Total and Unbound Pharmacokinetics of Once-Daily Darunavir/ritonavir in HIV-1-Infected Pregnant Women

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Background and Study Objectives

- **Physiologic changes during pregnancy may result in altered PK**
  - **e.g. blood volume expansion, alterations in hepatic metabolism, etc.**

Primary objective

- **Assess effect of pregnancy on PK of DRV/rtv during the 2nd and 3rd trimesters of gestation, compared to postpartum**

Secondary objectives

- **Document antiviral activity during gestation and postpartum**
- **Describe the safety and tolerability of DRV/rtv-based, ARV regimens during gestation and postpartum**
- **Compare DRV concentrations between maternal and cord blood at the time of delivery**
- **Assess outcomes for infants of women treated with DRV/rtv during pregnancy**

Baseline Disease Characteristics

Parameter, n (%)	Subjects
Clinical stage of HIV infection	
Category A	16 (94)
Category B	1 (6)
CD4 count, median (range), cells/mm^3	
100 to <200	0
200 to 350	5 (29)
≥350	12 (71)
Viral load, median (range), copies/mL	
<50	10 (59)
50 to <400	6 (35)
400 to 1000	0
≥1000	1 (6)
Previous ARV experience	
PIs: 0	2 (12)
PIs: 1	13 (77)
PIs: ≥2	2 (12)
NNRTIs: 0	11 (65)
NNRTIs: 1	6 (35)
Hepatitis B surface antigen and hepatitis C antibody negative	17 (100)

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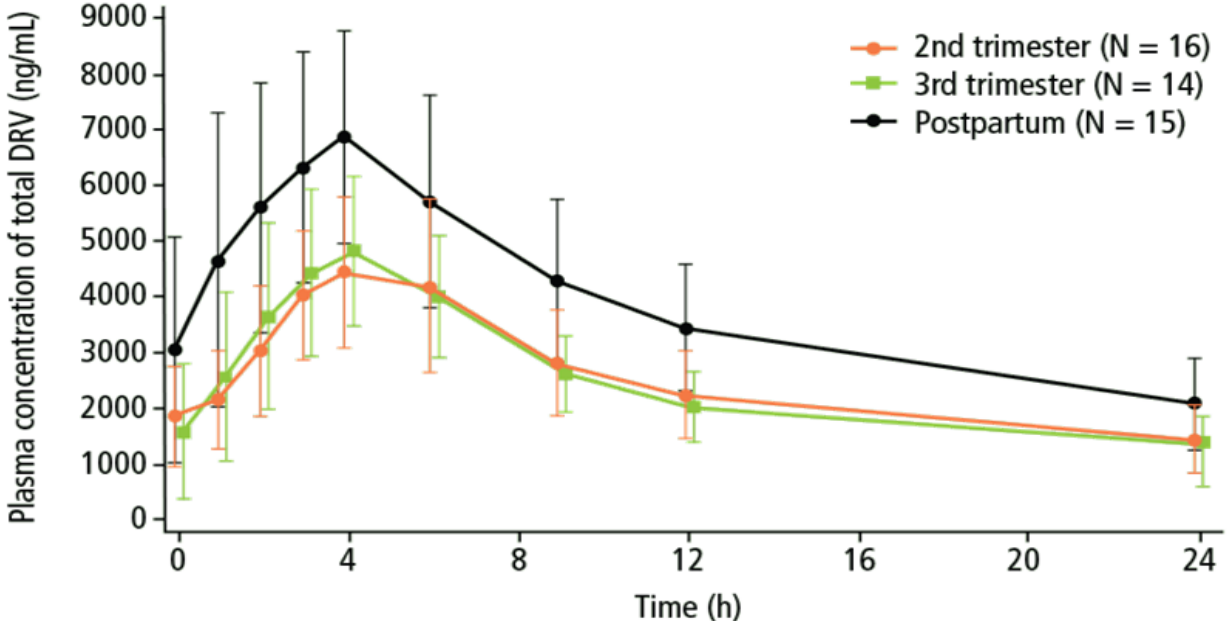
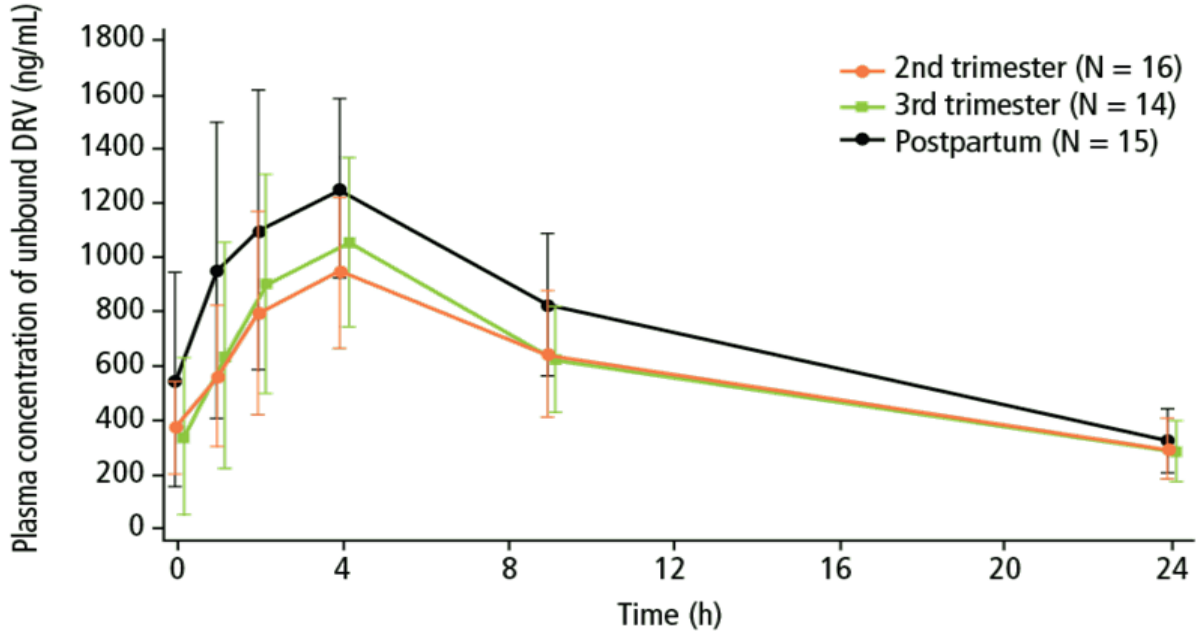
Results

Total DRV Plasma Concentrations



Unbound DRV Plasma Concentrations



Data presented as mean (SD) EC_{50} = 2.75ng/mL

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Results – Total and Unbound DRV PK

	Total DRV, % difference (LSMeans ratio, 90% CI)	
	2nd trimester vs. postpartum	3rd trimester vs. postpartum
AUC_{24h}	↓34% (0.66, 0.60-0.74)[a]	↓35% (0.65, 0.57-0.74)[c]
C_{min}	↓32% (0.68, 0.56-0.83)[b]	↓50% (0.50, 0.35-0.73)[d]
C_{max}	↓34% (0.66, 0.59-0.75)[a]	↓31% (0.69, 0.63-0.77)[c]

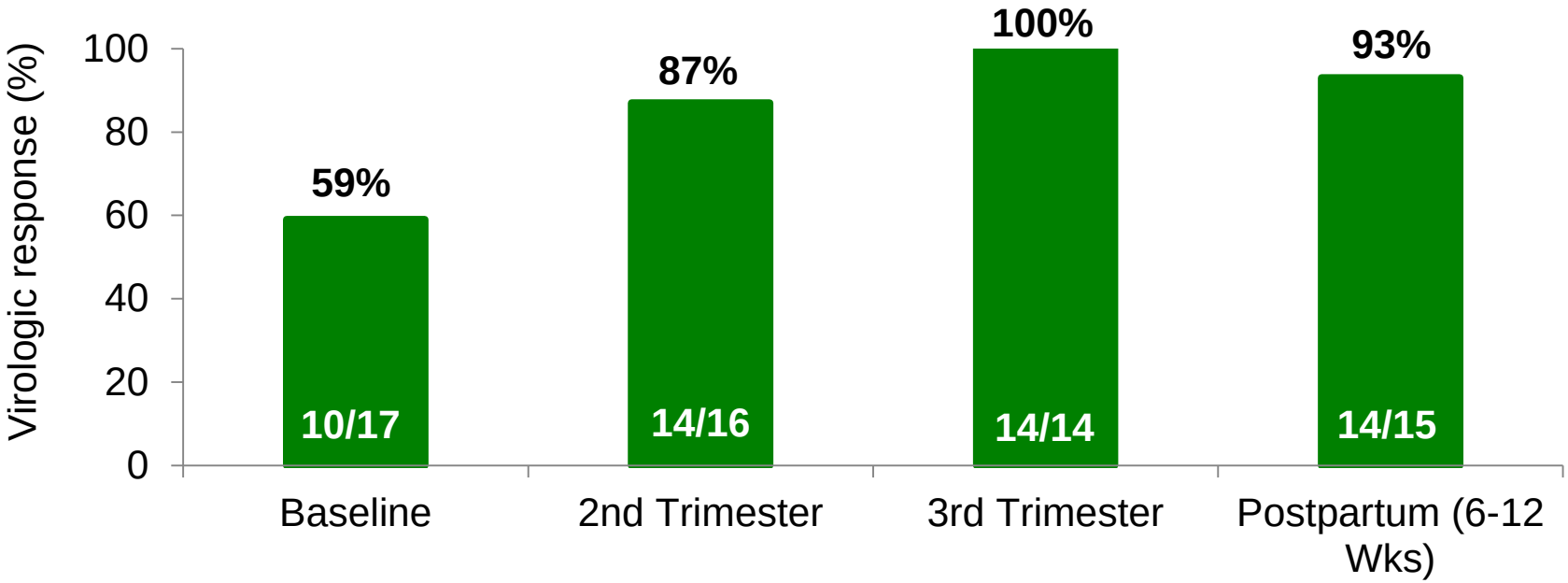
	Unbound DRV, % difference (LSMeans ratio, 90% CI)	
	2nd trimester vs. postpartum	3rd trimester vs. postpartum
AUC_{24h}	↓24% (0.76, 0.67-0.85)[e]	↓20% (0.80, 0.71-0.89)[c]
C_{min}	↓13% (0.87, 0.69-1.10)[b]	↓38% (0.62, 0.43-0.90)[d]
C_{max}	↓25% (0.75, 0.65-0.87)[e]	↓16% (0.84, 0.74-0.96)[c]

[a]N=15 for reference and N=16 for test; [b]N=12 for reference and N=15 for test; [c]N=15 for reference and N=14 for test; [d]N=12 for reference and N=14 for test; [e]N=15 for reference and N=15 for test

- **Unbound DRV C_{min} >10-fold above the unbound EC_{50} for wild-type HIV (2.75 ng/mL) in all subjects at all times**
- **Mean ratio Cord/Maternal total DRV Plasma Conc: 0.18 (104% coefficient of variation)**

Efficacy Results:

Viral Suppression (<50 c/mL) Over Time



- **Median (range) CD4 count (cells/mm^3) increased over time**
  - **Baseline [N=17]: 493 (200-1136); 2nd trimester [N=16]: 610 (284-1320); 3rd trimester [N=14]: 737 (334-1524); postpartum [N=15]: 809 (330-1792)**
- **All 16 infants were born HIV-1 negative**

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DRV/rtv QD During Pregnancy: Safety Results

- **3/16 infants were born prior to Week 37 (at Weeks 33, 36, and 36)**
- **Six serious AEs in treatment phase**
  - **All considered pregnancy-related**
  - **Only 1 (gestational diabetes) considered possibly related to DRV/rtv**
  - **No deaths occurred during the study**

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DRV/rtv QD During Pregnancy: Conclusions

- **Despite lower DRV exposure during the 2nd and 3rd trimester of pregnancy, in this small study of HIV-1-infected women without DRV resistance-associated mutations, DRV/rtv 800/100mg QD provided adequate exposure to achieve viral suppression and was safe and well tolerated**
  - **Consideration should be given to additional conditions (e.g. Non-adherence) or use of concomitant medications that may further decrease DRV exposure**
- **Results for DRV/rtv 600/100 mg BID have been previously reported and shown to be a treatment option for HIV-1-infected pregnant women with or without DRV resistance-associated mutations[1]**
- **This study is ongoing, and a DRV/cobicistat 800/150mg QD treatment arm is currently in development**
- **Please see poster Abst#_1 during the poster sessions**

1. Zorrilla C, et al. *HIV Med* 2014;5(1):50-6. doi: 10.1111/hiv.12047.
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