# Darunavir/Ritonavir

## Therapeutic area: Antiviral HIV

## Overall summary of data in pregnancy

Darunavir co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. Darunavir is primarily metabolised by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir considerably.

Darunvir/ritonavir is not indicated for use in pregnancy

Darunavir shows increased exposure in HIV-1 infected patients compared to healthy subjects, this may be explained by the higher concentrations of α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in higher darunavir binding to plasma AAG, lower clearance and, therefore, higher plasma concentrations.

Several authors have published or reviewed pharmacokinetic data in pregnancy:

**\*\*Zorrilla 2014\*\*** studied the pharmacokinetics in 16 patients in the second and third trimester and postpartum (6- 12 weeks). Patients were given 600/100 mg of darunavir and ritonavir respectively, twice a day.

Mean total and unbound darunavir plasma concentrations were higher during the postpartum period compared with the second and third trimesters of pregnancy. The maximum plasma concentration of total darunavir during the second and third trimesters was 28 and 19% lower, respectively, *\_vs.\_* postpartum. The median Tmax for total darunavir was 3 h in all periods examined. Total darunavir AUC12h during pregnancy was 24 and 17% lower in the second and third trimesters, respectively, *\_vs.\_* postpartum.

Mean baseline albumin and AAG concentrations were 31 and 617 g/L and postpartum concentrations were 38 and 790 g/L, respectively, resulting in a 22 to 28% decrease during pregnancy *\_vs.\_* postpartum. The free fraction of darunavir (ratio of unbound plasma concentration *\_vs.\_* total plasma concentration) was slightly higher during pregnancy *\_vs.\_* postpartum. Unbound darunavir Cmax was 22 and 18% lower during the second and third trimesters, respectively, *\_vs\_* postpartum. The median Tmax of unbound darunavir was approximately 3 h during pregnancy and 2 h postpartum. Unbound darunavir AUC12h was 8 and 7% lower during the second and third trimesters, respectively, *\_vs.\_* postpartum.

Mean total ritonavir plasma concentrations were higher during the postpartum period compared with the second and third trimesters of pregnancy. Median total ritonavir plasma concentrations peaked 4 h after drug administration during pregnancy and at 6 h in the postpartum period. Total ritonavir Cmax during the second and third trimesters of pregnancy was 34 and 37% lower, respectively, *\_vs.\_* postpartum based on the LSM ratios. Total ritonavir AUC12h during pregnancy was 28 and 33% lower in the second and third trimesters, respectively, *\_vs.\_* postpartum.

These data are consistent with published reports demonstrating a decrease in total drug exposure (AUC) of darunavir/ritonavir 600/ 100 mg bid during pregnancy ranging from 29 to 36%. However, the current study also assessed free plasma darunavir levels, which were higher during pregnancy *\_vs.\_* postpartum. Therefore, the difference in unbound Cmax and AUC12h at postpartum compared with values found during pregnancy was minimal.

The response rate (< 50 copies/mL) increased significantly from 33% (five of 15) at baseline to 73% (eight of 11) and 90% (nine of 10) during the second and third trimesters, respectively, and was 80% (eight of 10) at 12 weeks postpartum. Three patients had detectable viral loads during pregnancy; two patients had detectable viral load during the second but not the third trimester [72 copies/mL in one patient (100% reported adherence in both trimesters) and 123 copies/mL in the other (87.5% reported adherence in the second trimester, and 100% reported adherence in the third)]. The third patient had detectable viral load during both trimesters (813 copies/mL in the second trimester and 59 copies/mL in the third trimester), with 100% reported adherence for both trimesters. Of these three patients with detectable viral load during pregnancy, two had undetectable viral load in the postpartum and follow-up periods.

**\*\*Khoo 2017\*\*** reviewed 5 pharmacokinetic studies from clinicaltrails.gov that had been performed in pregnant women. Doses were darunavir/ritonavir 800/100 mg OD or 600/100 BID.

This review includes the data of Zorrilla (above). As part of the same study, the 800/100 mm QD dose of darunavir/ritonavir was also evaluated. Total minimal darunavir concentrations were reduced by 32- 50% during pregnancy versus post-partum. However unbound darunavir Cmin was reduced by 13- 38%. Similar trends were observed for darunavir Cmax and AUC. At the third trimester all 14 women with data available had a plasma HIV-1 RNA levels of <50 copies/ml and all 16 infants were born HIV negative.

A second study performed in France studied 33 HIV-1 positive pregnant women given similar doses of 800/100 mg OD or 600/100 BID. Plasma darunavir concentrations were evaluated during the three trimesters of pregnancy and at delivery. For mothers receiving the 800/ 100 mg dose mean darunavir 24 hour concentrations were 999, 1,351 and 1,083 ng/ml during the first second and third trimester versus 419 ng/ml at delivery. For Mothers receiving the 600/100 mg BID doses. The mean darunavir 12 hour concentrations were 1,996, 1,746 and 2059 ng/ml during the first, second and third trimester of pregnancy, respectively versus 1,719 ng/ml at delivery. Darunavir concentrations reductions were -25% between first and second trimesters and -20% between first and third trimesters. All women except one had a median Cmin above the drunavir protein-binding adjusted EC50 for resistant HIV (~550 ng/ml) irrespective of the regimen. All 19 infants with available outcome data were HIV-1 negative.

The PANNA study (also **\*\*Colbers 2015\*\***) employed the same doses and studied women during the third trimester of pregnancy and postpartum. HIV-infected pregnant women recruited from HIV treatment centres in Europe. HIV-infected pregnant women. Treated with darunavir (800/100 mg once daily or 600/100 mg twice daily) as part of their combination ART. Pharmacokinetic curves were recorded in the third trimester and post-partum. AUCtau was 22% and 34% lower in the third trimester than post-partum for 600/100 mg twice daily and 800/100 mg once daily, respectively. Cmax was 24% and 22% lower during pregnancy and C12/C24 was 11% and 42% lower for the twice-daily regimen and the once-daily regimen, respectively. Mean protein-free fraction of darunavir (95% CI) was similar 12% (11%–13%, 44 samples of 19 patients) in the third trimester and 10% (9%–11%, 30 samples of 14 patients) post-partum.

Ritonavir exposure (AUCtau) was markedly decreased during pregnancy: 26% and 41% for the twice-daily regimen and the once-daily regimen, respectively; Cmax was even more affected: 37% and 41% lower for the twice-daily regimen and the once daily regimen, respectively.



The HIV RNA levels close to delivery were <300 copies in all but two patients. All children were HIV-1 negative.

In the IMPAACT P1026s study, the same doses were also employed and samples taken in the second and third trimester and postpartum. Darunavir AUC was reduced by 38% and 39% in the second and third trimesters respectively with QD dosing and 26% in both trimester for BID dosing.

For women treated with800/100 mg QD, 19/30 had HIV RNA <50 copies/ml at delivery, while 28/30 had <400 copies/ml. For the women treated with 600/100 mg BID, 14/28 had HIV-1 RNA <50 copies/ml, while 22/28 had <400 Overall conclusion.

The Dublin study (also **\*\*Lambert 2014\*\***) utilised the same doses and utilised a sparse sampling approach, determining only Cmin in all trimesters and postpartum in 20 women. Darunavir (geometric mean; 95% CI) was 3790 ng/mL at T1 (n1); 1288 ng/mL (663-1913) at T2 (n9); 1086 ng/mL (745-1428) at T3 (n18, 1 undetectable) and 2324 ng/ mL (1369-3279) at PP (n14, 1 undetectable). There was no significant difference in [DRV] between T2 and PP (p0.158); however, there was between T3 and PP (p0.021). Nineteen of twenty (95%) and 16 of 20 (80%) women achieved [DRV] above the estimated MEC for WT (55 ng/mL) and PI resistant HIV-1 (550 ng/mL) throughout pregnancy. Eighteen of the 20 mothers had plasma HIV RNA suppression at delivery. There were no cases of mother to child transmission.

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| **Summary Statistics** | | | **Mean** | | |
|  | **From (h)** | **To (h)** | **TMax (h)** | **CMax (ng/mL)** | **AUC (ng/mL.h)** |
| **CBlood (ng/mL)** | 0.00 | 96.00 | 0.96 | 1.08E+01 | 5.03E+01 |

## Overall conclusion

Lower AUCs and troughs for both darunavir and ritonavir are documented in pregnancy, however when measured, protein binding is also seen to decrease, resulting in less difference in free concentrations. Exposure is similar across second and third trimesters but there is very limited data in the first trimester. In most cases, sufficient concentrations are maintained for efficacy [1].

It has been proposed that the higher frequency BID dosing could be beneficial in pregnant women.

# Bibliography

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| [1] | “Yahoo,” [Online]. Available: https://yahoo.com. |