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Pharmacokinetics and Safety of Darunavir/Ritonavir in HIV-Infected Pregnant Women

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Abstract

The dosage of darunavir/ritonavir is 800/100 mg once daily for treatment-naive patients or treatment-experienced patients with no prior darunavir resistance associated mutations, and 600/100 mg twice daily for treatment-experienced patients with one or more darunavir resistance associated mutations.

Results from the five available pharmacokinetic studies show reductions in total darunavir plasma concentrations of between 20-50% during the third trimester of pregnancy. The unbound darunavir concentrations have been measured only in subsets of patients in two of the five pharmacokinetic studies. The unbound concentrations were 11% higher during pregnancy in one study of the 600/100 mg twice-daily dosage, and 13-38% lower during pregnancy for the 800/100 mg once-daily dosage. Ratios of darunavir concentration in cord blood compared to maternal plasma are in the range of 0.11-0.18, suggesting that darunavir does not have high trans-placental penetration.

Despite the decrease in exposure, the darunavir/ritonavir 800/100 mg once-daily regimen in HIV-positive pregnant women in combination with background antiretroviral therapy has been effective in preventing mother-to-child transmission in the studies included in this review. Among the 137 infants born across the five studies, there was one case of mother-to-child transmission, which was in a mother taking the 600/100 mg twice-daily dose but who had documented poor adherence to treatment. **(AIDS Rev. 2017;19:16-23)**

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Key words

Darunavir. Pharmacokinetics. Pregnancy. Vertical transmission.

Introduction

Darunavir is a widely used HIV protease inhibitor, boosted with low-dose ritonavir and in combination with two nucleoside analogues. The dosage of darunavir/ritonavir is 800/100 mg once daily (QD) for treatment-naive patients or treatment-experienced patients with no prior darunavir resistance associated mutations, and 600/100 mg twice daily (BID) for treatment-experienced patients with one or more darunavir resistance associated mutations. Darunavir/ritonavir should be taken with food to optimize drug levels[1].

In treatment-naive patients, darunavir/ritonavir 800/100 mg QD has shown superior virological efficacy compared with lopinavir/ritonavir, showing a lower risk of lipid elevations and gastrointestinal side effects[2]. In treatment-experienced patients, darunavir/ritonavir 600/100 mg BID has also shown improved virological

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efficacy and safety compared with lopinavir/ritonavir, with a reduced risk of treatment-emergent drug-resistance[3]. In the ODIN study, which recruited treatment-experienced patients with no darunavir-associated mutations, the 800/100 mg QD dose of darunavir/ritonavir showed non-inferior efficacy compared to the 600/100 mg BID dose and an improved safety profile[4].

Pregnant women have a range of treatment options, including combinations of two nucleoside analogues with either an integrase inhibitor (typically raltegravir), a non-nucleoside, or a ritonavir-boosted protease inhibitor. For women using protease inhibitors, darunavir/ritonavir has been recommended for use in pregnancy, at the 600/100 mg BID dose, in the Department of Health and Human Services (DHHS) perinatal guidelines[5]. Treatment guidelines in Europe also recommend the use of darunavir/ritonavir in pregnancy. In the DHHS, the International AIDS Society-USA, and in French guidelines, the recommended dose is 600/100 mg BID[5-7]. There is a range of advice on dosing in other treatment guidelines from the European AIDS Clinical Society (EACS)[8] and the British HIV Association (BHIVA)[9]. The BHIVA guidelines recommend continuation of the 800/100 mg QD dose in pregnant women who have plasma HIV RNA suppression[9]. According to the prescribing information from the Food and Drug Administration (FDA)[1], darunavir/ritonavir 800/100 mg once daily should only be considered in certain pregnant patients who are already on a stable regimen of darunavir/ritonavir 800/100 mg once daily prior to pregnancy, are virologically suppressed (HIV-1 RNA < 50 copies/ml), and in whom a change to twice-daily darunavir/ritonavir 600/100 mg might compromise tolerability or compliance.

Three main factors are associated with a residual risk of perinatal transmission of HIV-1, despite antiretroviral (ARV) treatment, in the absence of breastfeeding: detectable maternal plasma HIV-RNA at delivery, prematurity, and a short duration of ARV treatment before delivery[10,11]. To minimize the risk of perinatal transmission, initiating combined antiretroviral therapy (cART) is recommended as soon as pregnancy is planned[12]. With such a strategy, the rate of mother-to-child transmission of HIV-1 is as low as 0.5% in non-breastfeeding mothers who deliver at term while receiving ARV therapy with a plasma HIV RNA < 500 copies/ml in the French Perinatal Cohort[13].

For any ARV to be used in pregnancy, potential benefits must outweigh any risks. Key considerations are potential risks of teratogenicity, mitochondrial toxicity, premature birth, and fetal harm assessed through reproductive toxicology studies and clinical safety reporting. Moreover, the doses used should be optimized to maintain adequate therapeutic concentrations throughout pregnancy.

Pharmacological considerations for the use of antiretrovirals in pregnancy

There are three potentially important pharmacokinetic considerations for ARVs in pregnant women. Firstly, plasma levels of the ARV in the mother should not be substantially reduced during pregnancy compared to their normal therapeutic plasma levels. The most widely studied measures of drug exposure are the area under the curve (AUC) over a 12 or 24 hour dosing interval, the maximum drug concentration (C_{max}), and the minimum drug concentration (C_{min}). Pregnancy-associated alterations in hepatic drug-metabolizing enzyme activity and other physiological changes may affect the metabolism and disposition of a wide range of drugs. Pregnancy can lead to significant reductions in ARV drug exposures, particularly during the third trimester[14]. After absorption into the blood, some ARVs are bound to albumin and alpha-1-acid glycoprotein. The concentrations of these plasma proteins can change during pregnancy as a result of hemodilution, which tends to lower levels of albumin more than alpha-1-acid glycoprotein[15]. Since only unbound ARVs exert an antiviral effect, measurement of the free concentration of drug provides a more accurate measure of drug activity.

Secondly, significant penetration of ARVs in cord blood may protect the fetus from infection *in utero* or during labor via transplacental passage, yet expose the fetus to unwanted drug effects. *In vivo* and *ex vivo* placental transfers of ARVs have been evaluated in some studies to assess fetal drug exposure[16].

Thirdly, if ARVs are present in breast milk, this may prevent HIV transmission from breastfeeding. During breastfeeding, some ARVs are transferred (for example the non-nucleoside efavirenz), whereas the protease inhibitor lopinavir/ritonavir is not transferred[17]. However, breastfeeding is not recommended for women living with HIV.

In this review, we evaluate the results available on the use of darunavir/ritonavir in pregnant women. The pharmacokinetic results are evaluated, together with available outcome data for infants born from mothers who have been treated with darunavir/ritonavir-based cART.

Table 1 A. Summary of pharmacokinetic and outcome data from studies of darunavir/ritonavir 800/100 mg once daily in pregnant women

Study	Crauwels 2014	PANNA	Stek 2015	Lambert 2014	Courbon 2012
Women enrolled	n = 17	n = 18†	n = 32	n = 20	n = 15
Total DRV PK*	–50% (C_{min})	–42% (C24h)	–39% (AUC)	–55% (C_{min})	–63% (C24h)
Unbound DRV PK*	–38% (C_{min})	n/a	n/a	n/a	n/a
DRV C/M ratio	0.18	0.13	0.18	0.11	0.18
Plasma HIV RNA < 50 c/ml	87-100%	78%	90% (< 400)	90%	50%

*Geometric mean ratio of C_{min} for third trimester compared to postpartum. For the Courbon 2012 study, this ratio was for the time of delivery versus during pregnancy (post-partum darunavir concentrations data were not available).
†1 woman was receiving 600/100 mg once daily.
AUC: area under curve; C24h: concentration 24 hours after drug intake; C/M ratio: cord blood/maternal concentration ratio; C_{min}: minimum drug concentration; DRV: darunavir; n/a: not available; PK: pharmacokinetics.

Table 1 B. Summary of pharmacokinetic and outcome data from studies of darunavir/ritonavir 600/100 mg twice daily in pregnant women

Study	Zorrilla 2014	PANNA	Stek 2015	Courbon 2012
Women enrolled	n = 16	n = 6	n = 34	n = 25
Total DRV PK*	–24% (AUC)	–11% (C12h)	–26% (AUC)	–8% (C24h)
Unbound DRV PK*	–7% (AUC)	n/a	n/a	n/a
DRV C/M ratio	0.15	0.13	0.18	0.18
Plasma HIV RNA < 50 c/ml	73-90%	50%	81% (< 400 copies/ml)	73%

*Geometric mean ratio of C_{min} for third trimester compared to postpartum. For the Courbon 2012 study, this ratio was for the time of delivery versus during pregnancy (post-partum darunavir concentrations data were not available).
AUC: area under curve; C12h: concentration 12 hours after drug intake; C24h: concentration 24 hours after drug intake; C/M ratio: cord blood/maternal concentration ratio; C_{min}: minimum drug concentration; DRV: darunavir; n/a: not available; PK: pharmacokinetics.

Pharmacokinetic studies of darunavir/ritonavir in pregnant women

Five studies have evaluated the pharmacokinetics of darunavir during pregnancy. The results are summarized in tables 1 A and 1 B. To find these clinical trials, we searched the database www.clinicaltrials.gov for studies of darunavir in pregnancy. In addition, we conducted a search for publications and conference presentations on this subject over the past three years.

TMC114HIV3015 study

In a prospective pharmacokinetic study[18], 16 pregnant women receiving an ARV regimen containing darunavir/ritonavir 600/100 mg BID were enrolled and 14 had results available for analysis. Total and unbound darunavir and ritonavir plasma concentrations were obtained over 12 hours during the second and third trimester of pregnancy and post-partum. In this study, the $AUC_{0\text{-}12h}$ for total darunavir was 17-24% lower during pregnancy than post-partum. The $AUC_{0\text{-}12h}$ for unbound darunavir was reduced by 7% during pregnancy versus post-partum. The minimum plasma concentration of darunavir (C_{min}) was reduced by 43-86% during pregnancy versus post-partum. However the C_{min} of unbound darunavir was 10-14% higher during pregnancy versus post-partum. The median ratio of darunavir concentrations in cord blood to maternal plasma, measured in nine mothers, was 0.15 (range, 0.01-0.36).

During treatment, the percentage of mothers with plasma HIV RNA suppression < 50 copies/ml ranged from 73-90%. All 12 infants born to women remaining in the study at delivery were HIV-1 negative. Four of the infants were born prematurely. The lack of change in unbound darunavir levels during pregnancy suggested that no dose adjustments are required for darunavir/ritonavir 600/100 mg BID in pregnant women[18].

As part of the same study, the 800/100 mg QD dose of darunavir/ritonavir was also evaluated[19]. There were 17 women enrolled, of whom 16 were evaluated for 24 hour pharmacokinetics of darunavir and ritonavir in the second and third trimester of pregnancy, and then post-partum. Concentrations of albumin and alpha-1-acid glycoprotein were also measured to assess the potential effects of plasma proteins on levels of unbound darunavir. Total minimal darunavir concentrations (C_{min}) were reduced by 32-50% during pregnancy versus post-partum. However, unbound darunavir C_{min} were reduced by 13-38%. Similar trends were observed for darunavir C_{max} and AUC_{24h}. Plasma protein levels decreased during pregnancy versus post-partum. The mean ratio of cord blood to maternal blood total darunavir plasma concentration was 0.18, with a coefficient of variation of 104%. At the third trimester, all 14 women with data available had plasma HIV-1 RNA levels < 50 copies/ml, and all 16 infants were born HIV-1 negative.

French study

A prospective, multicenter study conducted in France[20] enrolled 33 HIV-1-positive pregnant women receiving darunavir/ritonavir-containing regimens. Of the 33 pregnancies, there were 26 live births (of which four were pre-term), one elective abortion, and one death *in utero.* The remaining women were still pregnant at the time of analysis. Sixteen mothers received 800/100 mg darunavir/ritonavir QD and 17 received the 600/100 mg BID dose. To achieve greater darunavir exposure, a small number switched QD to BID in their second (n = 1) and third trimesters (n = 3).

In this study, plasma darunavir concentrations were evaluated during the three trimesters of pregnancy and then at the time of delivery. For mothers receiving the 800/100 mg QD dose, the mean darunavir 24 hour concentrations were 999, 1,351, and 1,083 ng/ml during the first, second, and third trimesters of pregnancy, respectively, versus 419 ng/ml at the time of delivery. For mothers receiving the 600/100 mg BID dose, the mean darunavir 12 hour concentrations were 1,998, 1,746, and 2,059 ng/ml during the first, second, and third trimesters of pregnancy, respectively, versus 1,719 ng/ml at the time of delivery. However, it should be noted that not all mothers were evaluated at each time point so it is difficult to compare the results at different time points directly. In addition, there was a wide range of pharmacokinetic concentrations around the mean in each dosing group and time point.

All women except one (who was believed to be non-adherent), had median C_{min} above the darunavir protein-binding adjusted EC50 (concentration for 50% of maximal effect) for resistant HIV (approximately 550 ng/ml) irrespective of whether they received once or twice daily regimens. The median ratio of cord blood to maternal darunavir concentration was 0.18 (IQR: 0.10-0.24; n = 8). Darunavir plasma concentration reductions were –25% between first and second trimesters and –20% between first and third trimesters for women who remained on the same dose of darunavir/ritonavir. Unbound darunavir concentrations were not evaluated in this study. All 19 infants with available outcome data were HIV-1 negative.

PANNA study

The PANNA study[21] enrolled women receiving darunavir/ritonavir 600/100 mg BID or 800/100 mg QD during pregnancy. A 12 or 24 hour pharmacokinetic curve was obtained during the third trimester of pregnancy and post-partum. Where possible, a cord blood sample and matching maternal blood sample were taken at delivery. Data were available for 17 women receiving darunavir/ritonavir 800/100 mg QD and six receiving 600/100 mg BID. In this study, darunavir concentration (area under the plasma concentration-time curve for a dosing interval, AUC_{tau}) during pregnancy was decreased by 33% compared to post-partum for the 800/100 mg QD dose, and by 22% for the 600/100 mg BID dose. The unbound fraction of darunavir was not different during pregnancy (12%) versus post-partum (10%); these results were combined from the mothers taking either once or twice daily doses of darunavir/ritonavir, they were not presented for the two doses separately. The median (range) ratio of darunavir cord blood/maternal blood was 0.13 (0.08-0.35). The HIV RNA levels close to delivery were < 300 copies/ml in all but two patients. In this study, all children were tested HIV-1 negative and no birth defects were reported. There were no reports of pre-term deliveries in the PANNA study.

IMPAACT P1026s study

In the IMPAACT P1026s trial[22], women received ritonavir-boosted darunavir either as 600/100 mg BID or 800/100 mg QD as part of an ARV regimen during pregnancy and 6-12 weeks postpartum. The choice of dosing of darunavir/ritonavir was the decision of each mother's local care provider. All women had received

at least two weeks of ARVs at the time of the evaluation. Intensive steady-state 12 or 24-hour plasma pharmacokinetic profiles were performed during the third trimester and postpartum. Cord blood and maternal samples were taken at delivery when possible.

Pharmacokinetic data were available for 64 women (30 QD and 34 BID dosing). Median darunavir AUC and C_{max} were significantly reduced during pregnancy with both dosing regimens compared with postpartum, whereas the last measurable concentration (C_{last}) was also reduced during pregnancy with QD darunavir/ritonavir. Darunavir AUC with QD dosing was reduced by 38% during the second trimester and by 39% during the third trimester. With BID dosing, darunavir AUC was reduced by 26% in both trimesters. The median (range) ratio of cord blood/maternal delivery darunavir concentrations in 32 paired samples was 0.18 (range: 0-0.82). Unbound darunavir concentrations were not evaluated in this study.

The investigators concluded that lower troughs and AUC with QD compared to BID dosing combined with pregnancy lowering darunavir exposure suggests BID dosing should be used in pregnancy.

For the women treated with the 800/100 mg QD dose, 19/30 (63%) had HIV RNA < 50 copies/ml at delivery, while 28/30 (93%) had HIV RNA < 400 copies/ml at this time. For the women treated with the 600/100 mg BID dose, 14/28 (50%) had HIV RNA < 50 copies/ml at delivery, while 22/28 (79%) had HIV RNA < 400 copies/ml at this time.

There was one vertical transmission among 64 infants with data available at the time of this analysis. This infant was born at 38 weeks gestation to a mother on the BID arm who enrolled in the third trimester of pregnancy and had HIV RNA of 66,142 copies/ml at delivery. Her pre-dose darunavir concentration on the day of her pharmacokinetic assessment in the third trimester was below the limit of assay detection, suggesting poor adherence to ARV treatment.

Dublin study

In this prospective open-label study[23], HIV-positive pregnant women receiving darunavir/ritonavir 800/100 mg QD as part of their routine maternity care were enrolled. Darunavir C_{min} was determined in all trimesters of pregnancy and then post-partum.

There were 20 women enrolled in this study. There were 20 live births, all term deliveries. There was a significant difference in geometric mean darunavir C_{min} between the third trimester and post-partum (1,086 vs. 2,324 ng/ml; p = 0.021). Nineteen of 20 achieved darunavir concentrations above the estimated minimum effective concentration (protein-binding adjusted) for wild-type virus (55 ng/ml). Among 10 mothers with evaluable data, the median cord to maternal blood ratio was 0.11 (0.06-0.49). Eighteen of the 20 mothers (90%) had plasma HIV RNA suppression at the time of delivery. There were no cases of mother-to-child transmission in this study.

Placental transfer of darunavir in the *ex vivo* human cotyledon perfusion model

Determining fetal exposure to a specific drug is important in estimating its potential for pre-exposure prophylaxis, as well as its risk for toxicities in the fetus. Since data from animal studies are difficult to extrapolate to humans due to the differences in placental physiology, human studies are required. There are some data on cord blood concentrations of darunavir at delivery, but these data reflect only a single time point, and larger series are required for population pharmacokinetic modeling. The *ex vivo* human cotyledon is an accepted model in which to study and interpret the placental transfer of ARV drugs. The main limitation is that the model evaluates placental transfer at term and not during the entire pregnancy. The same is true for clinical cord blood data at delivery. Although the experiments do not entirely reproduce *in vivo* conditions, the mean (± standard deviation) fetal transfer rate (fetal/maternal concentration at steady state) was 15.0 ± 2.1%. This shows that darunavir crosses the placenta at a relatively low rate, resulting in fetal exposure. In this study, the *ex vivo* placental perfusion results were consistent with *in vivo* data previously obtained[24].

Reproductive animal toxicology studies

Reproduction studies conducted with darunavir showed no embryo toxicity or teratogenicity in mice and rats in the presence or absence of ritonavir as well as in rabbits with darunavir alone. In these studies, darunavir exposures (based on AUC) were higher in rats (threefold), whereas in mice and rabbits, exposures were lower (less than one fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir[1].

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility,

Table 2. Prevalence of birth abnormalities in infants born to antiretroviral-treated mothers (July 2015 database)

Antiretroviral	Treatment class	Defects/live births	Prevalence (95% CI)
Abacavir	NRTI	29/993	2.9% (2.0-4.2)
Lamivudine	NRTI	143/4,566	3.1% (2.6-3.7)
Zidovudine	NRTI	133/4,133	3.2% (2.7-3.8)
Stavudine	NRTI	21/810	2.6% (1.6-3.9)
Didanosine	NRTI	20/423	4.7% (2.9-7.2)
Tenofovir	N(t)RTI	60/2,608	2.3% (1.8-3.0)
Emtricitabine	NRTI	47/1,984	2.4% (1.7-3.1)
Nevirapine	NNRTI	32/1,105	2.9% (2.0-4.1)
Efavirenz	NNRTI	21/883	2.4% (1.5-3.6)
Ritonavir	PI	63/2,720	2.3% (1.8-3.0)
Lopinavir	PI	29/1,261	2.3% (1.5-3.3)
Nelfinavir	PI	47/1,215	3.9% (2.8-5.1)
Atazanavir	PI	24/1,093	2.2% (1.4-3.2)
Darunavir	PI	9/333	2.7% (1.2-5.1)
Indinavir	PI	7/289	2.4% (1.0-4.9)

95% CI: 95% confidence interval; NNRTI: nonnucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; N(t)RTI: nucleoside/tide reverse transcriptase inhibitor; PI: protease inhibitor.

and mating performance of offspring were not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir[1].

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 10 to 100% of the human exposure levels. In a four-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2-3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) 10% of the human plasma exposure levels[1].

Birth abnormalities in infants

The association between ARV treatment of pregnant women and the subsequent risk of birth abnormalities in their HIV-negative infants has been evaluated in large cohort studies and meta-analyses[25-27]. However, the clinical experience of darunavir treatment in pregnant women is more limited than for older treatments. There have been several case reports of darunavir treatment in pregnant women[28-34] that have not shown major birth abnormalities. However, these studies were not designed to evaluate these abnormalities. Moreover, no association was found in the French Perinatal Cohort between birth defects and ritonavir mostly used as a protease inhibitor booster with a power > 85% for an odds ratio of 1.5[25].

The international Antiretroviral Pregnancy Registry provides an early signal of birth abnormalities or teratogenicity associated with prenatal use of ARV drugs[35]. This registry defines a defect as any major structural malformation or chromosomal defect or two or more conditional defects occurring in infants or fetuses of at least 20 weeks gestational age. The results are predominantly from the USA (77%), but have been reported from 67 countries. The registry also describes birth outcomes in addition to birth defects. For darunavir, sufficient numbers of first-trimester pregnancies have been monitored to detect at least a twofold increase in the risk of overall birth defects. No such increases have been detected to date.

Table 2 shows the number of infants born to mothers treated with a range of ARVs, and the prevalence of

birth defects in these infants reported in the Antiretroviral Pregnancy Registry. In this registry, there were 532 infants born from mothers treated with darunavir/ritonavir, of whom 333 (63%) were treated in the first trimester. The reported prevalence of birth abnormalities in these infants was 2.7%. This is similar to the prevalence of abnormalities reported for infants whose mothers were treated with other ARVs, either within the same class of protease inhibitors, or other classes such as nucleoside analogues or non-nucleosides.

In a sub-analysis of the Antiretroviral Pregnancy registry[36], the birth outcomes were compared for 542 children born from mothers treated with darunavir/ritonavir versus 17,088 children born from mothers treated with other ARVs[36]. In this analysis, the percentage of live births was similar for the darunavir/ritonavir-treated mothers (91.9%) and non-darunavir-treated mothers (93.2%). Overall, the risk of adverse birth outcomes was similar for ARV regimens including darunavir versus those excluding darunavir. Spontaneous losses and low birth weight were more common for darunavir/ritonavir-treated mothers. However, this analysis was not adjusted for age, CD4 count, and CDC stage of disease. The mothers exposed to darunavir tended to have lower CD4 counts and a more advanced stage of HIV disease. This might be an explanation for the observed results.

While these results are encouraging, the number of mothers treated with darunavir/ritonavir in this database is relatively small compared to other ARVs. In addition, because reports of exposures are voluntary, they are subject to numerous potential selection biases. Teratogenic risk might also be associated with perinatal HIV infection or with risk behaviors associated with maternal HIV infection.

Conclusions

Results from the five available pharmacokinetic studies show reductions in total darunavir plasma concentrations of between 20-50% during the third trimester of pregnancy. In general, darunavir minimum concentrations remained well above the protein-binding adjusted EC50 (55 ng/ml) for wild-type virus, and non-adherence could have impacted the results for some women. The unbound darunavir concentrations have been measured only in subsets of patients in two of the five pharmacokinetic studies. The unbound concentrations were actually 11% higher during pregnancy in one study of the 600/100 mg BID dosage, and 13-38% lower during pregnancy for the 800/100 mg QD dosage. Ratios of darunavir concentration in cord blood compared to maternal plasma are in the range of 0.11-0.18, suggesting that darunavir does not have high transplacental penetration.

Previous trials with darunavir/ritonavir in protease inhibitor-naive HIV-infected patients did not show a relationship between darunavir pharmacokinetics and antiviral activity, and modeling and simulation indicated that a 50% reduction in total darunavir pharmacokinetics would still result in the same predicted mean virological response[37].

Despite the decrease in exposure, the darunavir/ritonavir 800/100 mg QD regimen in HIV-positive pregnant women, in combination with background antiretroviral therapy, has been effective in preventing mother-to-child transmission in the studies included in this review. Among the 137 infants born across the five studies, there was one case of mother-to-child transmission, which was in a mother taking the 600/100 mg twice-daily dose but who had documented poor adherence to treatment.

In summary, reductions in darunavir C_{min} were observed when boosted with ritonavir in the third trimester of pregnancy. The clinical significance of this is uncertain. However, the C_{min} of darunavir still lies considerably above the protein-binding adjusted EC50 for wild-type HIV, and the virologic response was generally preserved. In most treatment guidelines, the recommended dose of darunavir during pregnancy is 600/100 mg twice daily. It is important to note that these dosing recommendations apply when darunavir is boosted with ritonavir. The pharmacokinetics of darunavir when boosted with cobicistat in pregnancy are being currently evaluated (NCT00855335). In summary, when choosing a darunavir dose for pregnant women, antiretroviral treatment status and number of darunavir resistance associated mutations should be the main guide, but factors such as pill burden, simplicity, adherence, food intake, and use of concomitant medications are to be considered.

Declaration of interest

Kimberley Brown, Christiane Moecklinghoff, Charles La Porte and Maria Blanca Hadacek are employees of Janssen. Andrew Hill has received consultancy payments from Janssen.

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