Darunavir (Prezista, DRV)

(Last reviewed December 24, 2019; last updated December 24, 2019)

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 well as 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 predisposes rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to DRV (based on area under the curve [AUC]) were between 0.4-fold and 0.7-fold (in mice) and 0.7-fold and one-fold (in rats) the exposures observed in humans who received the recommended therapeutic doses of DRV/ritonavir (DRV/r) 600 mg/100 mg twice daily or DRV/r 800 mg/100 mg daily.[1]

Reproduction/Fertility

No effects on fertility and early embryonic development were seen in rats that received DRV.[1]

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in rats that experienced DRV exposures (based on AUC) that were three-fold 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 one-fold 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 due to the toxicity and mortality observed in juvenile rats dosed with DRV up to 23 to 26 days of age.[1]

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.[1]

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PKs) of DRV/r during pregnancy have been completed.[2-6] Compared with postpartum DRV plasma AUC, DRV plasma AUC during the third trimester 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.[2-5] Compared with postpartum DRV trough concentration, trough concentration during the third trimester 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.[3-5]

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.[2,4,5] 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-experienced patients.[3,7] The Food and Drug Administration recommends the use of once-daily DRV/r 800 mg/100 mg dosing only for pregnant women who are virally suppressed on a stable, once-daily DRV/r regimen prior to pregnancy and whose adherence or ability to tolerate a regimen may be compromised by a switch to twice-daily DRV/r.[1] After reviewing the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission does not recommend once-daily dosing of DRV/r in pregnancy. An 800-mg DRV dose administered twice daily did not increase DRV exposure in pregnant women; use of this increased twice-daily DRV dose during pregnancy **is not recommended**.[6]

Two studies describing the PK and safety of once-daily DRV/cobicistat (DRV/c) 800 mg/150 mg during pregnancy have been presented.[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 to postpartum PK parameters, total DRV AUC was reduced by 56% and 50% and trough concentration was reduced by 92% and 89%, respectively. Unbound DRV concentrations decreased during the second and third trimesters of pregnancy compared to postpartum, with AUC 45% and 40% lower and trough concentration 92% and 88% lower, respectively. Cobicistat (COBI) exposures were lower during pregnancy, with reductions during the second and third trimesters of 63% and 49% for AUC and 83% and 83% for trough concentration compared to postpartum. Six of seven participants remained virally suppressed during pregnancy. One woman who was not suppressed was found to be nonadherent to treatment after a 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 a larger study of 29 pregnant women who received the DRV/c combination. When PK parameters during the second and third trimesters were compared to postpartum PK parameters in these women, total DRV AUC was reduced by 33% and 48% and DRV trough concentrations were reduced by 71% and 75%.[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 between six and 14 subjects each, the median ratio of DRV concentration in cord blood to DRV concentration in maternal delivery plasma ranged from 13% to 24%.[2-4,9,12] No data are available that describe the breast milk passage of DRV in humans.

Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester DRV exposure that have been reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects is 3.1% (16 of 524 births; 95% confidence interval, 1.8% to 4.9%), whereas the total prevalence for the U.S. population is 2.7% based on Centers for Disease Control and Prevention surveillance.[13] This number of first-trimester exposures is sufficient to conclude that there is not a two-fold increase in the risk of overall birth defects among infants with first-trimester exposure to DRV compared to control populations.[13]

Excerpt from Table 8

Note: When using FDC tablets, refer to other sections in Appendix B and Table 8 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)** *Tablet:* • 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	**Standard Adult Doses** *ARV-Naive Patients:* • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food *ARV-Experienced Patients* If Patient Has No DRV Resistance Mutations: • DRV 800 mg plus RTV 100 mg once daily with food • DRV 800 mg plus COBI 150 mg once daily with food If Any DRV Resistance Mutations Are Present: • DRV 600 mg plus RTV 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 **Pregnancy** *PKs 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 600 mg plus RTV 100 mg with food) is recommended for all pregnant women. • Increased twice-daily DRV dose (DRV 800 mg plus RTV 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)	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.

[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, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/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; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RTV = ritonavir; TAF = tenofovir alafenamide

References

1. Darunavir [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021976s054,202895s025lbl.pdf.
2. Zorrilla CD, Wright R, Osiyemi OO, et al. Total and unbound darunavir pharmacokinetics in pregnant women infected with HIV-1: results of a study of darunavir/ritonavir 600/100 mg administered twice daily. *HIV Med*. 2014;15(1):50-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23731450.

3. Stek A, Best BM, Wang J, et al. Pharmacokinetics of once versus twice daily darunavir In pregnant HIV-infected women. *J Acquir Immune Defic Syndr*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25950206.

4. Colbers A, Molto J, Ivanovic J, et al. Pharmacokinetics of total and unbound darunavir in HIV-1-infected pregnant women. *J Antimicrob Chemother*. 2015;70(2):534-542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25326090.

5. Crauwels HM, Kakuda TN, Ryan B, et al. Pharmacokinetics of once-daily darunavir/ritonavir in HIV-1-infected pregnant women. *HIV Med*. 2016;17(9):643-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27187894.

6. Stek A, Best B, Capparelli E, et al. Pharmacokinetics of increased dose darunavir during late pregnancy and postpartum. Presented at: 23rd Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.

7. Schalkwijk S, Ter Heine R, Colbers A, et al. Evaluating darunavir/ritonavir dosing regimens for HIV-positive pregnant women using semi-mechanistic pharmacokinetic modelling. *J Antimicrob Chemother*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30715324.

8. Momper J, Best B, Wang J, et al. Pharmacokinetics of darunavir boosted with cobicistat during pregnancy and postpartum. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands.

9. Crauwels HM, Osiyemi O, Zorrilla C, Bicer C, Brown K. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen. *HIV Med*. 2019;20(5):337-343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30873741.

10. Darunavir/cobicistat (Prezcobix) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205395s009lbl.pdf.

11. Mandelbrot L, Duro D, Belissa E, Peytavin G. Placental transfer of darunavir in an *ex vivo* human cotyledon perfusion model. *Antimicrob Agents Chemother*. 2014;58(9):5617-5620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24982090.

12. Courbon E, Matheron S, et al. Efficacy, and pharmacokinetic of darunavir/ritonavir-containing regimen in pregnant HIV+ women. Presented at: 19th Conference on Retroviruses and Opportunistic Infections. 2012. Seattle, WA.

13. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: http://www.apregistry.com.