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Atazanavir and darunavir in pregnant women with HIV: evaluation of laboratory and clinical outcomes from an observational national study

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Background: Atazanavir and darunavir represent the main HIV PIs recommended in pregnancy, but comparative data in pregnant women are limited. We assessed the safety and activity profile of these two drugs in pregnancy using data from a national observational study.

Methods: Women with atazanavir or darunavir exposure in pregnancy were evaluated for laboratory measures and main pregnancy outcomes (e.g. preterm delivery, low birthweight, non-elective caesarean section and neonatal gestational age-adjusted birthweight *Z*-score).

Results: Final analysis included 500 pregnancies with either atazanavir ($n = 409$) or darunavir ($n = 91$) exposure. No differences in pregnancy outcomes, weight gain in pregnancy, drug discontinuations, undetectable HIV-RNA, haemoglobin, ALT, total cholesterol, HDL cholesterol and LDL cholesterol were observed between the two groups. At third trimester, exposure to darunavir was associated with higher levels of plasma triglycerides (median 235.5 versus 179 mg/dL; $P = 0.032$) and a higher total cholesterol/HDL cholesterol ratio (median 4.03 versus 3.27; $P = 0.028$) and exposure to atazanavir was associated with higher levels of plasma bilirubin (1.54 versus 0.32 mg/dL; $P < 0.001$).

Conclusions: In this observational study, the two main HIV PIs currently recommended by perinatal guidelines showed similar safety and activity in pregnancy, with no evidence of differences between the two drugs in terms of main pregnancy outcomes. Based on the minor differences observed in laboratory measures, prescribing physicians might prefer either drug in some particular situations where the different impacts of treatment on lipid profile and bilirubin may have clinical relevance.

Introduction

Current guidelines for HIV treatment usually recommend atazanavir and darunavir (with low-dose ritonavir) as preferred HIV PIs in pregnant women.[1,2] There is, however, limited comparative information for these two drugs with respect to metabolic profile in pregnancy, effective viral suppression before delivery and, in general, pregnancy and infant outcomes. In order to further explore this issue, we analysed a national cohort of pregnant women with HIV, comparing in women with gestational exposure to atazanavir or darunavir some laboratory parameters, such as plasma lipid profile, HIV viral load, liver function tests and haemoglobin, and some maternal and infant outcomes, such as preterm delivery, low birthweight, non-elective caesarean section and birthweight *Z*-score.

Patients and methods

Data from the Italian National Programme on Surveillance of Antiretroviral Treatment in Pregnancy were used. This is a national observational study of pregnant women with HIV established in Italy in 2001. The women and infants are followed during routine clinical care and treatments are decided by the treating physician, usually according to existing guidelines. Laboratory and clinical data are collected from hospital records of obstetrics, infectious diseases and paediatrics departments, following the women's consent, using a patient information sheet that has received approval by the competent Ethics Committee (National Institute for Infectious Diseases L. Spallanzani, Rome). Gestational age is determined on the basis of the last menstrual period, ultrasound biometry or both. Preterm and very preterm delivery are defined as delivery before 37 and 32 completed weeks of gestation, respectively, and low and very low birthweight by values below 2500 and 1500 g, respectively. Caesarean section is considered elective if performed before the rupture of membranes and the onset of labour and non-elective if performed after the rupture of membranes or onset of labour or both.

All the results reported here are based on data extracted from the general database on 20 June 2017 and refer to pregnancies that occurred since May 2004 (date of first reported exposure to atazanavir). The main outcomes evaluated were non-elective caesarean section, preterm and very preterm delivery, low and very low birthweight and gender- and gestational age-adjusted percentiles for birthweight (calculated according to national reference standards).[3] Other outcomes included HIV transmission, infant mortality and birth defects, defined according to the Antiretroviral Pregnancy Registry definition.[4] In women exposed to atazanavir or darunavir in pregnancy without discontinuation the following laboratory parameters were also compared: ALT, bilirubin, haemoglobin, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol and total cholesterol/HDL cholesterol ratio. Recommended drug dosages followed existing guidelines.

Laboratory indexes were summarized as medians with IQRs and compared using the Mann–Whitney *U*-test. Qualitative variables were compared using the χ^2 or Fisher's test. *P* values <0.05 were considered statistically significant. All analyses were performed using SPSS software, version 22 (IBM Corp, 2013, Armonk, NY, USA).

Ethics approval

Ethics approval was obtained from the Ethics Committee of the I.N.M.I. Lazzaro Spallanzani in Rome (ref. deliberation 578/2001, 28 September 2001).

Results

First exposure to atazanavir in pregnancy was reported in 2004 and first exposure to darunavir in 2007. Between May 2004 and June 2017, 3045 pregnancies were reported. Following exclusion of 140 recent pregnancies (4.6%) with possible reporting delay (outcome not reported within 18 months from expected date of delivery) and of 790 cases (25.9%) with missing outcome information >18 months from expected date of delivery, 2115 pregnancies (69.5%) with available information on pregnancy outcome were considered. Among the cases excluded, 580 had no information at all except for date of last menstrual period and age (the basic clinical information required for the initial report of the pregnancy). The remaining 350 excluded cases had some information available and were compared with the 2115 cases considered for subsequent analyses (Table 1, left side). For some laboratory variables, only a limited proportion of the 350 excluded cases had available information, because missing outcome was also associated with missing laboratory data at the start of pregnancy. No differences were found between the two groups for age, CD4 count, plasma HIV viral load, months since HIV diagnosis, total bilirubin, plasma triglycerides, total cholesterol, total cholesterol/HDL cholesterol ratio and ALT. The two groups were also similar for nationality, history of drug use, HCV seropositivity, diagnosis of HIV in pregnancy, history of hypertension, nephropathy and diabetes, and parity. Excluded women were more commonly on ART at conception and HBV positive (Table 1, left side). Among the 350 cases excluded, 66 had exposure to atazanavir, 22 to darunavir and 2 to both drugs.

Among the 2115 cases with known outcome, 409 (19.3%) had exposure to atazanavir during pregnancy, 91 (4.3%) to darunavir and 8 (0.4%) to both (sequentially). Cases sequentially exposed to both drugs were excluded from all comparisons, leaving 500 evaluable cases. Following the first exposure reported, the proportion of exposed pregnancies increased significantly over time for both drugs ($P < 0.001$, χ^2 for trend), with a peak in 2013 for atazanavir (62/173, 35.8% of all pregnancies) and in 2014 for darunavir (27/143, 18.9%). Among cases exposed in pregnancy to either drug, 315 (63.0%) were on treatment at the start of pregnancy, with no differences between groups (atazanavir: 255/409, 62.3%; darunavir: 60/91, 65.9%; $P = 0.522$, χ^2 test). Only a small fraction of such cases had a subsequent discontinuation (39/315, 12.4%), with no significant differences between groups (atazanavir: 34/255, 13.3%; darunavir: 5/60, 8.3%; $P = 0.290$, χ^2 test). In most of these discontinuations, atazanavir or darunavir was replaced by other drugs for treatment optimization, in the absence of toxicity or treatment inefficacy (data not shown).

The comparison of baseline characteristics (epidemiology, HIV infection and laboratory data) for the two treatment groups is shown in Table 1 (right side). At the start of pregnancy, women on atazanavir were older, had a shorter interval since HIV diagnosis, slightly higher median plasma HIV-RNA levels and significantly higher plasma total bilirubin levels. No other significant differences were found in laboratory measures or in demographic and clinical characteristics (Table 1, right side).

The comparison of the main laboratory indexes, performed in women with continued exposure in pregnancy to either drug without discontinuation, showed some significant differences between the two groups (Table 2). Treatment with darunavir was associated with higher levels of plasma triglycerides (significant at third trimester) and higher values of the total cholesterol/HDL cholesterol ratio (significant at both first and third trimesters), while treatment with atazanavir was associated with higher levels of plasma bilirubin (significant at both trimesters). No differences were observed at either trimester in levels of haemoglobin, ALT, total cholesterol, HDL cholesterol and LDL cholesterol, and in changes observed between first and third trimesters for all the above parameters (all *P* values ≥ 0.15; Table 2).

The main pregnancy outcomes for the two groups are summarized in Table 3. No significant differences were observed between the two groups, with similar rates of preterm and very preterm delivery, low and very low birthweight, pregnancies not ending in a live birth, emergency caesarean delivery, complications of delivery, neonatal death and birth defects. The two groups were also similar for increase in body weight in pregnancy (median 11 kg in both groups; IQR 8–14 for atazanavir, 7.5–13 for darunavir; $P = 0.669$) and for rates of urinary infections, vaginal infections, hypertension, glucose metabolism abnormalities and anaemia (data not shown). Among 353 infants with HIV status available, only one

Table 1. Baseline characteristics of the population studied according to outcome status (left side) and to exposure in pregnancy to the two drugs studied (right side)

	350 with outcome unknown		2115 with outcome known		P^a	409 with outcome known, atazanavir		91 with outcome known, darunavir		P^a
	n	median (IQR)	*n*	median (IQR)		*n*	median (IQR)	*n*	median (IQR)	
Age (years)	343	32 (27–37)	2096	33 (29–36)	0.233	409	34 (30–38)	91	32 (27–37)	0.012
CD4 count (cells/mm^3)	208	547 (404–696)	931	512 (360–710)	0.509	195	560 (389–752)	51	560 (361–725)	0.543
HIV-RNA (log copies/mL)	177	1.70 (1.60–3.35)	869	1.70 (1.60–3.04)	0.872	278	1.70 (1.57–3.48)	60	1.60 (1.57–2.15)	0.025
Months since HIV diagnosis	331	42 (8–101)	2044	53 (9–114)	0.084	401	68 (25–127.5)	89	89 (29.5–223)	0.022
Total bilirubin (mg/dL)	36	0.40 (0.33–0.52)	1007	0.50 (0.34–0.79)	0.101	270	1.03 (0.47–2.14)	58	0.35 (0.28–0.53)	<0.001
Plasma triglycerides (mg/dL)	27	91 (67–119)	952	90 (68–126)	0.746	239	86 (66–121)	47	93 (73–129)	0.274
Total cholesterol (mg/dL)	31	183 (155–195)	958	169 (147–194)	0.282	245	163 (143–183)	46	166 (150–190.25)	0.619
Total cholesterol/HDL cholesterol ratio	24	3.01 (2.48–3.47)	611	3.00 (2.57–3.56)	0.497	181	3.13 (2.65–3.56)	31	3.15 (2.50–3.83)	0.760
ALT (U/L)	15	15 (8–20)	345	16 (12–22)	0.171	127	16 (12–22)	48	14.5 (11–19.75)	0.230
	n	%	*n*	%		*n*	%	*n*	%	
Foreign nationality	337	59.1	1998	53.6	0.063	402	51.2	89	44.9	0.282
History of drug use	333	6.3	2064	6.2	0.914	407	5.9	89	4.5	0.801
HCV positive	318	13.5	1946	12.9	0.759	381	11.8	85	15.3	0.379
Diagnosis of HIV in pregnancy	331	21.5	2044	22.5	0.683	401	14.5	89	11.2	0.720
History of hypertension	328	3.0	2065	1.8	0.147	408	2.2	91	1.1	0.698
History of nephropathy	328	0.3	2060	0.9	0.254	407	1.2	91	1.1	1.000
History of diabetes	327	1.2	2057	2.1	0.273	404	3.2	91	2.2	1.000
At least one previous pregnancy	333	76.6	2064	75.6	0.694	407	78.1	91	73.6	0.353
On treatment at conception	345	62.3	2067	55.7	0.021	409	62.3	91	65.9	0.522
HBV positive	306	15.0	1954	10.5	0.019	393	11.7	87	14.9	0.405

[a]Mann-Whitney *U*-test for quantitative variables; χ^2 or Fisher's test for categorical variables.

case of HIV transmission (0.3%) was observed (in the atazanavir group). Among the five neonatal deaths reported, three were in severely preterm infants (<30 weeks), likely caused by complications related to prematurity, one was due to respiratory failure in an infant with congenital defects and the other occurred in a term infant with neonatal streptococcal sepsis.

Discussion

Current guidelines for pregnant women with HIV usually recommend atazanavir or darunavir (both with low-dose ritonavir) as the preferred PIs for use in pregnancy.[1,2] The present analysis, based on 500 pregnancies exposed, provides new comparative information. The proportion of evaluable cases reflects the earlier introduction and more common use of atazanavir compared with darunavir. Reassuringly, all the main pregnancy and infant outcomes were equally frequent in the two groups and the rate of HIV transmission was minimal, with only one case reported.

Although this case series is to our knowledge the largest comparing these two drugs in pregnant women, caution is necessary in the interpretation of outcome data for several reasons. The number of events, particularly for some infrequent outcomes (such as very preterm delivery and very low birthweight), was small and the absence of significant differences should be considered within the context of the statistical power of the study, which can be adequate to detect only large differences between groups. Overall, the rates of all main events were similar to those of the entire study population of pregnant women with HIV, as shown in Table 3, but for some outcomes the numbers show some variability between groups that should be explored in larger studies, possibly pooling data from multiple cohorts.

In terms of laboratory outcomes, the two drugs were equally effective in producing an undetectable viral load at the end of pregnancy, indicating comparable virological efficacy in pregnancy, with even higher rates of viral suppression compared with the entire study population (Table 3). Some differences were observed in some laboratory indexes: atazanavir was clearly associated with higher levels of bilirubin, but with no higher rates of drug discontinuation or adverse outcomes, in line with other observations that indicate that the clinical impact of this drug effect in both mothers and infants is generally limited.[5–7] Apart from bilirubinaemia, the only other significant differences observed between the two drugs in laboratory parameters involved a slightly better metabolic profile with atazanavir. This drug has shown a favourable lipid profile in clinical trials[8,9] and in pregnancy[10] compared with lopinavir, but there are less consistent findings regarding the comparison with darunavir in terms of lipid profile.[11–15] The present study indicates in pregnant women a better lipid profile with atazanavir compared with darunavir, with lower triglyceride levels (contrary to some studies in the general population that showed an opposite effect)[12,13] and a lower total cholesterol/HDL cholesterol ratio (consistent with Martinez *et al.*,[11] 2014). Although pregnancy may

Table 2. Laboratory measures at first and third trimesters of pregnancy and changes over time in women receiving either atazanavir or darunavir during entire pregnancy

	First trimester, median (IQR)			Third trimester, median (IQR)			Median change (IQR), first to third trimester		
	atazanavir	darunavir	*P*	atazanavir	darunavir	*P*	atazanavir	darunavir	*P*
Plasma total bilirubin (mg/dL) (*n*: atazanavir 129, darunavir 29)	1.70 (0.96–2.50)	0.31 (0.25–0.64)	<0.001	1.54 (1.03–2.30)	0.32 (0.25–0.47)	<0.001	−0.15 (−0.74 to + 0.45)	−0.02 (−0.15 to + 0.01)	0.331
ALT (U/L) (*n*: atazanavir 73, darunavir 30)	16 (12.0–21.5)	18 (12.0–22.2)	0.428	18 (12–27)	16 (13–26.5)	0.780	2 (−2.5 to + 9.5)	−1 (−4.2 to + 8.0)	0.497
Haemoglobin (g/dL) (*n*: atazanavir 75, darunavir 28)	12.5 (11.9–13.2)	12.5 (12.1–13.1)	0.809	11.8 (10.8–12.3)	11.5 (10.5–12.2)	0.276	−0.7 (−1.8 to − 0.1)	−1.0 (−2.35 to − 0.42)	0.240
Plasma triglycerides (mg/dL) (*n*: atazanavir 95, darunavir 20)	87 (68–128)	111.5 (80.5–158.7)	0.072	179 (148–224)	235.5 (177.7–352.5)	0.032	90 (61–126)	119 (59.5–159.2)	0.150
Plasma total cholesterol (mg/dL) (*n*: atazanavir 96, darunavir 20)	163.5 (140.2–184.7)	161.5 (146.0–189.2)	0.778	211 (189.5–251.5)	201 (179.7–293.2)	0.962	54 (32.2–75.0)	58.5 (1.25–103.0)	0.792
Plasma HDL cholesterol (mg/dL) (*n*: atazanavir 71, darunavir 13)	55 (46–67)	50 (45–56)	0.115	68 (55–82)	59 (56–72.5)	0.350	11 (2–23)	14 (10.5–18.5)	0.380
Plasma LDL cholesterol (mg/dL) (*n*: atazanavir 46, darunavir 9)	86.5 (70.7–108.0)	116 (79–132)	0.111	111 (83–129.7)	132 (90.5–187)	0.092	19 (4.0–50.2)	40 (4.5–66.5)	0.158
Total cholesterol/HDL cholesterol ratio (*n*: atazanavir 71, darunavir 13)	2.97 (2.45–3.48)	3.62 (2.80–4.11)	0.018	3.27 (2.58–3.90)	4.03 (3.28–4.90)	0.028	0.282 (−0.117 to + 0.734)	0.475 (−0.582 to + 1.362)	0.591

All *P* values: Mann–Whitney *U*-test.

Table 3. Pregnancy outcomes

	Entire study population[a]	Atazanavir	Darunavir	P^b
HIV viral load <50 copies/mL at third trimester, %	73.8 (1013/1372)	81.6 (239/293)	83.6 (56/67)	0.669
Pregnancy not ending in a live birth, %[c]	9.8 (114/1168)	8.3 (21/253)	15.3 (9/59)	0.103
Non-elective caesarean section, %	18.7 (326/1746)	18.6 (67/361)	18.3 (13/71)	0.961
Preterm delivery (<37 weeks), %[d]	19.0 (338/1780)	17.4 (63/362)	18.9 (14/74)	0.755
Very preterm delivery (<32 weeks), %	2.1 (37/1780)	1.9 (7/362)	2.7 (2/74)	0.653
Low birthweight (<2500 g), %[d]	20.7 (345/1666)	20.4 (70/343)	16.9 (12/71)	0.500
Very low birthweight (<1500 g), %[d]	2.7 (45/1666)	2.6 (9/343)	4.2 (3/71)	0.440
Small by gestational age, %[e]	12.7 (197/1553)	12.0 (39/326)	11.3 (8/71)	0.869
Large by gestational age, %[e]	6.9 (107/1553)	5.8 (19/326)	5.6 (4/71)	0.605
Complications of delivery, %[f]	6.4 (110/1722)	9.3 (33/353)	5.6 (4/71)	0.488
Neonatal/infant death, %	0.7 (13/1847)	1.3 (5/374)	0	0.404
Birth defects, %[g]	4.8 (44/921)	5.8 (12/207)	7.7 (3/39)	0.713

[a]All cases followed since May 2004.
[b]Comparison between atazanavir- and darunavir-exposed women, χ^2 or Fisher's test.
[c]Calculated on cases exposed (on treatment) at the start of pregnancy.
[d]Livebirths only.
[e]Birthweight <10th (small) or >90th (large) percentile by age and gender, singletons only.
[f]Mostly represented by anaemia, fever or wound infections.
[g]Livebirths from mothers on treatment at the start of pregnancy.

induce significant effects on lipid levels,[16] most of the observed differences were already present at the start of pregnancy and are therefore likely to reflect general differences in the metabolic profile of the two drugs and not a specific differential effect of pregnancy, as also suggested by the similar changes observed with the two drugs in all laboratory parameters between first and third trimesters. Finally, the differences in laboratory measures were not accompanied by substantial differences in clinical outcomes, including those potentially related to metabolic status, such as maternal weight gain and prevalence of large infants by gestational age.

Overall, given the increased cardiovascular risk associated with higher values of the total cholesterol/HDL cholesterol ratio[17]and the potential association of early hypertriglyceridaemia with subsequent occurrence of gestational diabetes, pre-eclampsia[18,19] and fetal macrosomia,[20] clinicians could consider atazanavir as a preferable choice in particular situations where additional risk factors for the above clinical conditions are present. On the other hand, darunavir may be preferred when hyperbilirubinaemia may pose some concern.

The main limitation of this study, together with the sample size considerations discussed above, is represented by the non-randomized attribution of treatment, which does not allow us to exclude some selection bias in prescribing. Randomized studies are, however, difficult to perform in pregnancy and almost all available information is based on studies with an observational design. Overall, this study provided new comparative information on use of atazanavir and darunavir in pregnancy, with a relatively large sample size that included 500 cases. Overall, the main study findings, showing no evidence of a difference in risk of adverse pregnancy outcomes, support current recommendations. Based on the minor differences observed in laboratory measures, prescribing physicians might prefer either drug only in particular situations where the expected impact of treatment on lipid profile and bilirubin may be clinically relevant.

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Transparency declarations

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