Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Darunavir (Prezista, DRV)

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Available data from the Antiretroviral Pregnancy Registry show no increase in the rate of overall birth defects with first-trimester darunavir exposure compared to control populations. The Antiretroviral Pregnancy Registry has monitored a sufficient number of first-trimester exposures to rule out a more than two-fold increase in the rate of birth defects.¹

Animal Studies

Carcinogenicity

Darunavir 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 darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (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 receiving the recommended therapeutic doses (600 mg/100 mg twice daily or 800 mg/100 mg daily).²

Reproduction/Fertility

No effects on fertility and early embryonic development were seen in rats receiving darunavir.²

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits with doses (based on AUC) three-fold higher in rats and lower (less than one-fold) in mice and rabbits compared to those obtained in humans receiving recommended darunavir/ritonavir (DRV/r) doses. In a rat prenatal and postnatal development study, a reduction in pup weight gain was observed with breast milk exposure of darunavir administered alone or with ritonavir during lactation. DRV/r is not recommended in pediatric patients <3 years of age due to toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age.²

Placental and Breast Milk Passage

No animal studies of placental passage of darunavir have been reported. Passage of darunavir into breast milk has been noted in rats.²

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PKs) of DRV/r during pregnancy have been completed.³⁻⁷ Compared with postpartum darunavir plasma AUC, darunavir 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.³⁻⁶ Compared with postpartum darunavir 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.⁴⁻⁶ Three studies measured darunavir protein binding during pregnancy. One study found no change in darunavir protein binding during the third trimester. The other two studies reported decreased unbound darunavir concentrations during pregnancy that were not considered clinically significant.¹⁻⁵,⁶ Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, especially for antiretroviral-experienced patients. The Food and Drug Administration (FDA) recommends the use of once-daily DRV/r 800 mg/100 mg 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.² Based on review of 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 darunavir dose administered twice daily did not increase darunavir exposure in pregnant women; use of this increased twice-daily darunavir dose during pregnancy is not recommended.7

Two studies describing the PK and safety of once-daily darunavir/cobicistat (DRV/c) 800 mg/150 mg during pregnancy have been presented.8,9 In a study of seven pregnant persons with HIV treated with DRV/c, no drug related adverse events were observed. When PK parameters during the second and third trimesters were compared to postpartum, total darunavir AUC was reduced by 56% and 50% and trough concentration was reduced by 92% and 89%, respectively. Unbound darunavir concentrations were similarly decreased during pregnancy, with AUC 45% and 40% lower and trough concentration 92% and 88% lower during the second and third trimesters than postpartum. Cobicistat exposures were lower during pregnancy, with reductions of 63% and 49% for AUC and 83% and 83% for trough concentration during the second and third trimesters compared to postpartum. Six of seven participants remained virally suppressed during pregnancy. One woman who was not suppressed was assessed to be nonadherent to treatment by pill count. All infants born to study mothers had not contracted HIV.8 Based on 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 darunavir and cobicistat during pregnancy.10 These findings were confirmed in 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 darunavir AUC was reduced by 33% and 48% and darunavir trough concentrations were reduced by 71% and 75%.9

Placental and Breast Milk Passage

In an ex vivo human cotyledon perfusion model, the mean fetal transfer rate of darunavir was 15%.11 In five studies that reported data from between six and 14 subjects each, the median of the ratio of darunavir concentration in cord blood to that in maternal delivery plasma ranged from 13% to 24%.3-5,8,12 No data are available that describe the breast milk passage of darunavir in humans.

Teratogenicity/Adverse Pregnancy Outcomes

Among cases of first-trimester darunavir exposure reported to the Antiretroviral Pregnancy Registry, prevalence of birth defects was 2.4% (11 of 456 births; 95% CI, 1.2% to 4.3%), which is a sufficient number of first-trimester exposures to conclude that there is no two-fold increase in the risk of overall birth defects compared to control populations.1
### Excerpt from Table 10

**Note:** When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation)</th>
<th>Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
</table>
| Darunavir (DRV)             | Prezista            | DRV (Prezista):                    | **Standard Adult Doses**                                    | Low placental transfer to fetus.  
**Note:** Must be combined with low-dose RTV or COBI boosting.  
A DRV/c regimen is continued during pregnancy, viral load should be monitored frequently. |
| Note:                       |                     | Tablet:                            | 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/COBI (Prezcobix):  
• 1 tablet once daily with food  
  
DRV/COBI/FTC/TAF (Symtuza):  
• 1 tablet once daily with food  
  
**Dosing in Pregnancy:**  
• The Panel does not recommend once-daily dosing during pregnancy or the use of DRV/COBI during pregnancy.  
If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently.  
• Decreased exposure in pregnancy with use of DRV/r.  
**For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., COBI, FTC, TAF)** |
| (DRV/COBI)                  | Prezcobix           | Oral Suspension:                   |                                                            |                                                                                 |
|                             |                     | • 100 mg/mL                        |                                                            |                                                                                 |
| (DRV/COBI/FTC/TAF)          | Symtuza             | DRV 800 mg plus COBI 150 mg tablet |                                                            |                                                                                 |
| **PK in Pregnancy:**        |                     | **Low placental transfer to fetus:** | 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/COBI during pregnancy or the use of DRV/COBI during pregnancy.  
If a DRV/c regimen is continued during pregnancy, viral load should be monitored frequently. |

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**Key to Acronyms:**  
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

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**References**


