Pharmacokinetics of Total and Unbound Darunavir in HIV-1–infected Pregnant Women Receiving a Darunavir/Cobicistat-based Regimen

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INTRODUCTION

- Combination antiretroviral (ARV) therapy is recommended for pregnant women living with human immunodeficiency virus (HIV)–1 infection[1]; however, physiologic changes during pregnancy may impact the pharmacokinetics (PK) of ARV agents in these women
- Darunavir (DRV) is a protease inhibitor (PI) for which the efficacy, safety, and high barrier to resistance have been demonstrated in nonpregnant individuals with HIV-1 infection[2,3]
- DRV needs to be administered with a PK booster (low-dose ritonavir [rtv] or cobicistat [cobi]) to optimize its systemic exposure. Both rtv and cobi increase DRV exposure to a similar extent
- DRV boosted with rtv has been evaluated in pregnant women with HIV-1 infection in several studies,[4] and is recommended in the US Perinatal Guidelines (twice-daily [BID] dosing only) and guidelines from the European AIDS Clinical Society (EACS)[1,5]
- The current study evaluated the PK of DRV and cobi during pregnancy and postpartum in women living with HIV-1 infection

OBJECTIVES

- To compare PK parameters for DRV and cobi during the second and third trimesters of pregnancy versus postpartum
- To assess antiviral activity, safety, and tolerability of DRV/cobi-based ARV regimens during gestation and postpartum
- To assess outcomes for infants of women treated with DRV/cobi-based ARV regimens during pregnancy

METHODS

Study Design

- This was a phase 3b, multicenter, open-label study evaluating the impact of pregnancy on the PK parameters of ARV agents including DRV boosted with rtv[6,7] or cobi, etravirine,[8] and rilpivirine,[9] as part of combination ARV therapy (ClinicalTrials.gov Identifier: NCT00855335); reported here are results from the DRV/cobi treatment arm only
- Treatment consisted of DRV/cobi 800/150 mg (fixed-dose tablet) taken once daily (QD) with a meal, in combination with other ARVs[10]
- Adherence to study medication was assessed by subject-reported missed doses (in the 4 days preceding a study visit) and pill counts. In addition, DRV predose concentrations below the limit of quantification (BLQ) were considered an indication of suboptimal adherence

Subject Population

- Key inclusion criteria
  - HIV-1–infected women ≥18 years of age in the second trimester of pregnancy (18-26 weeks gestation)
  - Receiving DRV/cobi 800/150 mg QD at the time of study entry
  - Normal obstetrical exam (within 2 weeks of the screening visit) and normal fetal ultrasound
- Key exclusion criteria
  - Documented DRV resistance-associated mutations (RAMs)
    - Women previously treated with DRV/rtv 600/100 mg BID without historical genotypic resistance testing, or who could not have a genotypic resistance test performed due to virologic suppression, were eligible for inclusion if their viral load (VL) had not been >200 copies/mL in 2 consecutive evaluations while using a DRV/cobi 800/150 mg QD-based regimen within 6 months of the screening visit
  - Active acquired immunodeficiency syndrome (AIDS)–defining illness (except stable cutaneous Kaposi sarcoma or wasting syndrome due to HIV infection)

Pharmacokinetic Evaluations

- Blood samples were collected at clinic visits during the second trimester (24-28 weeks gestation) and third trimester (34-38 weeks gestation) of pregnancy, and 6 to 12 weeks postpartum, over the 24-hour dosing interval
  - PK parameters included predose plasma concentration (C_{0h}), minimum plasma concentration (C_{min}), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and area under the plasma concentration-time curve over 24 hours (AUC_{24h})
- Matching cord blood and maternal plasma samples were taken at the intrapartum visit, when feasible
- Plasma concentrations of total DRV and cobi were determined using a validated high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) method, with a lower limit of quantification (LLOQ) of 5.00 ng/mL for both analytes
  - The unbound DRV fraction was determined via separation through ultrafiltration of ^{14}C-DRV–fortified plasma samples and liquid scintillation counting

Antiviral Activity and Safety

- Antiviral response (HIV-1 RNA <50 copies/mL) and immunologic response were evaluated at each study visit
- Maternal safety was evaluated based on adverse events (AEs), clinical laboratory tests, and vital sign measurements. Infant AEs were also assessed

Statistical Analyses

- DRV (total and unbound) and cobi PK parameters were summarized per exposure period (second and third trimesters [tests] and postpartum [reference])
  - PK parameters were derived using noncompartmental analysis (WinNonlin) and compared for pregnancy versus postpartum using linear mixed effects modeling (SAS)
- Efficacy and safety data were summarized by period using descriptive statistics; no comparisons across exposure periods were performed

RESULTS

Subject Disposition

- Overall, 7 women were enrolled in the DRV/cobi treatment arm, and all received study medication
  - The number of enrolled women was lower than in other treatment arms of this study due to recruitment difficulties that led to premature closure of enrollment
    - Nevertheless, based on the moderate variability in this study for DRV and cobi PK parameter ratios (**Table 3**), the observed PK data are considered to provide a representative image of the changes in DRV and cobi PK during pregnancy
- Six (86%) women completed the study; 1 (14%) woman discontinued during the second trimester (after the second trimester visit) due to noncompliance
  - Evaluable PK results were available for 7, 6, and 6 women for the second trimester, third trimester, and postpartum visits, respectively
- Six infants were born from the 6 women who completed the study (2 spontaneous deliveries and 4 cesarean sections)

Subject Population

- The median (range) age was 27 (24-36) years, and 5 of 7 (71%) women were black or African American (**Table 1**)
- The median (range) time since HIV-1 infection diagnosis was 0.9 (0.2-20) years
- Four (57%) women had a baseline VL <50 copies/mL; the remaining 3 women had a VL of 65, 79, and 1,140 copies/mL
- Five (71%) women had a CD4$^+$ cell count ≥350 cells/µL at baseline. All 7 women had a clinical stage of HIV-1 infection at the time of screening that was classified as Category A
- All 7 women used 2 nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) in their background regimen at baseline
  - Five (71%) women had used ≤4 ARVs prior to enrollment in the study
- Genotyping and phenotyping were successful for 2 (29%) women at screening or baseline; both women showed sensitivity to all ARVs tested
  - One woman had 4 PI RAMs (M36I, D60E, I62V, and L63P; none were primary PI or DRV RAMs)
  - The other woman had 4 PI RAMs (L10I, I13V, L63P, and V77I), 1 primary PI RAM (M46L), 1 DRV RAM (V11I), and 1 nonnucleoside reverse transcriptase inhibitor RAM (V179L)
- The median (range) duration of DRV/cobi intake in the study was 22.7 (3-25.4) weeks, including 13.9 (3-18.6) weeks prebirth and 7.8 (6.9-11.4) weeks postbirth

Table 1. Baseline Demographic and Disease Characteristics

Demographic characteristics	N = 7
Age at screening, median (range), y	27 (24-36)
Race/ethnicity, n (%)*	
White	1 (14)
Black or African American	5 (71)
Hispanic	1 (14)
BMI, median (range), kg/m^2	33 (21-40)
First pregnancy, n (%)	
Yes	2 (29)
No	5 (71)
Time since conception, median (range), days	162 (144-170)
Disease characteristics†	
Known duration of HIV infection, median (range), y	0.9 (0.2-20)
VL, copies/mL, n (%)	
<50	4 (57)
50 to <400	2 (29)
400 to <1,000	0
≥1,000	1 (14)
CD4$^+$ cell count, cells/µL, n (%)	
<50	0
50 to <100	0
100 to <200	0
200 to <350	2 (29)
≥350	5 (71)
Combination ARVs used at baseline, n (%)‡	
Emtricitabine + TDF	5 (71)
Lamivudine + zidovudine	2 (29)

BMI, body mass index; TDF, tenofovir disoproxil fumarate.
*Percentages may not total 100% due to rounding.
†All women had negative hepatitis A, B, and C tests at baseline.
‡In addition to DRV/cobi. All women remained on the same N(t)RTI background regimen from screening to baseline.

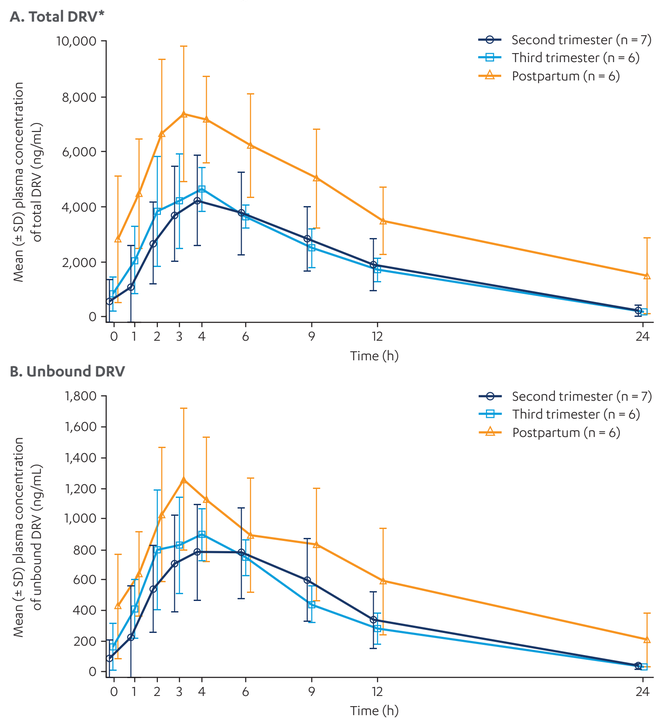
Pharmacokinetics of DRV

- Total DRV exposure was lower during pregnancy than postpartum, and comparable between the second and third trimesters of pregnancy; the decrease in unbound (ie, pharmacodynamically active) DRV was less pronounced than for total DRV (**Figure 1**, **Tables 2** and **3**)
  - For total DRV, during the second and third trimesters of pregnancy, respectively:
    - AUC_{24h}: 56% and 50% lower
    - C_{max}: 49% and 37% lower
    - C_{min}: 92% and 89% lower
  - For unbound DRV, during the second and third trimesters of pregnancy, respectively:
    - AUC_{24h}: 45% and 40% lower
    - C_{max}: 41% and 23% lower
    - C_{min}: 92% and 88% lower
- The median cord/maternal plasma ratio on the day of delivery was 16.1% (range: 12.3%-31.5%; n = 5) for total DRV and 32.4% (range: 29.1%-62.6%; n = 4) for unbound DRV

Pharmacokinetics of Cobi

- Cobi exposure was lower during pregnancy than postpartum, and comparable between the second and third trimesters of pregnancy (**Figure 2**, **Tables 2** and **3**)
  - For cobi, during the second and third trimesters of pregnancy, respectively:
    - AUC_{24h}: 63% and 49% lower
    - C_{max}: 50% and 27% lower
    - C_{min}: 83% and 83% lower
- The median cord/maternal plasma ratio of cobi on the day of delivery was evaluable for 2 women; the values were 10% and 7.7%

Figure 1. Mean (± SD) plasma concentration-time profiles of DRV during pregnancy and postpartum over the 24-hour dosing interval.



SD, standard deviation; EC_{50}, half maximal effective concentration.
*Protein-binding–corrected EC_{50} = 55 ng/mL.

Figure 2. Mean (± SD) plasma concentration-time profiles of cobi during pregnancy and postpartum over the 24-hour dosing interval.

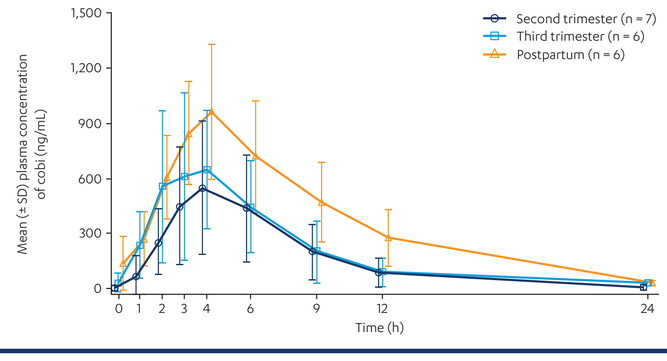


Table 2. Arithmetic Mean (± SD)* PK Parameters for Total and Unbound DRV, and Cobi, During Pregnancy and Postpartum

	Second trimester	Third trimester	Postpartum
n	7	6	6
Total DRV			
C_{0h}, ng/mL	540 ± 803	824 ± 630	2,811 ± 2,296
C_{min}, ng/mL	168 ± 149	184 ± 99.0	1,538 ± 1,344
C_{max}, ng/mL	4,340 ± 1,616	4,910 ± 970	7,918 ± 2,199
t_{max}, h	4.00 (3.00-6.00)	3.50 (2.00-6.00)	4.00 (2.00-6.00)
AUC_{24h}, ng·h/mL	47,293 ± 19,058	47,991 ± 9,879	99,613 ± 34,862
Unbound DRV			
C_{0h}, ng/mL	81.6 ± 127	162 ± 152	427 ± 342
C_{min}, ng/mL	25.3 ± 22.9	30.7 ± 17.1	224 ± 177
C_{max}, ng/mL	864 ± 313	988 ± 148	1,323 ± 424
t_{max}, h	4.05 (1.03-6.00)	4.00 (2.00-4.00)	3.50 (2.00-6.00)
AUC_{24h}, ng·h/mL	9,088 ± 3,528	8,953 ± 1,895	15,810 ± 6,506
Cobi			
C_{min}, ng/mL	BLQ	BLQ	41.4 ± 49.1
C_{max}, ng/mL	571 ± 350	759 ± 366	996 ± 323
t_{max}, h	4.03 (2.00-6.00)	3.50 (2.00-4.00)	4.00 (2.00-4.00)
AUC_{24h}, ng·h/mL	3,862 ± 2,703	4,736 ± 2,917	8,643 ± 3,187

*t_{max} reported as median (range).

Table 3. Within-subject Comparison of Total and Unbound DRV, and Cobi: PK Parameters During Pregnancy Versus Postpartum

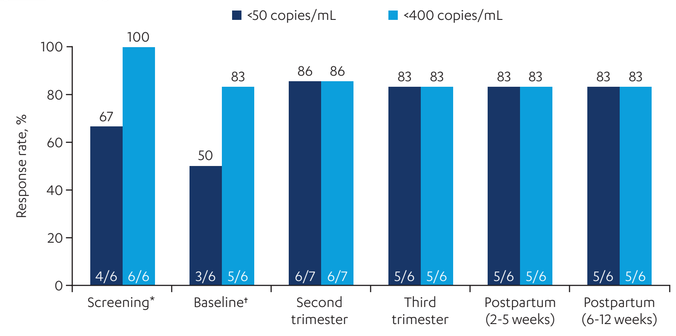
	LS mean ratio (90% CI)	
	Second trimester versus postpartum	Third trimester versus postpartum
n	(7 vs 6)	(6 vs 6)
Total DRV		
C_{min}*	8.49 (1.44-50.09)	11.31 (4.23-30.24)
C_{max}	50.69 (29.94-85.83)	62.72 (49.54-79.43)
AUC_{24h}	43.88 (24.10-79.90)	49.59 (37.22-66.08)
Unbound DRV		
C_{min}†	8.11 (1.58-41.6)	11.79 (5.17-26.89)
C_{max}	59.31 (34.38-102.32)	76.89 (59.05-100.12)
AUC_{24h}	54.89 (28.37-106.20)	60.28 (43.66-83.23)
Cobi		
C_{min}‡	16.64 (4.57-60.58)	16.85 (3.82-74.38)
C_{max}	50.44 (27.98-90.94)	72.93 (52.31-101.67)
AUC_{24h}	37.08 (17.48-78.65)	51.33 (32.85-80.21)

LS, least squares; CI, confidence interval.
*BLQ values were excluded for C_{min}. With this exclusion, second trimester, n = 6; third trimester, n = 6; and postpartum, n = 5. Statistical analyses were also performed including the BLQ values (included as 0.5 × LLOQ); the LS mean ratio (90% CI) for the second trimester versus postpartum was then 10.65 (0.48-236.11), and for the third trimester versus postpartum was then 32.17 (2.57-402.89).
†BLQ values were excluded for C_{min}. With this exclusion, second trimester, n = 6; third trimester, n = 6; and postpartum, n = 5. Statistical analyses were also performed including the BLQ values (included as 0.5 × LLOQ); the LS mean ratio (90% CI) for the second trimester versus postpartum was then 11.66 (0.50-270.52), and for the third trimester versus postpartum was then 37.39 (2.87-486.86).
‡BLQ values included as 0.5 × LLOQ.

Efficacy

- At baseline, 3 of 6 (50%) women with available data were virologically suppressed. Viral suppression was reached or maintained in 6 of 7 (86%) women at the second trimester visit, 5 of 6 (83%) women at the third trimester visit, and 5 of 6 (83%) women at study completion (visit at 6-12 weeks postpartum; **Figure 3**)
  - One woman who was not compliant (as assessed by pill count) was considered to have a virologic failure, but completed the study
    - Her VL at screening was between 50 and <400 copies/mL. An initial decrease was observed at the second trimester visit; however, her VL was ≥1,000 copies/mL from the third trimester visit until the 4-week follow-up visit
    - She used DRV/cobi + lamivudine + zidovudine through delivery, and intravenous zidovudine was added on the day of delivery. From then on, she continued using DRV/cobi with a background regimen of emtricitabine + TDF
    - No emerging RAMs were observed, and susceptibility to ARVs was maintained
- Median (range) CD4$^+$ cell count increased from baseline (671 [230-892] cells/µL) to the visit at 2 to 5 weeks postpartum (815 [394-1,343] cells/µL)
- Among the 6 infants of women who completed the study, all had 16-week postpartum data, and no mother-to-child transmission was observed

Figure 3. Virologic response over time.



*One woman did not have a screening visit.
†One woman did not have a baseline visit.

Safety

- Five of 7 (71%) women experienced ≥1 AE (**Table 4**)
  - None of the AEs led to study discontinuation, and none were considered by the investigator to be at least possibly related to study medication
  - One (14%) woman experienced a serious AE (SAE)
    - The SAE was grade 2 increased blood pressure, and it was resolved after 3 days
    - Approximately 3 weeks later, the woman experienced a nonserious episode of increased blood pressure; this AE resolved after 8 days. The investigator considered both episodes of increased blood pressure to be related to pregnancy (and not related to study medication or HIV-1 infection)

Table 4. Summary of AEs

Incidence, n (%)	N = 7
Any AE	5 (71)
Any AE leading to discontinuation	0
Any AE considered at least possibly related to study medication	0
Any SAE	1 (14)
Any grade 3 AE	1 (14)
Most common AE (occurring in >1 woman)	
Vulvovaginal mycotic infection	2 (29)

- Overall, 4 of the 6 (67%) infants born to women who completed the study experienced ≥1 AE
  - All infant AEs were grade 1 or 2 in severity, and the most common (occurring in >1 infant) AE was neonatal jaundice (observed in 2 [33%] infants)
  - SAEs were reported for 2 (33%) infants; the SAEs were omphalitis and transient tachypnea of the newborn
  - For 2 (33%) infants, the reported AEs (omphalitis and neonatal jaundice) were considered by the investigator to be related to pregnancy. Relatedness to study medication was not assessed for infant AEs

CONCLUSIONS

- **DRV/cobi exposures were substantially lower during pregnancy than postpartum and may require more frequent VL monitoring**
  - **The decrease in DRV exposure was more pronounced with DRV/cobi compared to DRV/rtv. In the DRV/rtv QD treatment arm of this study (reported previously), total DRV exposure (AUC_{24h}) was 34% to 35% lower during pregnancy (unbound DRV exposure 20%-24% lower), and rtv exposure was 46% to 47% lower during pregnancy[7]**
  - **The decrease in cobi exposure in the current study was in line with that observed in pregnant women using elvitegravir/cobi. In a prior study, exposures to both elvitegravir and cobi were lower during the second and third trimesters of pregnancy versus postpartum (43%-50% lower for elvitegravir and 54%-57% lower for cobi)[11]**
- **DRV/cobi was generally well tolerated in women and their infants**
- **No evidence of mother-to-child transmission was observed, and 5 of 6 women were virologically suppressed at study completion**
- **Health care providers should evaluate the risk/benefit ratio of DRV/cobi, including consideration of patient adherence, when initiating or continuing therapy and managing pregnant women living with HIV-1 infection**

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