Pharmacokinetic, Safety and Efficacy of Darunavir/Ritonavir in HIV+ Pregnant Women

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Abstract #O_01

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Background

- **Darunavir/ritonavir** (DRV/r) is the most popular protease inhibitor recommended to prevent the risk of **HIV mother-to-child transmission**

- However, a decrease of DRV plasma exposure during the 3rd trimester might limit the efficacy of the ARV strategy

DRV/r and pregnancy

- French national guidelines (2015) recommend to switch from **DRV/r 800/100mg QD** to **DRV/r 600/100mg BID** at the beginning of the 3rd trimester
- However, it might be important to dissociate:
  - Women receiving initially DRV/r before conception (as maintenance treatment): ie **DRV/r 800/100mg QD**
  - Women receiving DRV/r after conception (as induction treatment):

    ie **DRV/r 600/100mg BID**
  - Patients switching from **DRV/r 800/100mg QD** to **DRV/r 600/100mg BID**

What effect on C_{min} (DRV) was observed during pregnancy ?

Litterature

Study n patients	Courbon *et al*, 2012 n=33	PANNA, 2012 n=9	Dublin, 2014 n=20	Zorilla *et al*, 2014 n=30	P1026s, 2015 n=64	Stek *et al*, 2016, n=18
DRV/r 600/100 mg BID	n=17	n=3	n=0	n=14	n=34	N/A
DRV/r 800/100 mg QD	n=16	n=6	n=20	n=16	n=30	n=17 **(DRV/r 800/100mg BID)**
Effect on DRV Cmin*	**-20%**	**-37% (AUC)**	**-55%**	**-32 to -86%**	**-26% to -38%**	**-36% (AUC)**
DRV C/M ratio**	0.18	0.11-0.67	0.11	0.15	0.18	N/A
Plasma HIV RNA <50 c/mL	100%	n/a	90%	73-90%	57%	94%
Live births	19	9	20	12	24	18
MTCT	0	0	0	0	1	0 (6 pending)

*Geometric mean ratio of Cmin for third trimester compared to *post-partum*
**DRV C/M Ratio : DRV Cord blood/maternal concentration ratio
Adapted from S. Khoo, et al (submitted)

Objectives

- To assess **maternal DRV plasma concentrations** during pregnancy in patients receiving
  - **DRV/r 800/100mg QD** throughout the pregnancy
  - **DRV/r 600/100mg BID** throughout the pregnancy
  - **DRV/r 800/100mg QD** then **DRV/r 600/100mg BID**

- To describe the **safety and efficacy** of DRV/r containing regimen

Study design

- **Multicenter, cohort & non interventional** study

- **Eligiblity criterions:**
  - HIV-1/2 infection
  - Adult & pregnant
  - Receiving DRV/r 800/100mg QD or 600/100mg BID
  - RAL add-on was authorized
  - Availability of demographical, clinical and biological data

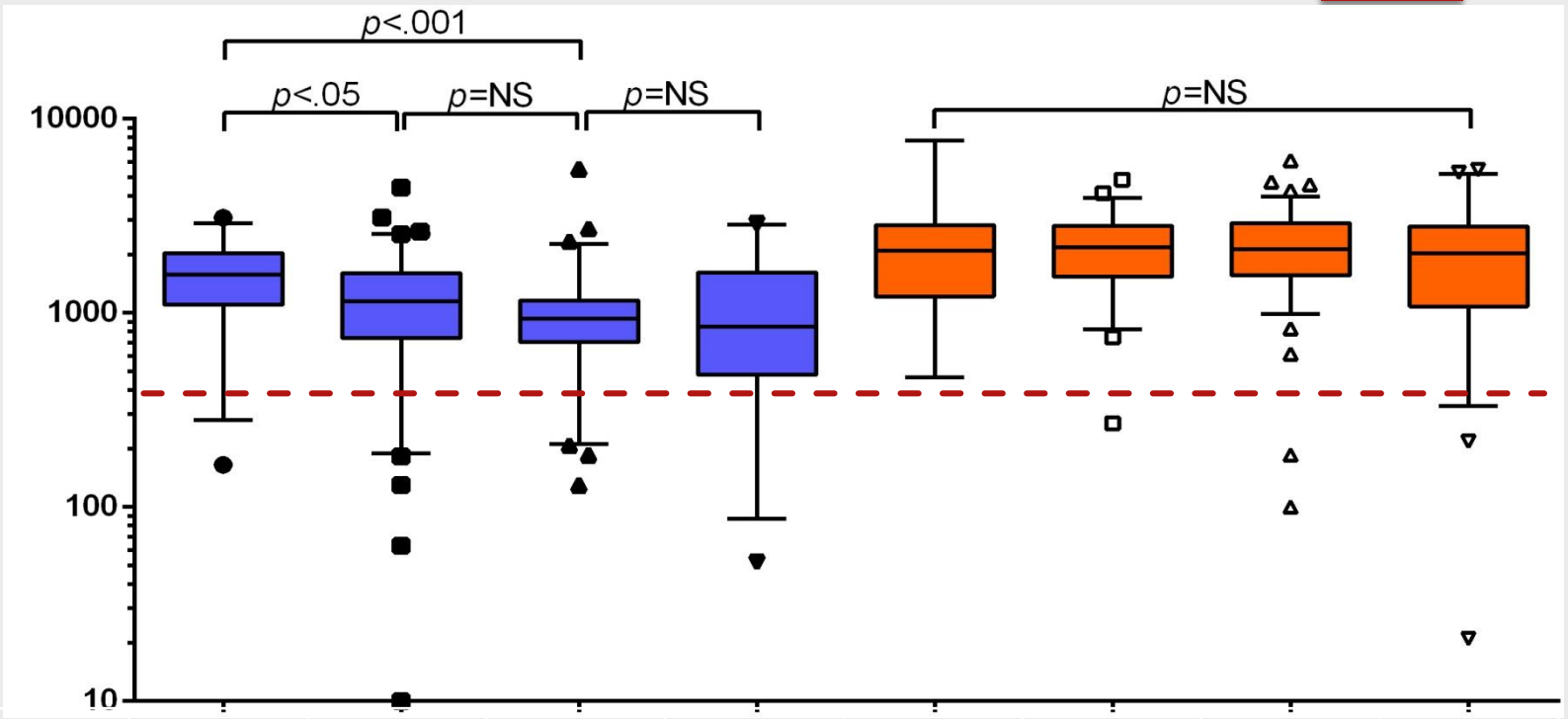
- **Exclusion criteria:**
  - Receiving DRV/r at other dosing regimen than 800/100mg QD or 600/100mg BID
  - Receiving any drug with relevant CYP450 inducer properties: NNRTIs (efavirenz, nevirapine,etravirine,…), rifampin/rifabutin, etc…

- Data were collected during the **3 trimesters of pregnancy & at delivery**
- **ARV plasma concentration determination** at steady state using UPLC-MS/MS (Waters Acquity® UPLC-TQD, Milford, MA, USA)
- **Limit of Quantification**: 5 ng/mL
- **DRV efficacy threshold**: 550 ng/mL (corresponding to 10 fold protein adjusted IC50 on WT virus)
- **Virological failure**: 2 successive plasma RNA-HIV(pVL) > 50 copies/mL in the 2 months preceding delivery
- **Statistical analysis**: descriptive: median(IQR25-75%), non parametric tests (Mann-Whitney and Kruskal-Wallis tests)

Patients' baseline characteristics

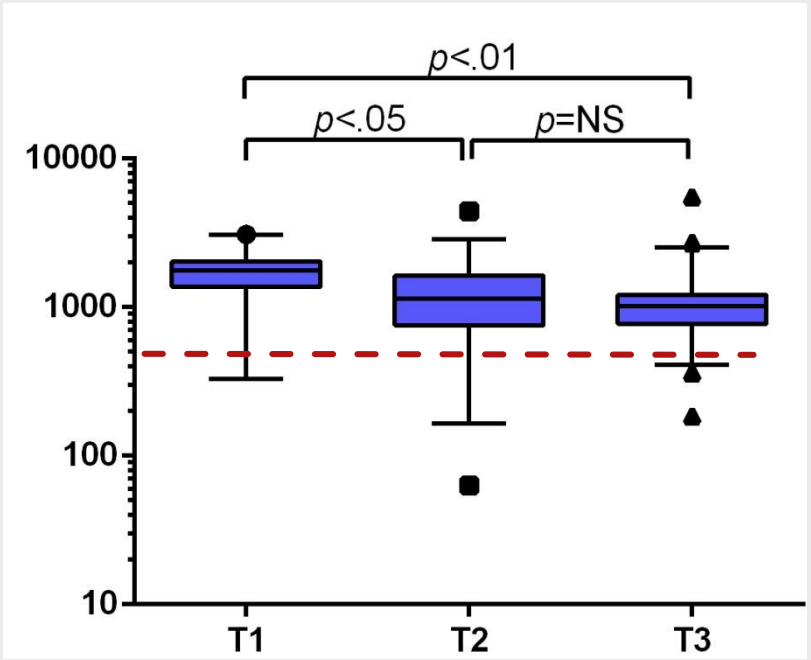
Parameters	Median (IQR25-75%)
Patients, n	**220**
Age, years	**32** (28-36)
Geographic origin, (%)	
Sub-saharan African	**94%**
Caucasian	5%
South american	1%
Time since HIV diagnosis, years	**6** (6-12)
Time since ARV instauration, years	**4** (1-9)
Time since DRV/r start, months	**10** (0-27)
cART-experienced patients, n (%)	**83%**
DRV/r dosing regimen at the beginning of pregnancy	
800/100mg QD, n (%)	149 (68%)
- throughout the pregnancy, n(%)	**88** (40%)
- Switch to 600/100mg BID, n(%)	**61** (28%)
600/100mg BID throughout the pregnancy, n (%)	**71** (32%)
cART started for prevention of mother to child transmission, %	**34%**
DRV/r started during pregnancy, %	**17%**
HIV-1 infection, %	**98%**
HBV co-infection, %	12%
HCV co-infection, %	4%
Body Mass Index before pregnancy (>6 months), kg/m^2	27 (23-30)
CD4 nadir, $cells/mm^3$	270 (164-391)
ARV backbone, %	
FTC/TDF	**60%**
3TC/ABC	15%
NRTIs/RAL	10%
3TC/ZDV	5%

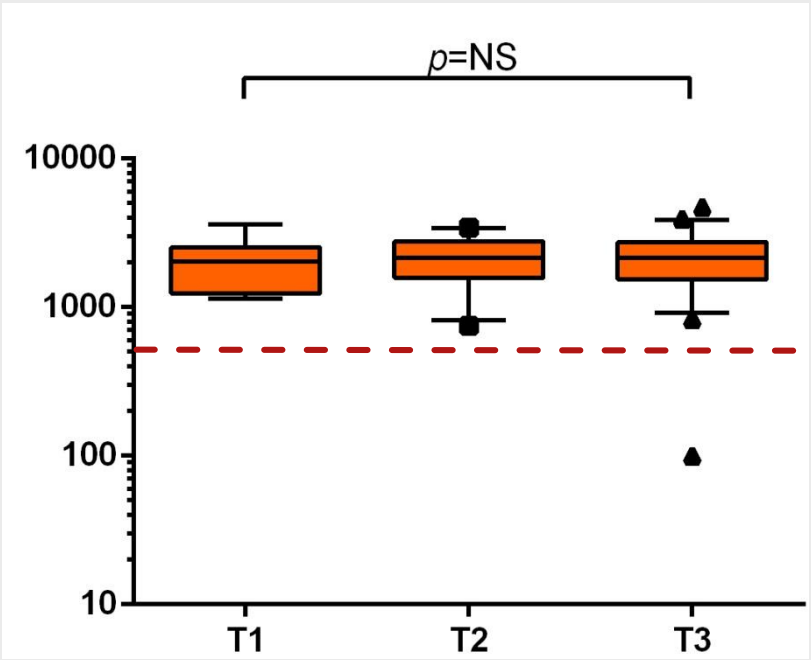
Overall DRV C24h & C12h during pregnancy (ng/mL)



	DRV QD T1	DRV QD T2	DRV QD T3	DRV QD D	DRV BID T1	DRV BID T2	DRV BID T3	DRV BID D
N	33	81	74	30	13	49	98	53
DRV C24h/C12h (ng/mL), median	**1,574**	**1,144** (-27% vs T1)	**934** (-40% vs T1)	**854**	**2,088**	**2,174**	**2,134**	**2,033**
IQR25-75%	1,101-2,033	743-1,605	707-1,160	480-1,617	1,219-2,835	1,534-2,812	1,560-2,893	1,081-2,793
%DRV C24h/C12h <550 ng/mL	9%	**19%**	**12%**	**30%**	8%	**2%**	**2%**	**9%**
CV(%)	46%	60%	67%	74%	75%	41%	45%	60%

DRV C24h & C12h throughout pregnancy (ng/mL)

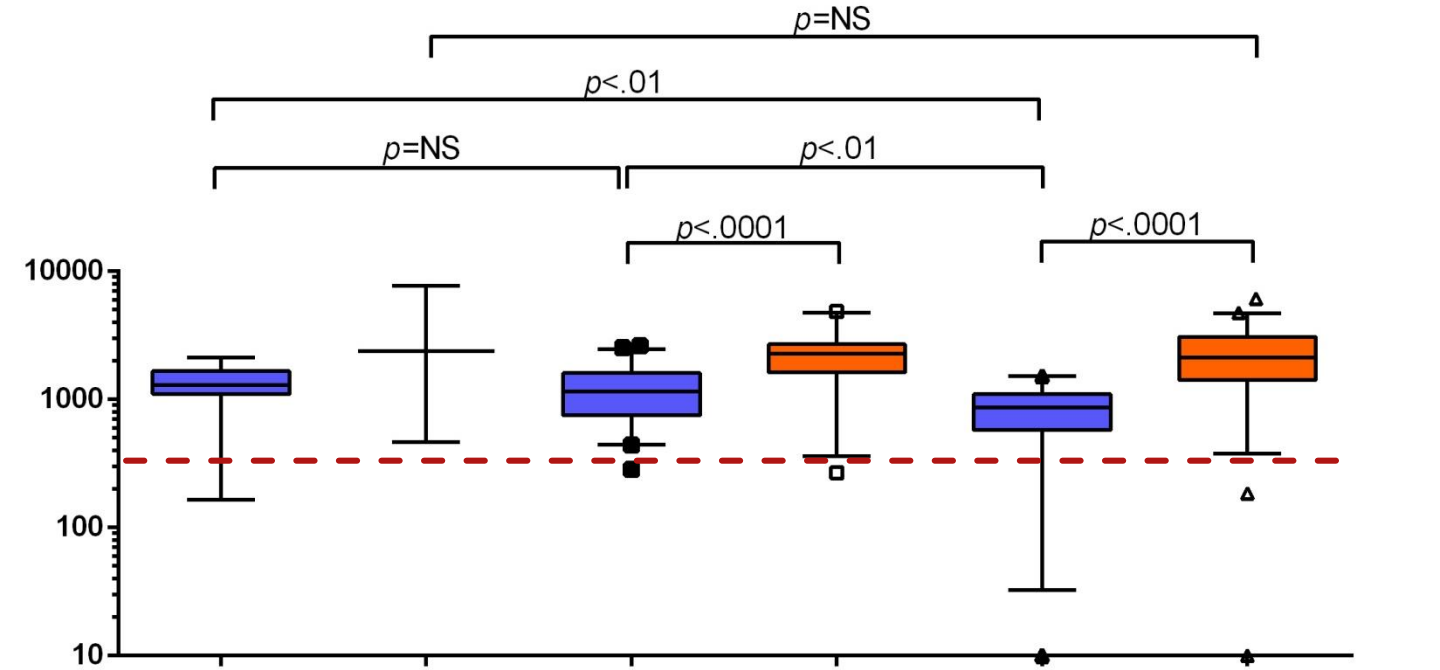




N	19	36	49
DRV C24h (ng/mL), median	1,764	1,148 **(-27% vs T1)**	1,022 **(-42% vs T1)**
IQR25-75%	1,368-2,033	758-1,634	775-1,215
%DRV C24h/C12h <550 ng/mL	11%	14%	10%
CV(%)	43%	64%	70%

N	10	28	49
DRV C12h (ng/mL), median	2,036	2,157	2,162
IQR25-75%	1,231-2,528	1,572-2,778	1,547-2,752
%DRV C24h/C12h <550 ng/mL	0%	0%	2%
CV(%)	40%	35%	40%

DRV C24h & C12h: switch during pregnancy (ng/mL)



	DRV QD T1	DRV BID T1	DRV QD T2	DRV BID T2	DRV QD T3	DRV BID T3
N	13	3	41	21	24	48
DRV C24h/C12h (ng/mL), median	**1,296**	**2,386**	**1,150**	**2,269**	**863**	**2,125**
IQR25-75%	1,101-1,663	465-7,715	752-1,605	1,636-2,696	576-1,108	1,424-3,078
%DRV C24h/C12h <550 ng/mL	8%	33%	**15%**	**5%**	**21%**	**4%**
CV (%)	41%	107%	46%	44%	50%	53%

Immunological results

CD4 cell count evolution during pregnancy

CD4 Cell count (/mm³)	At start of pregnancy	3rd trimester and at delivery (T3+D)
n	124	141
Median (IQR25-75%)	507 (325-718)	500 (371-659)

- No modification of CD4 cell count was observed during pregnancy

Virological results

Plasma HIV-RNA evolution during pregnancy

Plasma HIV-RNA (pVL)	At start of pregnancy	3rd trimester and at delivery (T3+D)
n	120	142
pVL<50 copies/mL, n (%)	81 (68%)	117 (82%)
pVL if >50 copies/mL		
n	51	25
Median (IQR25-75%)	3342 (297-34,557)	109 (87-263)
pVL> 400 copies/mL, n (%)	36 (71%)	**5 (4%)**

- No difference in virological failure was reported between both dosing regimen
- At delivery, 4% of our patients presented pVL>400 copies/mL

Baby & Tolerance

- **Cord blood/maternal ratios** of DRV concentration were:
  - Overall: **0.16** (0.07-0.42, n=91)
  - **DRV/r 800/100mg**: **0.18** (0.07-0.42, n=47)
  - **DRV/r 600/100mg**: **0.14** (0.08-0.40, n=44)
- **No MTCT** reported to date
- **Newborn characteristics** (n=133):
  - Gestational age: 38 (35-40) weeks
  - Weight: 3,160 g (2,805-3,498)
  - APGAR score: 10

Discussion

- **Pharmacokinetics**
  - **DRV/r 800/100mg QD**: significant decrease of DRV C24h
    - -27% (T2 vs T1)
    - -42% (T3 vs T1)
  - **DRV/r 600/100mg BID**: remained stable throughout pregnancy
  - Proportion of patients with **DRV C24h <550ng/mL** during 2nd and 3rd trimesters were **higher than DRV C12h**
  - **Low cord blood/maternal ratio** of DRV, consistantly with the high protein binding, independantly of RTV dosing regimen
- **Immuno-virological efficacy**

  CD4 remained **stable** at **500/mm^3** and **96%** of pregnant women presented **pVL<400 copies/mL** at delivery
- **Tolerance**
  - **Good tolerance profile** for both mother and child

Conclusion

- In our population of Sub-Saharan African pregnant women, DRV/r remains a **treatment of choice** in the prevention of mother-to-child transmission

- However, a **dose adaptation** might be required from the **2nd trimester** of pregnancy for patients receiving DRV/r 800/100mg QD

- **Therapeutic Drug Monitoring** should be recommended to document probable efficacy, tolerance and adherence issues

Thank you for your attention

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