - 30 ng/mL for RTV, LPV, NFV and its M8 metabolite
 - 50 ng/mL for NVP
 - 100 ng/mL for T20
- Results (median, IQR) of maternal (MP) and cord (CP) and amniotic (AF) concentrations and corresponding ratio were presented
- LOQ/2 was considered to calculate medians and to perform statistical tests

Material et Methods (2)

- Determinants of membrane transfer:
 - Plasma Protein Binding and Molecular Weight were obtained from respective Product Labelling (FDA or Emea)
 - Log P values were found in pubchem <http://pubchem.ncbi.nlm.nih.gov/>
- Ex vivo model of double perfusion of human placental cotyledon reported in the literature with different ARV:
 - Clearance index was calculated as the ratio of clearance of the studied ARV to the clearance of antipyrine
 - Antipyrine is added in the maternal perfusate as an internal permeability control
 - Different Human Albumin concentrations had to be added in the maternal perfusate to increase the solubility of the ARV and to study the impact of the protein binding on the transfer ratio
- Statistical analysis using Spearman test and linear regression coefficient (Statview v50 SAS Inst Inc 1998)

Results: Patients characteristics at delivery

Main study	354 paired samples (MP and CP)
Age	31.4 yrs (28-35)
Treatment (standard doses)*:	
- LPV/r + ZDV/3TC	43%
- SQV/r + ZDV/3TC	7.5%
- IDV/r + ZDV/3TC	6.0%
- NVP + ZDV/3TC	5.8%
- LPV/r + ABC/3TC	4.4%
- NFV + ZDV/3TC	3.8%
- Other combinations	29.5%
Interval between last drug intake and sampling	12.8 hours (8.0-16.9)
Sub study	65 paired samples (MP,CP and AF)
Treatment (standard doses)*:	
- LPV/r + ZDV/3TC	26.2%
- IDV/r + ZDV/3TC	18.5%
-NFV + ZDV/3TC	4.6%
- Others combinations	50.7%

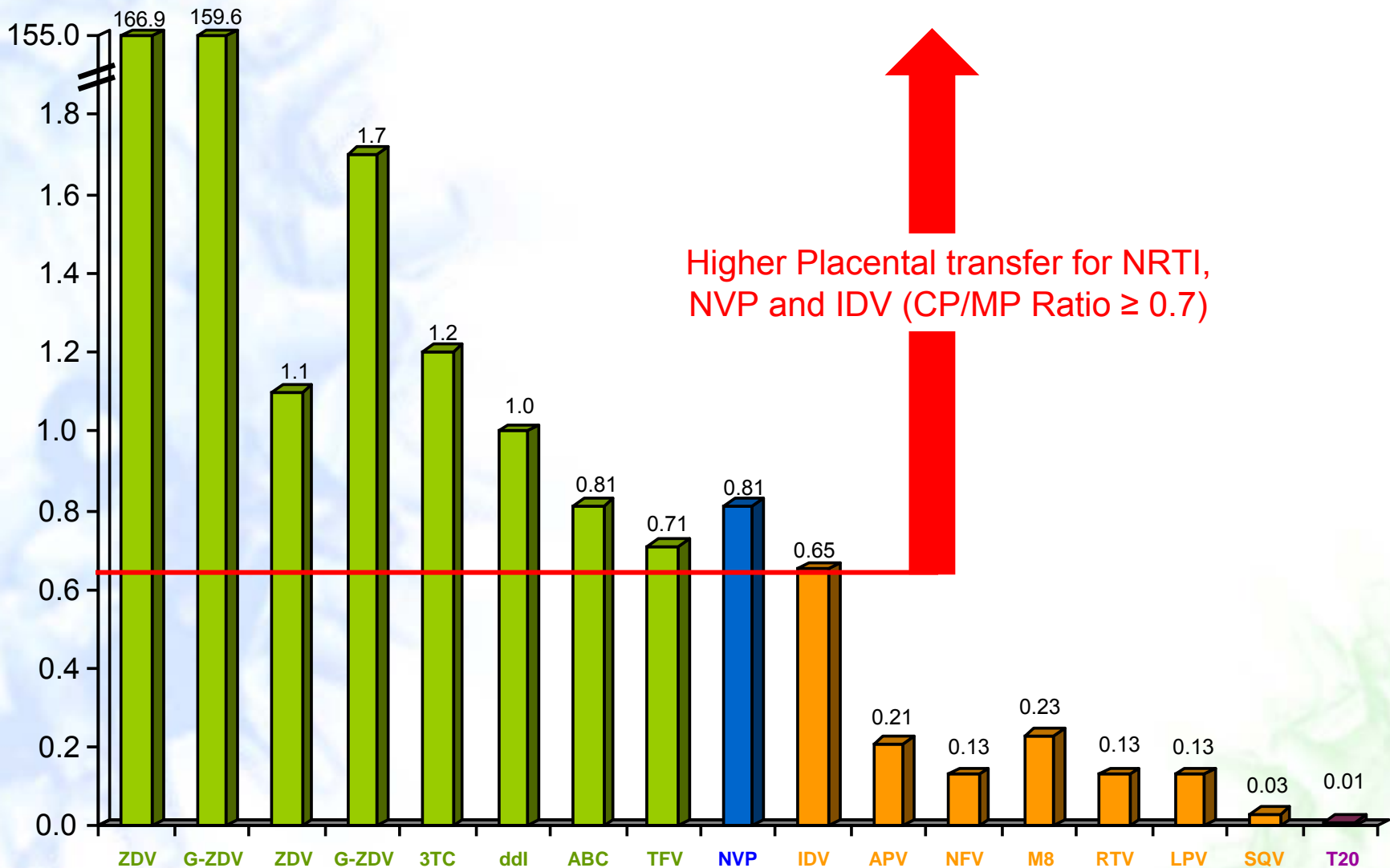
ZDV infusion: At delivery, women received intravenous ZDV as a 2 mg/kg of body weight bolus over 1 hour and a continuous ZDV 1 mg/kg/h infusion maintained until ligation of the umbilical cord

ARV concentrations in Maternal Plasma (MP) Cord Plasma (CP) and CP/MP Ratio

ARV Classes	Drug	n	MP (ng/mL)	CP (ng/mL)	CP/MP RATIO
NRTIs	ZDV	78	5	841	166.90
	G-ZDV	78	5	2366	159.60
	ZDV infusion	195	472	698	1.10
	G-ZDV infusion	195	1628	2634	1.70
	3TC	267	143	182	1.20
	ddl	21	5	5	1.00
	ABC	37	69	52	0.81
	TFV	20	59	50	0.71
NNRTI	NVP	21	3403	2885	0.81
PIs	IDV	19	64	20	0.65
	RTV	294	128	15	0.13
	LPV	204	3690	376	0.13
	NFV	14	1403	186	0.13
	M8	14	55	15	0.23
	SQV	30	632	10	0.03
	APV	12	1389	260	0.21
Fusion inhibitor	T20	5	1889	30	0.01

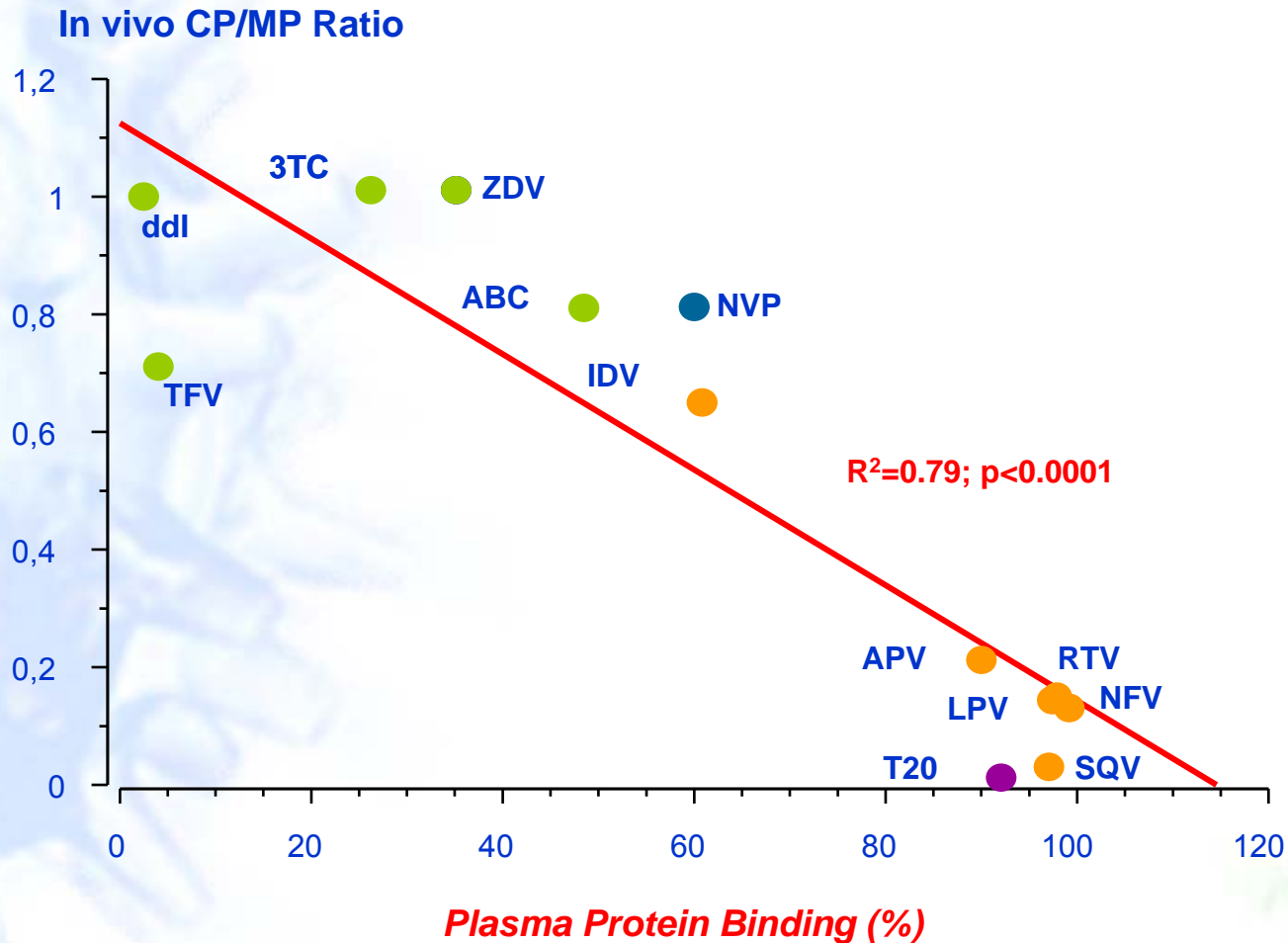
CP/MP Ratio according to the different ARV

CP/MP Ratio



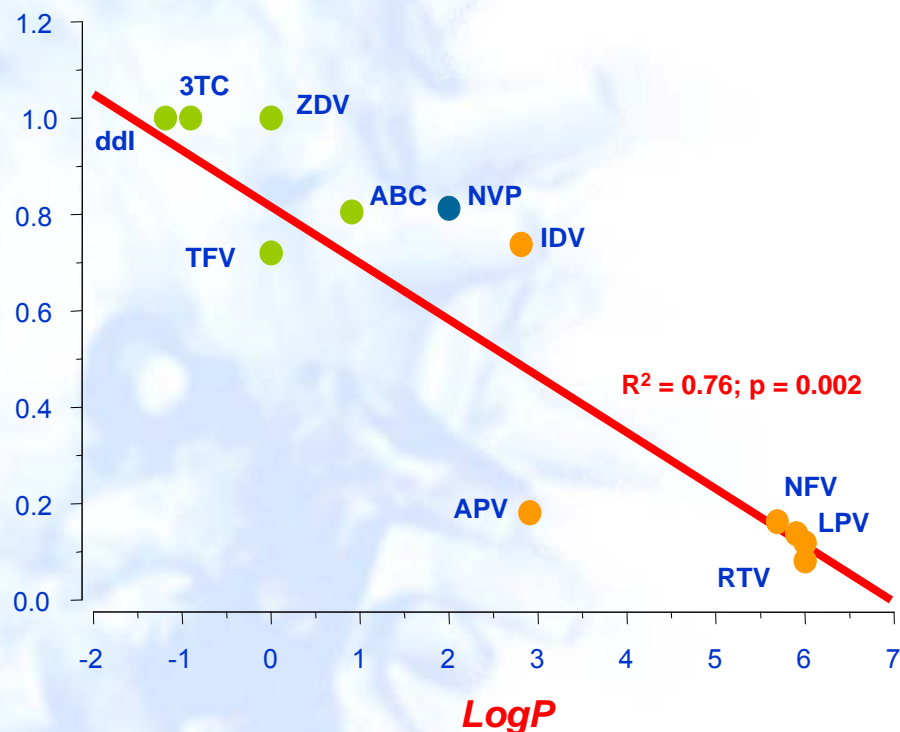
Higher Placental transfer for NRTI, NVP and IDV (CP/MP Ratio \geq 0.7)

Relationship between Plasma Protein binding and in vivo placental transfer of ARV

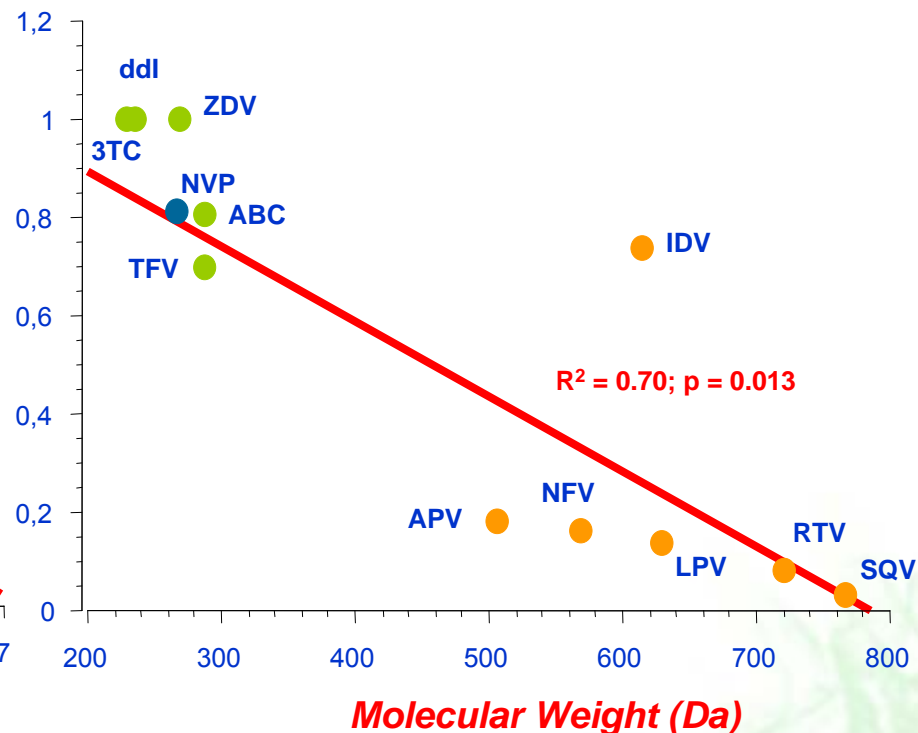


Relationship between LogP, Molecular Weight and in vivo placental transfer of ARV

In vivo CP/MP Ratio

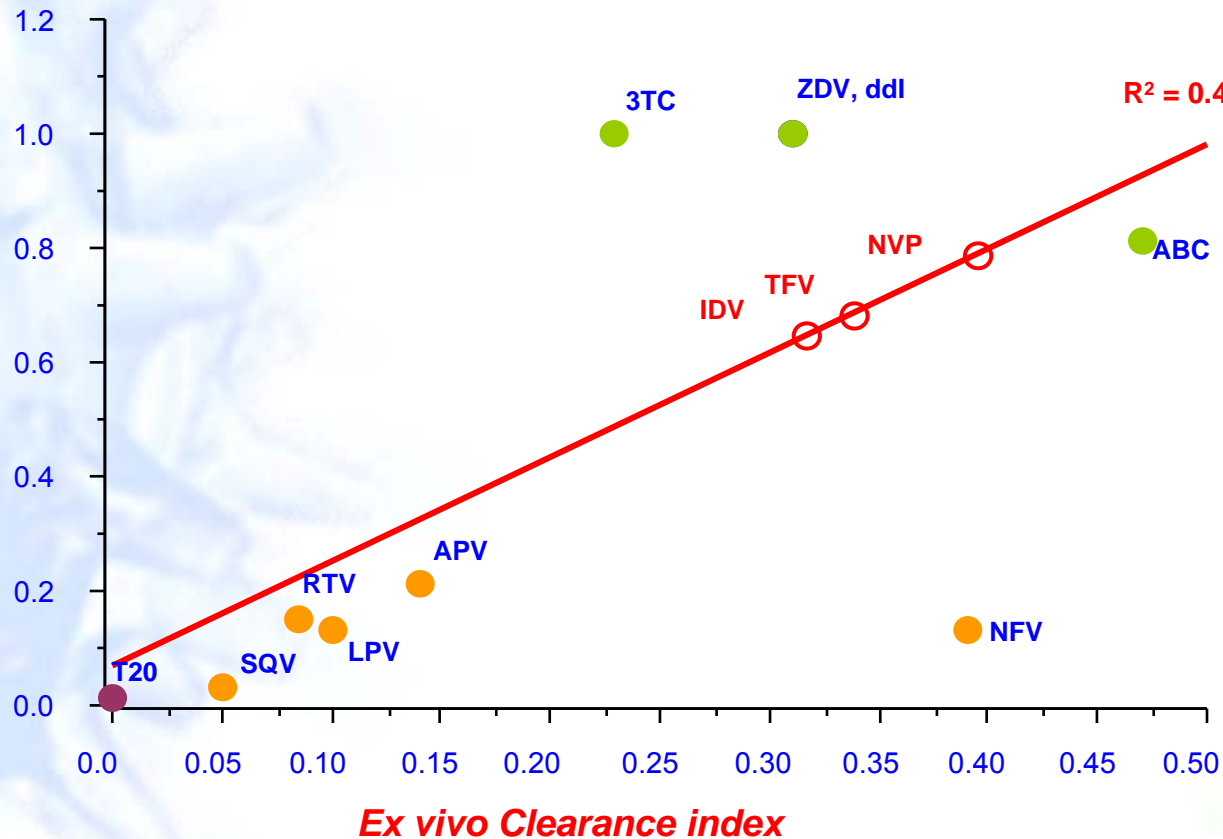


In vivo CP/MP Ratio



Relationship between *in vivo* and *ex vivo* placental transfer of ARV

In vivo CP/MP Ratio



Legend: ● both *ex vivo* and *in vivo* results ○ *in vivo* results

Sub study results: Amniotic Fluid concentrations (AF)

ARV Classes	Drug	n	MP (ng/mL)	AF (ng/mL)	CP (ng/mL)	CP/MP Ratio	AF/MP Ratio	AF/CP Ratio
NRTIs	ZDV	7	5	1747	617	123.40	349.40	2.98
	G-ZDV	7	5	10298	2282	66.80	323.60	3.67
	ZDV infusion	31	601	1515	628	0.80	2.84	2.04
	G-ZDV infusion	31	1871	7143	2137	0.94	3.67	3.07
	3TC	37	126	1604	182	1.35	10.73	6.08
	ABC	2	55	699	45	0.63	7.44	8.79
	TFV	4	30	254	3	0.11	6.55	84.67
PIs	IDV	19	110	141	18	0.16	1.00	8.60
	RTV	52	120	15	15	0.15	0.18	1.00
	LPV	31	2898	391	424	0.12	0.14	1.00
	NFV	3	166	78	15	0.12	0.47	3.97
	M8	3	15	15	15	1.00	1.00	1.00
	APV	2	1365	359	169	0.14	0.20	1.41
Fusion inhibitor	T20	2	2226	268	30	0.02	0.22	8.92

Summary

- The *in vivo* placental transfer is even better if the drug is weakly bound to plasma proteins (NRTIs > NVP > IDV > PIs > T20)
- While PIs (excepted IDV) and T20 did not cross the placental membrane, NRTIs and NVP reached easily the fetal compartment (transporters ?)
- A statistically significant (but poor) relationship was found between *ex vivo* (Clearance index) and *in vivo* (CP/MP ratio) placental transfer for ARV
- Particularly for NRTIs, AF/MP and AF/CP ratio inform on the accumulation in the amniotic compartment, probably because of the low reciprocity of the placental transfer (transporters ?)
- ARV demonstrating the higher CP/MP ratio demonstrate also the best penetration in cervico-vaginal fluids

Acknowledgments to patients and...

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