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**

Methods

- **Phase IIIb study, multicenter, open-label (NCT00855335)**
  - **HIV-1–infected pregnant women ≥18 years old, in 2nd trimester of pregnancy**
  - **Subjects received DRV/rtv (600/100mg BID or 800/100mg QD), ETR (200mg BID), or RPV (25mg QD), plus an optimized background regimen**
  - **Data presented here for DRV/rtv 800/100mg QD**
- **Pharmacokinetic analysis: 2nd, 3rd trimester, 6–12 wks post-partum**
  - **Sampling predose, 1, 2, 3, 4, 6, 9, 12 and 24 hours postdose**
  - **Darunavir and ritonavir total plasma concentrations: validated HPLC-MS/MS assay**
  - **Darunavir unbound fraction: separation through ultrafiltration of ^{14}C-Darunavir-fortified plasma samples and liquid scintillation counting**
  - **Pharmacokinetic parameters: non-compartmental analysis**
- **Safety and efficacy evaluated at each visit**
- **Albumin and AAG measured at each visit**

Baseline Demographics

Parameter	Subjects
Subjects enrolled and treated with DRV/rtv 800/100mg qd, N	17
Age at screening, median (range), years	24 (18-33)
Age ≤30 years, n (%)	16 (94)
30 years < age ≤45 years, n (%)	1 (6)
Race, n (%)	
Black or African American	5 (29)
Hispanic	2 (12)
White	7 (41)
Other/Multiple races	3 (18)
Body mass index, median (range), kg/m^2	28 (21-50)
First pregnancy, n (%)	
No	12 (71)
Yes	5 (29)
Time since conception, median (range), weeks	22 (16-25)
Time since HIV diagnosis, median (range), years	4 (0-23)

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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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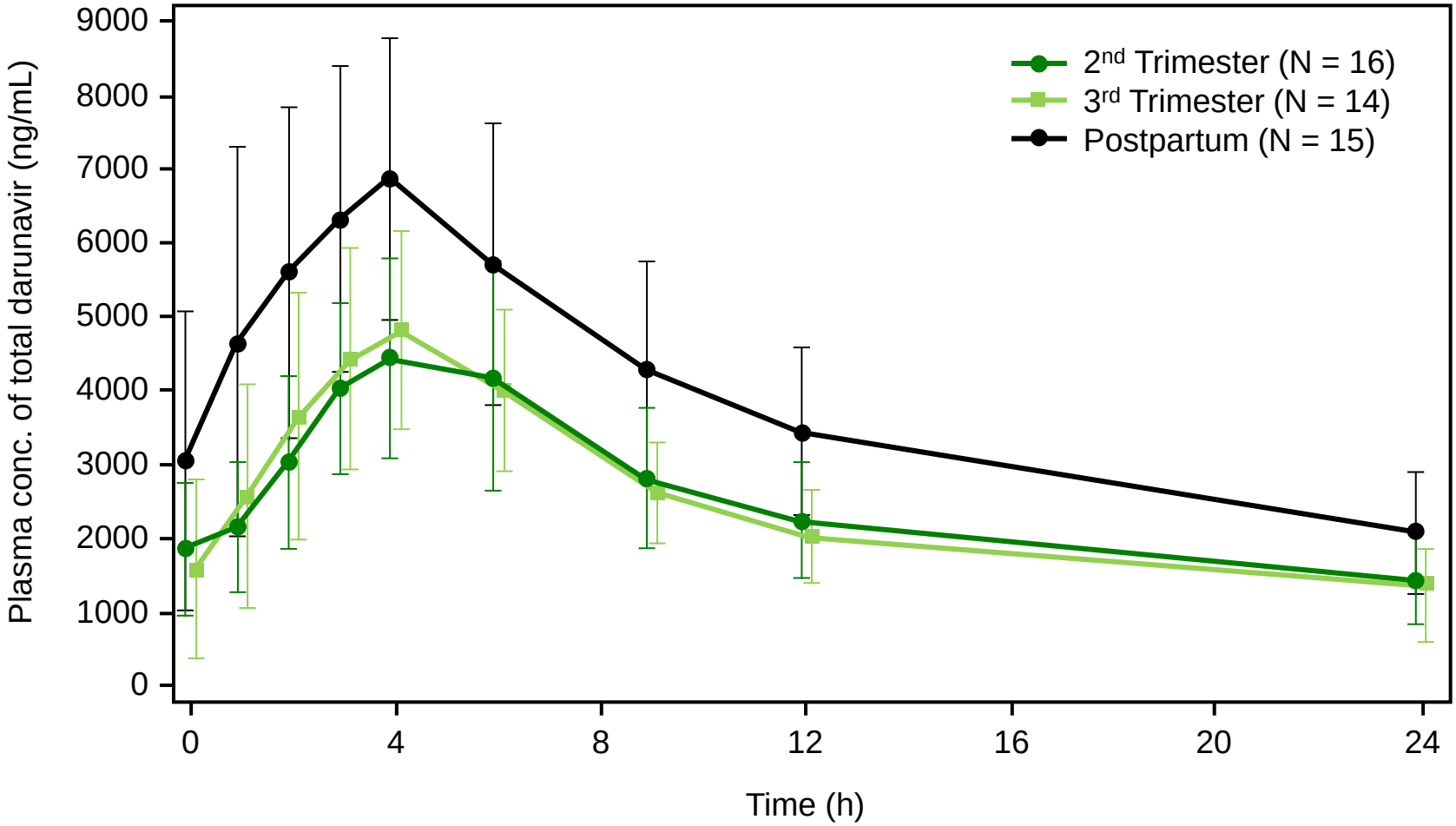
Results - Total DRV Plasma Concentrations



Data presented as mean (SD)

Protein-binding corrected EC_{50} = 55ng/mL

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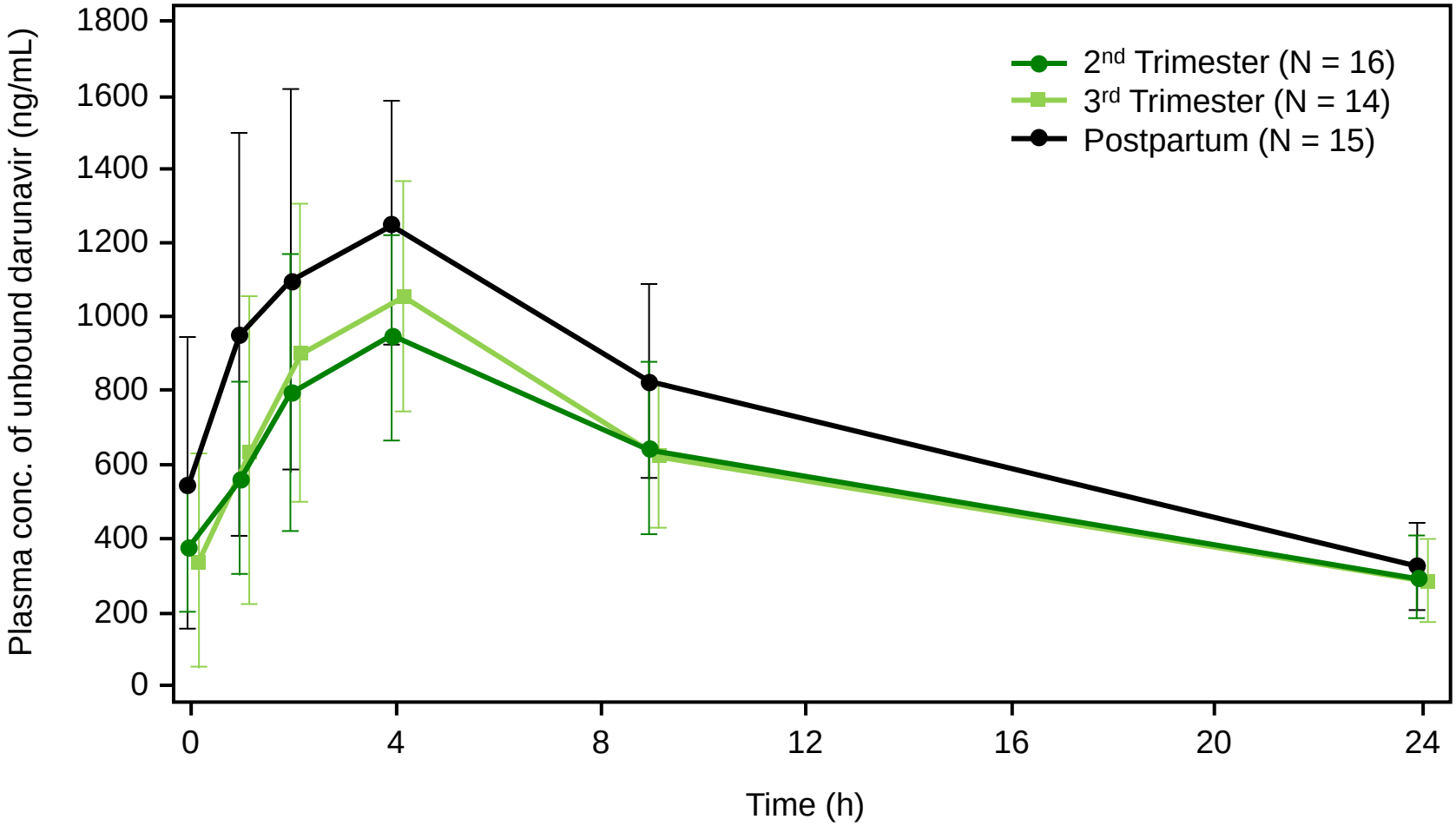
Results – Unbound DRV Plasma Concentrations



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)	↓35% (0.65, 0.57-0.74)
C_{min}	↓32% (0.68, 0.56-0.83)	↓50% (0.50, 0.35-0.73)
C_{max}	↓34% (0.66, 0.59-0.75)	↓31% (0.69, 0.63-0.77)

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

- **Plasma protein levels (albumin, AAG) decreased during pregnancy versus postpartum**
- **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)**

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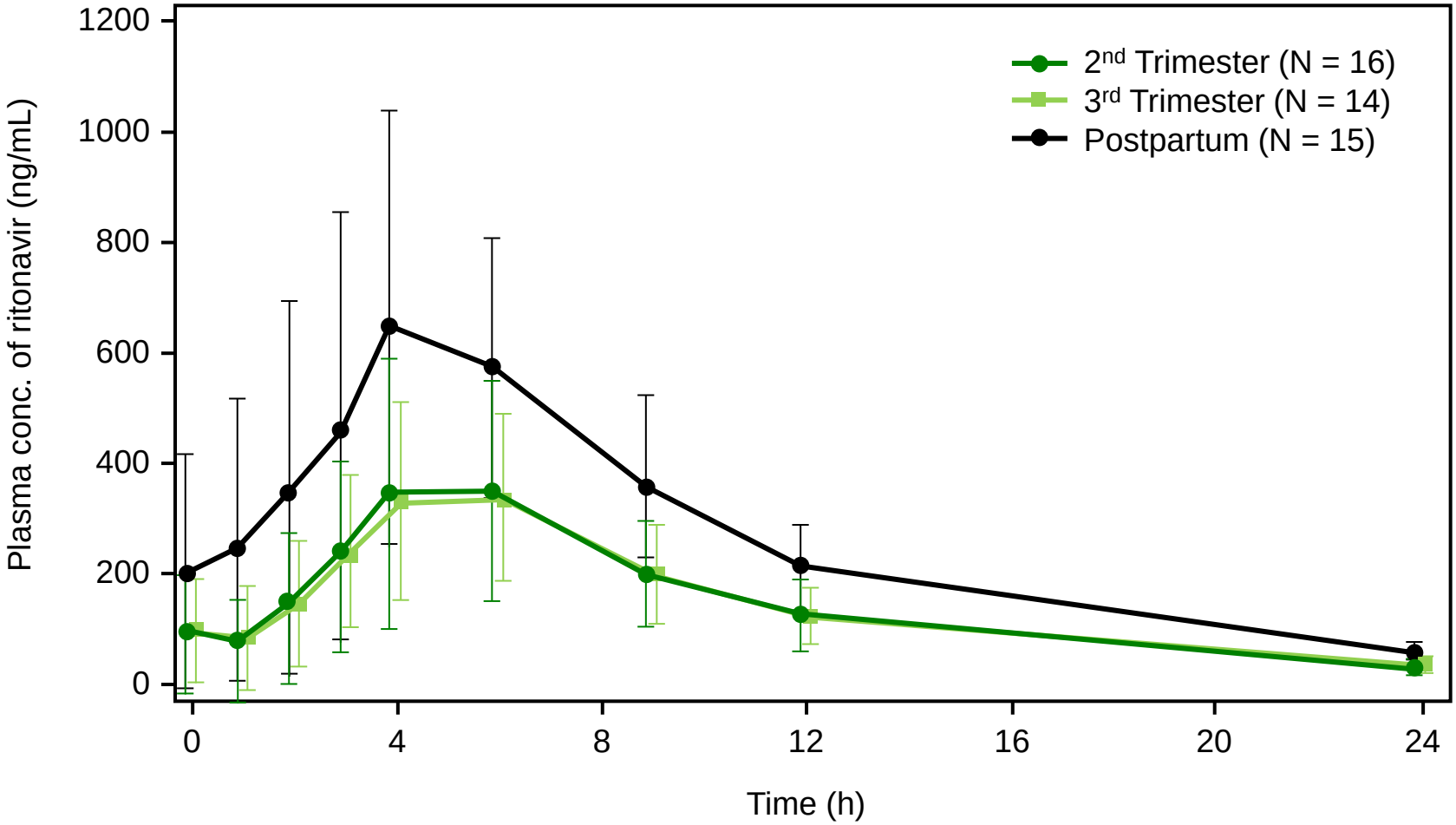
Results – Ritonavir Plasma Concentrations



Data presented as mean (SD)

Results – Ritonavir PK

	Ritonavir, % difference (LSMeans ratio, 90% CI)	
	2nd trimester vs postpartum	3rd trimester vs postpartum
AUC_{24h}	↓46% (0.54, 0.47-0.63)	↓47% (0.53, 0.43-0.66)
C_{min}	↓41% (0.59, 0.48-0.73)	↓35% (0.65, 0.51-0.83)
C_{max}	↓46% (0.54, 0.44-0.67)	↓49% (0.51, 0.41-0.63)

2nd Trimester N=15 for reference and N=16 for test; N=12 for reference and N=15 for test;
3rd Trimester N=15 for reference and N=14 for test; [b]N=12 for reference and N=11 for test CI, confidence interval

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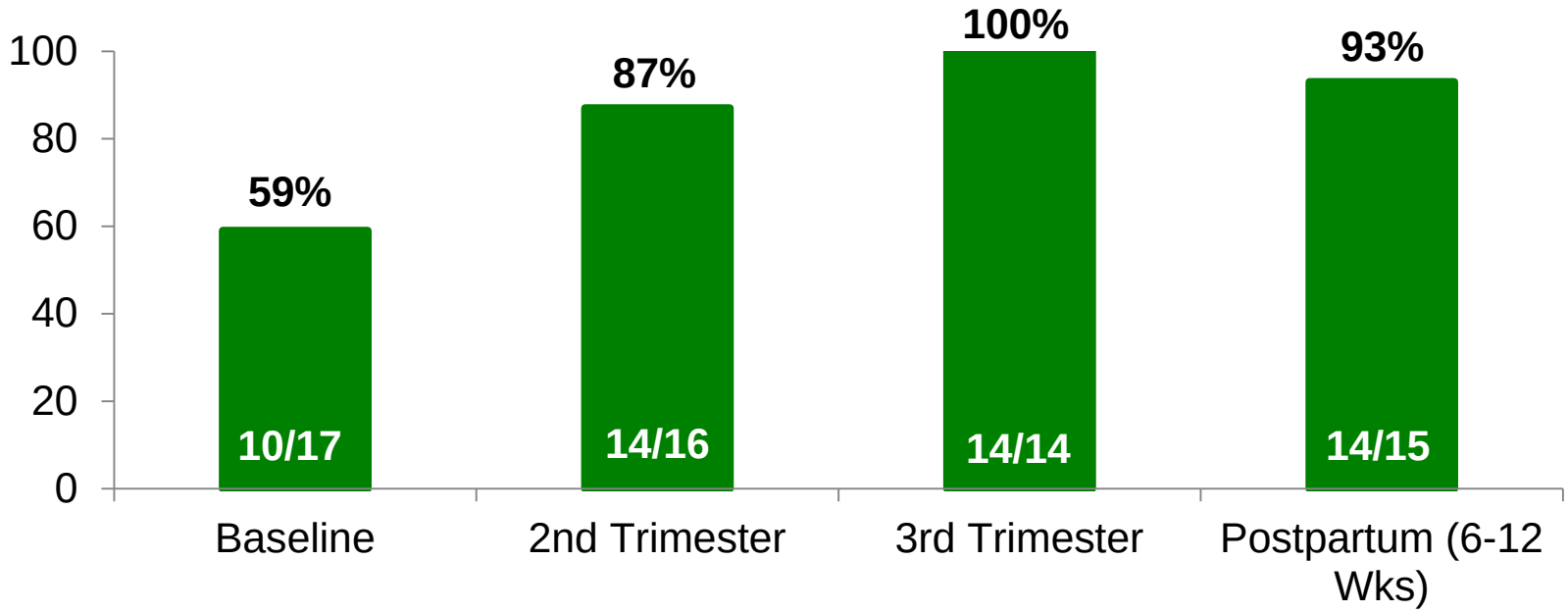
Efficacy Results:
Viral Suppression (<50 c/mL) Over Time



- **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: Summary

- **DRV total exposure decreased during the 2nd and 3rd trimesters compared to postpartum**
  - **AUC_{24h} by 34% and 35%, respectively**
  - **C_{min} by 32% and 50%, respectively**
- **DRV unbound concentrations also decreased during pregnancy, but to a lesser extent than total DRV concentrations**
  - **AAG and albumin decreased during pregnancy versus postpartum**
  - **C_{min} for unbound DRV >10x EC_{50} for wild-type virus (2.75 ng/mL)**
- **RTV exposure decreased during pregnancy versus postpartum**
- **High viral suppression rates were maintained throughout, there was no mother-to-child transmission, and the regimen was well tolerated**

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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 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**

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

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