Darunavir (Prezista, DRV)

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Summary

- Darunavir (DRV) trough concentrations (C_{trough}) are reduced during pregnancy by approximately 10% with use of DRV boosted with ritonavir (DRV/r) 600 mg/100 mg twice daily and by approximately 50% with use of DRV/r 800 mg/100 mg once daily.
- DRV C_{trough} are reduced during pregnancy by approximately 90% with use of DRV boosted with cobicistat (DRV/c) 800 mg/150 mg once daily.
- The Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission (the Panel) recommends the use of twice-daily dosing with DRV/r 600 mg/100 mg during pregnancy and does not recommend use during pregnancy of once-daily dosing with DRV/r 800 mg/100 mg or the use of DRV/c 800 mg/150 mg.
- First-trimester exposures to DRV have not been associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PK) of DRV/r during pregnancy have been completed.[1-4] During the third trimester, DRV plasma area under the curve (AUC) was reduced by 17% to 26% with DRV/r 600-mg/100-mg twice-daily dosing and by 33% to 39% with DRV/r 800-mg/100-mg once-daily dosing, compared with postpartum.[1-5] During the third trimester, DRV C_{trough} was reduced by 8% to 12% with DRV/r 600-mg/100-mg twice-daily dosing and by 42% to 58% with DRV/r 800-mg/100-mg once-daily dosing, compared with postpartum.[2-4]

Three studies measured DRV protein binding during pregnancy. One study found no change in DRV protein binding during the third trimester. The other two studies reported decreased unbound DRV concentrations during pregnancy that were not considered clinically significant.[1,3,4] Because of the low DRV trough levels that occur with once-daily dosing, twice-daily dosing of DRV is recommended during pregnancy, especially for antiretroviral (ARV)-experienced patients.[2,6] The U.S. Food and Drug Administration recommends the use of once-daily DRV/r 800-mg/100-mg dosing during pregnancy only when viral suppression was achieved on a stable, once-daily DRV/r regimen before pregnancy and when adherence or ability to tolerate a regimen may be compromised by a switch to twice-daily DRV/r.[7] After reviewing the available evidence, the Panel **does not recommend** once-daily dosing of DRV/r in pregnancy. Because use of 800-mg DRV doses administered twice daily did not increase DRV exposure in pregnant women, the Panel recommends the use of twice-daily 600-mg DRV dosing during pregnancy.[5]

Data are available from two studies describing the PK and safety of cobicistat (COBI) boosting of DRV during pregnancy. In both studies, DRV/c 800 mg/150 mg was administered during pregnancy.[8,9] In a study of seven pregnant women with HIV who were treated with DRV/c, no drug-related adverse events were observed. When PK parameters during the second and third trimesters were compared with postpartum PK parameters, total DRV AUC was reduced by 56% and 50%, and C_{trough} was reduced by 92% and 89%, respectively. Unbound DRV concentrations decreased during the second and third trimesters of pregnancy compared with postpartum, with AUC 45% and 40%

lower and C_{trough} 92% and 88% lower, respectively. COBI exposures were lower during pregnancy compared with postpartum, with AUC reductions during the second and third trimesters of 63% and 49%, respectively, and C_{trough} reductions of 83% and 83% during the second and third trimesters, respectively. Six of seven participants remained virally suppressed during pregnancy. One woman who was not virally suppressed was found to be nonadherent to treatment, based on pill count. No infants born to study mothers contracted HIV.[9] On the basis of these data, the package insert for the fixed-dose combination of DRV/c was edited to include a statement saying that this product **is not recommended** for use in pregnant women because of substantially lower exposures of DRV and COBI during pregnancy.[10] These findings are consistent with the larger PK study, which included data from 29 pregnant women who received DRV/c as part of clinical care and showed that when PK parameters during the second and third trimesters were compared with postpartum PK parameters in these women, total DRV AUC was reduced by 33% and 48%, respectively, and DRV C_{trough} were reduced by 71% and 75%, respectively.[8]

Placental and Breast Milk Passage

In an *ex vivo* human cotyledon perfusion model, the mean fetal transfer rate of DRV was 15%.[11] In five studies that reported data from 6 to 14 participants each, the median ratio of DRV concentration in cord blood–to-DRV concentration in maternal delivery plasma ranged from 13% to 24%.[1-3,9,12]

Breast milk transfer of DRV was low in two mother–infant pairs where the mother was receiving DRV/r while breastfeeding, with a median DRV breast milk–to–maternal plasma concentration ratio of 0.12, median estimated infant DRV dose of 0.05 mg/kg, and no detectable DRV in infant plasma.[13]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for DRV and other ARV drugs twice a year through an interim report released in June and December. The APR has monitored sufficient numbers of first-trimester exposures to DRV to allow detection of at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with DRV. Figure 1. Summary of Birth Defects Among First Trimester Exposures in the APR interim report provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to DRV and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals. The data in Figure 1 can compared with the prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births) according to the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 5.07 per 100 live births).

Animal Studies

Carcinogenicity

DRV was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas was observed in both male and female mice and rats, as was an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of DRV to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination; this predisposed rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to DRV (based on AUC) were between 0.4-fold and 0.7-fold higher in mice and 0.7-fold and onefold higher in rats than the

exposures observed in humans who received the recommended therapeutic doses of DRV/r 600 mg/100 mg twice daily or DRV/r 800 mg/100 mg once daily.[7]

Reproduction/Fertility

No effects on fertility or early embryonic development were seen in rats that received DRV.[7]

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in rats that experienced DRV exposures (based on AUC) that were threefold higher than those seen in humans who received recommended DRV/r doses; likewise, no embryotoxicity or teratogenicity was seen in mice and rabbits that experienced DRV exposures that were less than onefold those seen in humans who received the recommended DRV/r doses. Administering DRV alone or with ritonavir to female rats during lactation resulted in a reduction in pup weight gain during a rat prenatal and postnatal development study. DRV/r **is not recommended** for pediatric patients aged <3 years because of the toxicity and mortality observed in juvenile rats dosed with DRV up to 23 to 26 days of life.[7]

Placental and Breast Milk Passage

No animal studies of placental passage of DRV have been reported. Passage of DRV into breast milk has been noted in rats.[7]

Excerpt From Table 14

Note: When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
Darunavir (DRV) *Prezista* **Note:** Must be combined with low-dose RTV or COBI boosting. (DRV/c) *Prezcobix* (DRV/c/FTC/TAF) *Symtuza*	**DRV (Prezista)** *Tablets* • 75 mg • 150 mg • 600 mg • 800 mg *Oral Suspension* • 100 mg/mL **DRV/c (Prezcobix)** • DRV/c 800-mg/150-mg tablet **DRV/c/FTC/TAF (Symtuza)** • DRV 800-mg/COBI 150-mg/FTC 200-mg/TAF 10-mg tablet	**Pregnancy** *PK in Pregnancy* • Decreased exposure in pregnancy with use of DRV/r *Dosing in Pregnancy* • The Panel **does not recommend** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. • Twice-daily DRV/r dosing (DRV/r 600 mg/100 mg with food) is recommended during all pregnancies. • Increased twice-daily DRV dose (DRV/r 800 mg/100 mg with food) during pregnancy does not result in an increase in DRV exposure and **is not recommended.** For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF). **Standard Adult Doses** *Patients Who Are ARV-Naive* • DRV/r 800 mg/100 mg once daily with food • DRV/c 800 mg/150 mg once daily with food *ARV-Experienced Patients If Patient Has No DRV Resistance Mutations* • DRV/r 800 mg/100 mg once daily with food	Low placental transfer to fetus[b] No evidence of teratogenicity in mice, rats, or rabbits. No evidence of human teratogenicity. Must be boosted with low-dose RTV The Panel **does not recommend** once-daily dosing with DRV/r during pregnancy or the use of DRV/c during pregnancy. If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently. **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with DRV is contraindicated.

Excerpt From Table 14

Generic Name (Abbreviation) *Trade Name*	**Formulation**	**Dosing Recommendations**[a]	**Use in Pregnancy**
		• DRV/c 800 mg/150 mg once daily with food *ARV-Experienced Patients If Any DRV Resistance Mutations Are Present* • DRV/r 600 mg/100 mg twice daily with food *DRV/c (Prezcobix)* • One tablet once daily with food *DRV/c/FTC/TAF (Symtuza)* • One tablet once daily with food	

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B).

[b] Placental transfer categories are determined by mean or median cord blood–to–maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

Key: ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; FTC = emtricitabine; the Panel = Panel on Treatment of HIV During Pregnancy and Interventions to Reduce Perinatal HIV Transmission; PK = pharmacokinetics; RTV = ritonavir; TAF = tenofovir alafenamide

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