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Low Darunavir Exposure during Pregnancy with 800/100mg Darunavir/r QD Dosing

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ABSTRACT

- **BACKGROUND**: Perinatal guidelines include ritonavir-boosted darunavir (DRV/r) as an alternative protease inhibitor for use in antiretroviral (ARV)-naive pregnant women. The dosing recommendation for ARV-naive patients is DRV/r 800/100mg QD but pharmacokinetic data on this dose in pregnant women are limited.
- **METHODOLOGY**: Patients treated with DRV/r (800/100mg QD) during pregnancy had intensive steady-state 24-hour PK profiles in the 3rd trimester and at least 2 weeks postpartum. Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for PK parameters 3rd trimester/postpartum. Unbound concentrations were determined using an ultracentrifugation method.
- **RESULTS**: 15 patients were included in the analysis, 11 were treatment experienced at conception. 7 patients were Black and 8 Caucasian. Seven paired PK curves (3rd trimester and postpartum) were available.
  Median gestational age at delivery was 38 (36-41) weeks. Approaching delivery 73% had an HIV viral load <50 cps/mL, 93% <1000 cps/mL. Two weeks prior to delivery one patient still had a significant viraemia: (28,711 copies/mL). This patient was thought to be non-adherent and had directly observed therapy until delivery. All children were born uninfected. No congenital abnormalities were reported.
  GMR (90% CI) of DRV PK parameters 3rd trimester/postpartum were: 0.63 (0.51-0.77) for AUC; 0.72 (0.57-0.93) for C_{max}; 0.36 (0.22-0.58) for C_{24h}. Mean free fraction (95%CI) was 12% (11-14%) in the 3rd trimester and 10% (7-13%) postpartum. 2/15 of the patients showed DRV concentrations <0.55 mg/L (EC50 for resistant virus) in the 3rd trimester, versus none postpartum. The median (min-max) cord blood/maternal ratios (n=6) were 0.12 (0.08-0.35).
- **CONCLUSIONS**: Third trimester darunavir exposure when administered as 800/100mg QD was significantly lower than postpartum. Trough concentrations were approaching the C_{trough} target minimum, indicating that this dose is likely to lead to sub-therapeutic concentrations during pregnancy, especially for treatment experienced patients. This decrease seems not to be compensated by a higher free fraction during pregnancy. DRV/r 600/100mg BID is suggested to be the preferred dose during pregnancy for treatment experienced patients.

1. INTRODUCTION

- The risk of mother to child transmission (MTCT) of HIV has been reduced by the introduction of combination antiretroviral therapy (cART), reducing the risk from 15-40% to <2%.
- Perinatal guidelines include ritonavir-boosted darunavir (DRV/r) as an alternative protease inhibitor for use in antiretroviral (ARV)-naive pregnant women.
- During pregnancy physiological changes cause a decreased exposure to most HIV protease inhibitors.
- Although total darunavir exposure to DRV/r 600/100mg BID was decreased during pregnancy, no clinically relevant change in unbound (active) darunavir occurred during pregnancy, suggesting that no dose adjustment is required for DRV/r 600/100mg BID in pregnant women[Zorrilla, 2013].
- The general dosing recommendation for ARV-naive patients is DRV/r 800/100mg QD but pharmacokinetic data on this dose in pregnant women are limited.

Objective

- To study the effect of pregnancy on DRV/r 800/100mg QD.

2. METHODS

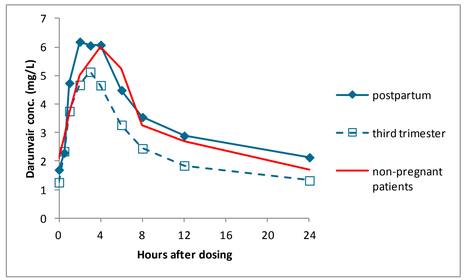
- This was a non-randomized, open-label, multi-centre phase-IV study in HIV-infected pregnant women recruited from HIV treatment centres in Europe (PANNA network: www.pannastudy.com). The PANNA network is a European network of hospitals collecting pharmacokinetic curves of several ARVs during pregnancy in a prospective study.
- Here, we report on pregnant HIV-infected patients treated with DRV/r 800/100mg QD as part of their cART.
- Blood was collected for a 24h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24h) after supervised intake of the medication in the third trimester. At least 2 weeks post-partum intensive PK sampling was repeated. Where possible a cord blood sample and matching maternal blood sample were taken at delivery.
- Target DRV trough concentration is defined as 0.55 mg/L (EC 50 for resistant virus).
- Safety and antiviral parameters were evaluated.
- DRV and RTV plasma concentrations were determined by validated UPLC method, free DRV concentrations were analyzed in two plasma samples per curve (high and low total DRV concentrations). Pharmacokinetic parameters were calculated using Phoenix/WinNonlin version 6.3.
- If the t=24h sample was not taken an extrapolation was made using lambda-z and the last measured concentration to assess DRV C_{24h}.
- Mixed linear model analysis was performed on the log-transformed data (using Phoenix).

Table 1: Demographics

General (n=15)	
Age (years)	30 (20-44)
White; black (n (%))	8 (53%); 7 (47%)
Treatment naive at conception (N(%))	5 (33%)
Conception on darunavir (N (%))	2 (13%)
Start darunavir per trimester (N (%))	4 (27%) 1st trim; 8 (53%) 2nd trim; 1 (7 %) 3rd
NRTIs (N (%))	tenofovir 12 (80%); emtricitabine 11 (73%);
Other ARVs (N(%))	raltegravir 4 (27%); maraviroc 2 (13%)
Third trimester (n=15)	
Gestational age (weeks)	35 (33-38)
Weight (kg)	80 (67-103)
HIV-RNA undetectable <50 (n (%))	10 (71%) / <200: 13 (93%) / one 28711
CD-4 count (copies/uL)	570 (151-1196)
Post partum (n=7)	
Time after delivery (weeks)	5 (4-9)
Weight (kg)	72 (62-100)
HIV-RNA undetectable <50 (n (%))	5 (71%) / <200: 7 (100%)
CD-4 count (cells/uL)	470 (149-829)
Pregnancy outcomes (n=14)	
Gestational age (weeks)	38 (36-41)
Caesarian section	12 (80%)
Birth weight (grams)	3080 (2380-3718)
Infant HIV DNA PCR negative (n (%))	15 (100%)

Median (range) for continuous variables, n for categorical variables.

Figure 1: Mean DRV concentrations



3. RESULTS

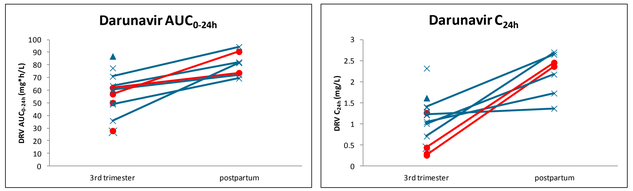
- Data are available for 15 HIV-infected women who used DRV/r 800/100mg QD during pregnancy.
- Evaluable paired PK curves (3rd trimester and postpartum) were available for 7 patients. Three patients withdrew consent, 2 were lost to follow-up, for 1 patient all postpartum samples were below LLOQ (probably due to non-adherence), for 1 patient the postpartum curve was incomplete and therefore not evaluable.
- Exposure (AUC_{tau}) during pregnancy (3rd trimester) to DRV was 37% lower than post-partum , RTV exposure was decreased by 33%.
- Mean DRV free fraction (95%CI) was 12% (11-14%) in the 3rd trimester and 10% (7-13%) postpartum.
- 2/15 of the patients showed DRV concentrations <0.55 mg/L (EC50 for resistant virus) in the 3rd trimester, and for 2 additional patients extrapolated DRV C_{24h} concentrations were <0.55 mg/L, versus none postpartum.
- The median (min-max) cord blood/maternal ratios (n=6) were 0.12 (0.08-0.35).

Table 2: Pharmacokinetic parameters

	Third Trimester*	Postpartum*	GM Ratio (90% CI)** Third Trimester / Postpartum
Darunavir	(n=15)	(n=7)	
AUC_{0-24h} (h*mg/L)	53.2 (44.1-64.1)	80.1 (71.9-89.2)	0.63 (0.51-0.77)
C_{max} (mg/L)	5.38 (4.52-6.41)	6.97 (6.12-7.94)	0.72 (0.57-0.93)
T_{max} (h)	3 (1.5-6)	3 (2-7.08)	
C_{24h} (mg/L)	0.90 (0.62-1.29)	2.15 (1.71-2.71)	0.36 (0.22-0.58)
t_{half} (h)	13 (9-19)	20 (14-29)	0.63 (0.36-1.08)
free fraction	12% (11-14%)	10% (7-13%)	
Ritonavir	(n=15)	(n=7)	
AUC_{0-24h} (h*mg/L)	3.56 (2.70-4.69)	4.87 (3.61-6.57)	0.67 (0.47-0.96)
C_{max} (mg/L)	0.31 (0.22-0.44)	0.50 (0.34-0.75)	0.57 (0.35-0.92)
T_{max} (h)	4 (1.5-8)	3.83 (3-7.08)	
C_{24h} (mg/L)	0.04 (0.025-0.056)	0.05 (0.027-0.091)	0.73 (0.47-1.14)
t_{half} (h)	7 (6-8)	6 (5-8)	1.03 (0.79-1.35)

* Geometric mean (95% confidence interval); except for Tmax: median (min-max)
** mixed model analysis

Figure 2 Individual pharmacokinetic values



Blue X : VL undetectable; **Blue** ▲: VL undetectable; **red** ●: VL detectable

3. RESULTS (continued)

Safety and efficacy

- No congenital abnormalities were reported.
- None of the children were HIV infected.
- HIV VL was detectable for 4 patients around delivery. Two of these patients showed extrapolated DRV C_{24h} <0.55mg/L in the 3rd trimester, one of these patients was suspected to be non-adherent.

Discussion

- The PK parameters as determined post-partum are in line with the reference values for DRV/r 800/100mg QD (ARTEMIS trial).
- Contrary to the previously published DRV exposure to DRV/r 600/100mg BID, the decrease in exposure seems not to be compensated by a higher free fraction during pregnancy.

4. CONCLUSIONS

- Transplacental passage of DRV is low.
- 800/100mg DRV/r generates 37% lower darunavir exposure during pregnancy.
- Trough concentrations were approaching the C_{trough} target minimum, indicating that this dose is likely to lead to sub-therapeutic concentrations during pregnancy, especially for treatment experienced patients.
- DRV/r 600/100mg BID is suggested to be the preferred dose during pregnancy for treatment experienced patients.

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