Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Darunavir (Prezista, DRV)

(Last reviewed November 14, 2017; last updated November 14, 2017)

Available reports to the Antiretroviral Pregnancy Registry indicate no increase in the rate of overall birth defects with first trimester darunavir exposure compared to control populations and are of sufficient number to rule out a more than 2-fold increase in the rate of birth defects.

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) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats) those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg/day).

Reproduction/Fertility

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

Teratogenicity/Adverse Pregnancy Outcomes

No embryotoxicity or teratogenicity was seen in mice, rats, or rabbits. Because of limited bioavailability of darunavir in animals and dosing limitation, the plasma exposures were approximately 50% (mice and rats) and 5% (rabbits) of those obtained in humans. In the rat prenatal and postnatal development study, a reduction in pup weight gain was observed with darunavir alone or with ritonavir exposure via breast milk during lactation. In juvenile rats, single doses of darunavir (20 mg/kg–160 mg/kg at age 5–11 days) or multiple doses of darunavir (40 mg/kg–1,000 mg/kg at age 12 days) caused mortality. The deaths were associated with convulsions in some of the animals. Within this age range, exposures in plasma, liver, and brain were dose- and age-dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the cytochrome P450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. Sexual development, fertility, or mating performance of offspring was not affected by maternal treatment.

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.

Human Studies in Pregnancy

Pharmacokinetics

Several studies of the pharmacokinetics (PK) of darunavir/ritonavir during pregnancy have been completed. Darunavir plasma area under the curve (AUC) during the third trimester compared with postpartum was reduced by 17% to 26% with 600 mg/100 mg twice a day dosing and by 33% to 39% with 800 mg/100 mg once a day dosing. Darunavir trough concentration during the third trimester compared with postpartum was reduced by 8% to 12% with 600 mg/100 mg twice a day dosing and by 42% to 58% with 800 mg/100 mg once a day dosing. 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 felt to be clinically significant. Because of low trough levels with once-daily dosing, twice-daily dosing of darunavir is recommended during pregnancy, especially for antiretroviral-experienced patients.
The FDA guidance indicates that once-daily darunavir/ritonavir 800 mg/100 mg could be considered in pregnant women who are already on a stable once-daily darunavir/ritonavir regimen prior to pregnancy, are virologically suppressed, and in whom a change to a twice daily darunavir/ritonavir regimen may compromise tolerability or adherence; however, based on review of available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission continues not to recommend once-daily dosing of darunavir in pregnancy. A study of use of an increased twice-daily darunavir dose (800 mg) during pregnancy reported no increase in darunavir exposure in pregnant women receiving the increased dose; use of this increased twice-daily darunavir dose during pregnancy is not recommended. The PK and safety of darunavir/cobicistat during pregnancy have not been studied.

Placental and Breast Milk Passage

In an ex vivo human cotyledon perfusion model, the mean fetal transfer rate was 15%. In 4 studies reporting data from between 8 and 14 subjects each, the median ratio of darunavir concentration in cord blood to that in maternal delivery plasma ranged from 13% to 24%. No data are available describing 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 2.5% (10 of 407 births; 95% CI, 1.2% to 4.5%), which is a sufficient number of first-trimester exposures to conclude that there is not a two fold increase in the risk of overall birth defects compared to control populations.

Other Safety Issues

No safety issues have been observed in case reports and PK studies of darunavir in pregnancy.
### Excerpt from Table 9

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir (DRV) Prezista</td>
<td>DRV Tablets: • 75 mg • 150 mg • 600 mg • 800 mg DRV Oral Suspension: • 100 mg/mL Prezobix Tablet (Co-Formulated): • DRV 800 mg plus COBI 150 mg</td>
<td>Standard Adult Dose 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 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: • DRV 600 mg plus RTV 100 mg twice daily with food 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. • Twice-daily DRV/r dosing (DRV 600 mg plus RTV 100 mg with food) 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 darunavir exposure and is not recommended. • No pregnancy PK/safety data for DRV/c co-formulation, so not recommended for use in pregnancy.</td>
<td>Low placental transfer to fetus. Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio: High: &gt;0.6 Moderate: 0.3–0.6 Low: &lt;0.3 Key to Acronyms: ARV = antiretroviral; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; PK = pharmacokinetic; RTV = ritonavir</td>
</tr>
</tbody>
</table>

Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult and Adolescent Guidelines, Appendix B, Table 7). Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

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

### References


