J Antimicrob Chemother 2014; **69**: 1377–1384
doi:10.1093/jac/dkt497 Advance Access publication 25 December 2013

Journal of Antimicrobial Chemotherapy

Atazanavir and lopinavir profile in pregnant women with HIV: tolerability, activity and pregnancy outcomes in an observational national study

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Received 6 September 2013; returned 19 October 2013; revised 18 November 2013; accepted 27 November 2013

Background: Atazanavir and lopinavir represent the main HIV protease inhibitors recommended in pregnancy, but comparative data in pregnant women are limited.

Methods: Women from a national observational study, exposed in pregnancy to either atazanavir or lopinavir, were compared for glucose and lipid profiles, liver function tests, CD4 count, HIV RNA and main pregnancy outcomes. Statistical methods included univariate and multivariable analyses.

Results: The study population included 428 pregnancies (lopinavir, 322; atazanavir, 106). The lopinavir group was characterized by higher rates of HIV diagnosis in pregnancy and treatment indication for maternal health, lower CD4 counts, higher HIV RNA levels, less frequent antiretroviral treatment at conception and shorter duration of drug exposure during pregnancy. No differences in pregnancy outcomes, glucose metabolism and weight gain were observed. The two groups also showed in a multivariable analysis similar odds for detectable HIV RNA in the third trimester (adjusted OR 0.85, 95% CI 0.35–2.10, $P=0.730$). Total lipid levels were significantly higher in the lopinavir group (median values in the third trimester 239 versus 221 mg/dL for total cholesterol and 226 versus 181 mg/dL for triglycerides; $P<0.001$ for both comparisons) and bilirubin levels were significantly higher in the atazanavir group (1.53 versus 0.46 mg/dL, $P<0.001$).

Conclusions: In this observational study atazanavir and lopinavir showed similar safety and activity in pregnancy, with no differences in the main pregnancy outcomes. Atazanavir use was associated with a better lipid profile and with higher bilirubin levels. Overall, the study findings confirm that these two HIV protease inhibitors represent equally valid alternative options.

Keywords: pre-term delivery, HIV RNA, cholesterol, triglycerides, bilirubin

Introduction

The significant progress of antiretroviral treatment in HIV infection has led to a remarkable decline in HIV-associated morbidity and mortality and to a dramatic reduction in mother-to-child transmission of HIV.[1–3] Although growing evidence indicates that antiretroviral treatment in pregnancy has overall a very favourable risk–benefit profile, it is important to maintain monitoring of the safety and efficacy of individual drugs and drug classes in order to optimize treatment recommendations.

Protease inhibitors are commonly used in pregnancy, usually in combination with nucleoside or nucleotide reverse transcriptase inhibitors, with no apparent increase in the risk of birth defects associated with their use.[4] There are, however, for this class of drugs some concerns regarding metabolic disturbances and pre-term delivery[5–7] that require further evaluation. Based on the experience of use and available information, current guidelines for HIV treatment usually recommend atazanavir and lopinavir as preferred HIV protease inhibitors in pregnancy.[8–10] Despite these recommendations, there is limited comparative information in pregnancy for these two drugs; in particular, it is not known to what extent the better metabolic profile and higher impact on bilirubin levels shown by atazanavir in clinical and observational studies is also maintained in pregnancy, in which hormonal changes induce significant metabolic changes. There is also no comparative information on the efficacy of these two drugs in obtaining an undetectable HIV viral load at the end of pregnancy, and, in general, on their impact on pregnancy outcomes. In order to further explore this issue, we studied a national cohort of pregnant women with HIV who had had antenatal exposure to either lopinavir or atazanavir, evaluating glucose and plasma lipid profiles, HIV viral load, bilirubin levels and liver function test abnormalities, and some major pregnancy outcomes, such as pre-term delivery, low birthweight, non-elective Caesarean section and neonatal gestational age-adjusted birthweight Z-score.

Patients and methods

Data from the Italian National Program on Surveillance on Antiretroviral Treatment in Pregnancy were used. This is a national observational study of pregnant women with HIV established in Italy in 2001, reflecting routine clinical care. Only HIV-positive pregnant women are included and no specific guidance is given in terms of treatment of HIV infection or prophylaxis for mother-to-child transmission, which are decided by the treating physician. Laboratory and clinical data are collected from hospital records of the obstetrics, infectious diseases and paediatrics departments after the women have given consent. Information on smoking and substance use (heroin, cocaine or methadone) and on the HIV status of the current partner is based on the woman's subjective report. Information and measurements are collected at routine visits performed during pregnancy (with no restrictions on gestational age at entry into prenatal care), at delivery, during the post-partum period and during follow-up of mothers and newborns for up to 18 months. Voluntary pregnancy terminations and miscarriages are reported only by some of the participating centres. The time of HIV diagnosis (reported in months) is calculated using the date difference between HIV diagnosis and the last menstrual period. Gestational age at birth is determined on the basis of the last menstrual period, ultrasound biometry or both. Pre-term delivery is defined as delivery before 37 completed weeks of gestation, 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. Information on newborns includes gender, birthweight, gestational age, Apgar score, HIV status and presence of congenital or functional/biochemical abnormalities. Informed consent is required for all enrolled women, using a patient information sheet that has received approval by the competent ethics committee (National Institute for Infectious Diseases L. Spallanzani, Rome).

All the results reported here are based on data extracted from the general database on 10 June 2013, and refer to pregnancies that occurred between December 2001 and June 2013. For the present analysis, we considered all pregnancies with either atazanavir or lopinavir exposure ending in live births, excluding miscarriages, terminations and intrauterine deaths or stillbirths. The time of initiation of treatment in pregnancy was described in weeks of gestation, and women on antiretroviral treatment at the last menstrual period were considered to be on treatment at conception. In order to focus on metabolic and efficacy differences between the two drugs in women on treatment in late pregnancy, the main outcomes evaluated were glucose and lipid profiles and viral load in the third trimester. Other laboratory and clinical outcomes were represented by bilirubin levels and liver function test abnormalities, defined by one or more of the following: serum alanine or aspartate aminotransferase levels >60 U/L; serum bilirubin values >1.8 mg/dL; and serum γ-glutamyl transferase levels >150 U/L. The outcome of pregnancy was evaluated through rates of non-elective Caesarean section and pre-term delivery. Neonatal outcomes included low and very low birthweight, gender- and gestational age-adjusted Z-scores, and percentiles for birthweight (calculated according to national reference standards).[11] HIV transmission and infant mortality were not analysed because of limited event rates, and birth defects data by antiretroviral treatment were also not analysed because of recent published work on this issue.[12]

In order to be eligible for the comparison, the following criteria were required: available information on gestation week of delivery and on time of start and end of treatment; start of lopinavir and atazanavir no later than 22 weeks of pregnancy; and combination antiretroviral treatment during the third trimester, continued until delivery, and no switch to or from different protease inhibitors during pregnancy. Usual dosages for lopinavir and atazanavir were 400 mg twice daily with 100 mg ritonavir twice daily and 300 mg once daily with ritonavir 100 mg daily.

Demographic data were summarized with descriptive statistics. Quantitative data between women with atazanavir or lopinavir exposure were compared using the Mann–Whitney *U*-test. Categorical data were compared using the χ^2 test or the Fisher test, as appropriate. Where necessary, in order to adjust for potential confounders, the associations found in univariate analyses were evaluated in multivariable forward conditional logistic regression models (which allowed only variables significant at a level of 0.05 to enter the final model) and were expressed as adjusted ORs and 95% CIs. For all the analyses, *P* values <0.05 were considered statistically significant. The analyses were performed using SPSS software version 20.0 (IBM, Somers, NY, USA).

Ethics approval

Ethics approval was obtained on 28 September 2001 from the Ethics Committee of the Istituto Nazionale per la Malattie Infettive Lazzaro Spallanzani in Rome (Deliberation no. 578).

Results

Overall, among 3166 pregnancies with an initial registration as of 10 June 2013, 2071 (65.4%) had information on pregnancy outcome (categorized as live birth, termination, miscarriage or intrauterine death). Following exclusion of pregnancies not ending in a live birth ($n=286$), not exposed to either lopinavir or atazanavir ($n=1108$) or exposed to both drugs during pregnancy ($n=37$), 640 pregnancies had exposure to either lopinavir ($n=509$) or atazanavir ($n=131$). Among these pregnancies, 54 (lopinavir 48, atazanavir 6) also had exposure to other HIV protease inhibitors in pregnancy, 36 (lopinavir 31, atazanavir 5) had missing information on time of delivery or timing of treatment in pregnancy, 91 (lopinavir 81, atazanavir 10) had a late start (>22 weeks) of lopinavir or atazanavir in pregnancy and 31 (lopinavir 27, atazanavir, 4) did not continue lopinavir or atazanavir until delivery. Following exclusion of these cases, the final analysis was based on 428 pregnancies (lopinavir 322, atazanavir 106) and 433 live

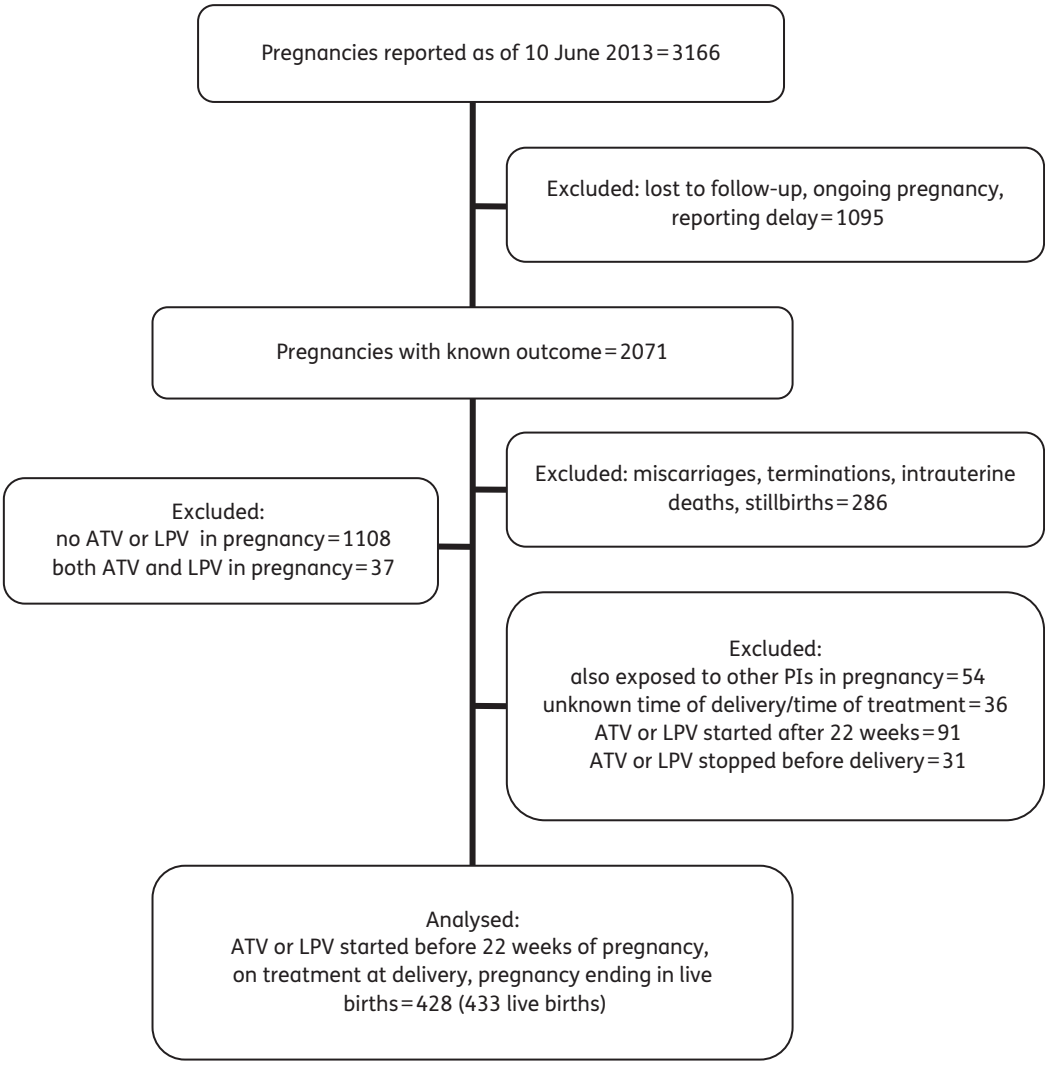

Figure 1. Flow chart of cases eligible for the analysis. ATV, atazanavir; LPV, lopinavir; PIs, protease inhibitors.

births (lopinavir 325, atazanavir 108). The case selection process is summarized in Figure 1.

The main maternal characteristics of the population studied are reported in Table 1. The two groups had overall similar demographic and clinical characteristics, but women in the lopinavir group were more commonly antiretroviral naive and diagnosed with HIV in pregnancy, and had a lower CD4 cell count and more commonly had an indication for treatment for their own health (i.e. not only for prevention of mother-to-child transmission). Duration of exposure during pregnancy was also lower for this group, with less frequent ongoing antiretroviral treatment at conception and a higher rate of discontinuous treatment during pregnancy (Table 1). Both groups had a good immunological status (median CD4 cell count 521 cells/mm^3 for atazanavir and 474 cells/mm^3 for lopinavir) and a very infrequent history of past clinical AIDS-defining events (8.6% and 5.7%, respectively). At delivery, 101 women in the atazanavir group (95.3%) and 317 women in the lopinavir group (98.4%) were on treatment with at least two other drugs ($P = 0.07$), usually (98.1% for atazanavir and 97.8% for lopinavir) nucleoside reverse transcriptase inhibitors.

Potential metabolic differences between the two drugs were analysed by assessing weight gain, glucose metabolism and lipid profile in the third trimester of pregnancy. Occurrence of glucose metabolism abnormalities in pregnancy had similarly frequency (atazanavir 7.5%, lopinavir 5.3%; OR = 1.46, 95% CI 0.61–3.50, $P = 0.388$), and no significant differences between the two treatment groups were observed in weight gain during pregnancy, insulin levels and homeostasis model of assessment–insulin resistance (HOMA–IR) values, available for a small subgroup of women (Table 2). Conversely, lipid metabolism appeared to be differently influenced by the two drugs, with atazanavir use associated with lower triglyceride and total cholesterol values in the third trimester and with less pronounced increases from the first to the third trimester for these two parameters. No significant differences between the two groups were observed for high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol and for the total cholesterol/HDL-cholesterol ratio (Table 2).

Table 1. Characteristics of pregnant women in the two treatment groups

	No. with available information		Median (IQR) or percentage with the characteristic		
	atazanavir	lopinavir	atazanavir	lopinavir	*P* value
Age, years (*n*=427)	106	321	34 (30–37)	32 (29–36)	0.058[a]
Body mass index, kg/m^2 (*n*=304)	86	218	23.1 (20.2–26.2)	22.3 (20.3–25.2)	0.228[a]
Time between HIV diagnosis and pregnancy, months (*n*=422)	105	317	69 (23–143)	56 (5–109)	**0.026**[a]
Pregnancy week of start of ARV (*n*=428)	106	322	1 (1–14)	12 (1–16)	**<0.001**[a]
CD4 cell count, cells/mm^3[b] (*n*=320)	90	230	456 (363–594)	406 (279–572)	**0.048**[a]
HIV RNA, $\log_{10}$ copies/mL[b] (*n*=299)	81	218	1.70 (1.60–3.10)	3.00 (1.70–4.20)	**<0.001**[a]
Exposure to atazanavir or lopinavir in pregnancy, weeks (*n*=428)	106	322	35 (24–37)	26 (21–36)	**<0.001**[a]
Twin pregnancy (*n*=428)	106	322	1.9	0.9	0.362[c]
At least one previous pregnancy (*n*=426)	106	320	74.5	71.6	0.554[c]
African ethnicity (*n*=423)	106	317	37.7	34.4	0.532[c]
History of intravenous drug use (*n*=423)	105	318	6.7	5.0	0.522[c]
Smoking >10 cigarettes/day (*n*=384)	100	284	15.0	9.9	0.161[c]
Recent substance use[d] (*n*=413)	104	309	4.8	3.6	0.568[c]
Diagnosis of HIV in current pregnancy (*n*=422)	105	317	13.3	23.3	**0.029**[c]
HBV coinfection (*n*=381)	92	289	7.6	9.3	0.611[c]
HCV coinfection (*n*=414)	102	312	11.8	11.2	0.880[c]
CD4 count <200 cells/mm^3[b] (*n*=320)	90	230	8.9	10.0	0.763[c]
History of AIDS-defining events (*n*=421)	105	316	8.6	5.7	0.297[c]
Indication for ARV for their own health[e] (*n*=400)	104	296	7.7	20.6	**0.003**[c]
Antiretroviral naive at start of pregnancy (*n*=423)	104	319	20.2	34.2	**0.007**[c]
On ARV at conception (*n*=422)	106	316	69.8	50.2	**0.001**[c]
No interruption of atazanavir or lopinavir treatment during pregnancy (*n*=428)	106	322	93.4	84.8	**0.023**[c]

ARV, antiretroviral therapy.
Bold is used for *P* values <0.05.
[a]Mann–Whitney *U*-test.
[b]First trimester.
[c]χ^2 test.
[d]Opiates, benzodiazepines or cocaine.
[e]ARV indicated for maternal health and not only for prevention of mother-to-child transmission.

With respect to pregnancy outcomes, the median duration of pregnancy in the entire group (*n*=428) was 38 weeks (IQR 37.0–38.0), with a pre-term delivery rate of 20.8% (*n*=89/428). The most common mode of delivery was elective Caesarean section (*n*=337/425, 79.3%), followed by non-elective Caesarean section (*n*=76/425, 17.9%) and vaginal delivery, which involved only 2.6% of the women (*n*=11). Median birthweight was 2885 g (IQR 2542–3185) and rates of low (<2500 g) and very low birthweight (<1500 g) were 20.5% (*n*=83/405) and 1.0% (*n*=4/405), respectively. Complications of delivery, most commonly represented by surgical wound infections and fever, involved 4.5% of women (*n*=19/418). For all the above outcomes, as also for the proportions of small (<10th percentile) and large (>90th percentile) by gestational age infants, no significant differences were found between women exposed to atazanavir and those exposed to lopinavir (Table 3).

The two protease inhibitors, as expected, had different impacts on bilirubin values, with consistently higher total bilirubin levels associated with atazanavir use (median values in the third trimester 1.53 versus 0.46 mg/dL, $P<0.001$). This translated into a higher risk of liver function test abnormalities during pregnancy with atazanavir (OR after adjusting for HCV coinfection 2.30, 95% CI 1.07–4.91, $P=0.032$), which, however, did not necessitate any change in atazanavir treatment. No cases of renal lithiasis were reported in pregnant women receiving atazanavir, with one case reported in the lopinavir group.

Finally, given the significant ($P<0.05$ in univariate analyses) imbalance between the two groups in some variables relevant for the achievement of an undetectable viral load at the end of pregnancy, we evaluated the predictors of detectable end-of-pregnancy HIV RNA in a multivariable logistic regression model that adjusted for pregnancy week of start of treatment, first-trimester CD4 cell count, HIV RNA levels and drug interruptions during pregnancy. These variables were selected based on their significance in univariate analyses ($P<0.05$ required for inclusion), causal relevance for the outcome and potential redundancy. The multivariate analysis showed that, after adjustment for covariates, the presence of detectable HIV RNA in late

Table 2. Metabolic indexes in the third trimester of pregnancy

	No. with available information in each group		Median (IQR)		
	atazanavir	lopinavir	atazanavir	lopinavir	*P* value
Weight increase during pregnancy (kg) (*n*=299)	84	215	11 (8–15)	11 (8–14)	0.537
Fasting plasma glucose (mg/dL) (*n*=367)	94	273	75 (68–82)	72 (67–78)	0.060
Fasting insulin (μU/mL) (*n*=60)	13	47	9.9 (6.8–21.2)	9.2 (5.91–11.9)	0.311
HOMA-IR[a] (*n*=57)	12	45	1.75 (1.21–4.10)	1.61 (0.95–2.28)	0.347
Plasma triglycerides (mg/dL), third trimester (*n*=286)	74	212	181 (142–236)	226 (182–309)	**<0.001**
Plasma total cholesterol (mg/dL), third trimester (*n*=287)	75	212	221 (194–250)	239 (201–272)	**<0.001**
Plasma HDL-cholesterol (mg/dL), third trimester (*n*=213)	59	154	64 (57–73)	65 (56–75)	0.629
Plasma LDL-cholesterol (mg/dL), third trimester (*n*=145)	37	108	115 (90–145)	124 (97–154)	0.404
Total cholesterol/HDL-cholesterol ratio (*n*=212)	59	153	3.5 (2.9–4.0)	3.5 (3.0–4.4)	0.317
Plasma triglycerides (mg/dL), increase between first and third trimesters (*n*=212)	63	149	84 (60–133)	130 (76–184)	**0.002**
Plasma total cholesterol (mg/dL), increase between first and third trimesters (*n*=209)	64	145	54 (24–74)	68 (33–99)	**0.033**
Plasma HDL-cholesterol (mg/dL), increase between first and third trimesters (*n*=149)	48	101	12 (−1.5–22.7)	10 (2–18.5)	0.624
Plasma LDL-cholesterol (mg/dL), increase between first and third trimesters (*n*=98)	30	68	29 (3.2–53)	26 (2.2–55.7)	0.732

Bold is used for *P* values <0.05.
[a]Calculated as fasting insulin (in μU/mL) × fasting glucose (in mmol/L)/22.5.

Table 3. Main pregnancy outcomes in mothers exposed to atazanavir or lopinavir

	Atazanavir		Lopinavir				
Outcomes	*n/N*	%	*n/N*	%	OR[a]	OR 95% CI	*P* value
Non-elective Caesarean section (*n*=413)	15/103	14.6	61/310	19.7	0.70	0.38–1.29	0.248
Complications of delivery[b] (*n*=418)	7/105	6.7	12/313	3.8	1.79	0.69–4.68	0.228
Preterm delivery (*n*=428)	20/106	18.9	69/322	21.4	0.85	0.49–1.48	0.573
Low birthweight (<2500 g) (*n*=405; twins included)	21/103	20.4	62/302	20.5	0.99	0.57–1.73	0.976
Very low birthweight (<1500 g) (*n*=405; twins included)	3/103	2.9	1/302	0.3	9.03	0.93–87.6	0.058
Undetectable (<50 copies/mL) HIV-RNA in third trimester (*n*=346)	78/90	86.7	176/256	68.8	**2.95**	**1.52–5.73**	**0.001**
Small by gestational age (<10th percentile)[32] (*n*=391, singletons only)	13/100	13.0	36/291	12.4	1.06	0.54–2.01	0.870
Large by gestational age (>90th percentile) (*n*=391, singletons only)	4/100	4.0	29/291	10.0	0.38	0.13–1.10	0.074

Bold is used for *P* values <0.05.
[a]Reference category=atazanavir.
[b]Usually represented by surgical wound infections and fever.

pregnancy was not significantly associated with the treatment received during pregnancy (adjusted atazanavir/lopinavir OR for HIV RNA >50 copies/mL 0.85, 95% CI 0.35–2.10, *P*=0.730), but appeared to be independently associated with low CD4 counts, drug interruptions during pregnancy and increasing HIV RNA levels at the start of pregnancy (Table 4).

Discussion

Current guidelines for pregnant women with HIV concur in recommending either lopinavir or atazanavir (both with low-dose ritonavir) as the preferred protease inhibitor for use in pregnancy.[8–10] The present analysis provides some comparative information from an observational national study of pregnant women with HIV, based on more than 400 pregnancies exposed. The proportion of evaluable cases reflects the more common use and larger experience with lopinavir compared with the more recently introduced atazanavir.[4,13] Despite the limits of a non-randomized design, which are, however, common to studies and registries of HIV and pregnancy, this study adds new information that might be of interest. A reassuring finding is that the rates of all the main pregnancy outcomes were substantially similar for lopinavir

Table 4. Multivariable analysis of predictors of detectable (>50 copies/mL) HIV RNA in the third trimester

	AOR	AOR 95% CI	*P* value
Treatment group (reference = atazanavir)	0.85	0.35–2.10	0.730
Any interruption of atazanavir or lopinavir during pregnancy	**3.52**	**1.29–9.61**	**0.014**
CD4 cell count <200 cells/mm^3 at first trimester	**5.90**	**2.03–17.1**	**0.001**
HIV RNA viral load at first trimester (per additional log)	**2.00**	**1.43–2.80**	**<0.001**
Pregnancy week of start of antiretroviral treatment (per additional week)	1.01	0.95–1.08	0.637

AOR, adjusted OR.
Bold is used for *P* values <0.05.
The multivariable analysis was performed in order to adjust for significant differences between the two groups in potentially relevant predictors. Variables were selected for the model based on a significant (<0.05) *P* value in the univariate analyses of Table 1, causal relevance for the outcome and potential redundancy/overlapping (i.e. indication to ARV/CD4 count; treatment status at conception/pregnancy week of start of ARV).

and atazanavir. This is particularly relevant for pre-term delivery, non-elective Caesarean section and low birthweight, because such outcomes, and pre-term delivery in particular, are associated with significant neonatal morbidity.[14] An analysis of HIV transmission and neonatal mortality was not performed because both these outcomes represent infrequent events (<2%) that require very large samples for comparative analyses. Study data on birth defects for the subgroup of pregnancies with first-trimester exposure[12] (roughly half of the cases shown here) were consistent with reference data from the Antiretroviral Pregnancy Registry, which indicate for both drugs no major increase in rate of birth defects for first trimester exposure.[4]

In terms of virological efficacy, achieving an end-of-pregnancy undetectable viral load is a key objective of antiretroviral treatment in pregnancy, given the major role of HIV RNA plasma levels in determining HIV vertical transmission.[15,16] In this context, following adjustment for confounders (pregnancy week of start of treatment, first-trimester CD4 cell count, HIV RNA levels and drug interruptions during pregnancy), the two drugs were equally effective in determining an undetectable viral load at the end of pregnancy, suggesting comparable virological efficacy in pregnancy.

Atazanavir confirmed its role in inducing hyperbilirubinaemia; this occurrence was responsible for a significantly higher frequency of liver function test abnormalities in pregnancy, which, however, had no impact on continuation of atazanavir, further supporting the hypothesis that the clinical significance of atazanavir-induced hyperbilirubinaemia is generally limited.[17,18] Recent studies have also shown that this occurrence in pregnancy seems to have no adverse consequence in the newborn.[19]

It is as yet uncertain whether protease inhibitors further increase the risk of glucose metabolism abnormalities in pregnancy, because published studies were not always consistent, and cofactors such as ethnic origin and body mass index may play a confounding role.[20–25] Our study provides new comparative information, showing for atazanavir and lopinavir a similar impact on glucose metabolism. It is important to note that this conclusion is also based on fasting insulin and HOMA–IR data collected in a subgroup of women. It is also important to underline that the rate of glucose metabolism abnormalities observed was well below the rates observed in other studies based on populations with different demographic and clinical characteristics.[25] Finally, the identical weight gain in pregnancy with lopinavir or atazanavir is reassuring in terms of potential complications related to excessive weight gain.

Apart from hyperbilirubinaemia, the only significant metabolic difference between the two drugs was represented by a different impact on triglyceride and cholesterol levels, which were significantly lower with atazanavir. This indicates that the difference in lipid profile between the two drugs observed in clinical trials[26,27] is maintained also in the particular context of pregnancy, where lipid values are subject to a significant and progressive increase from the first to the third trimester, with remarkable rates of hypertriglyceridaemia and hypercholesterolaemia.[28] Although the clinical consequences of lipid changes in pregnancy may be limited, early hypertriglyceridaemia has been associated with subsequent occurrence of gestational diabetes and pre-eclampsia,[29,30] and might contribute to the development of fetal macrosomia.[31] Interestingly, in this respect we observed a higher proportion of large-by-gestational-age infants (>90th percentile) with lopinavir (10.0% versus 4.0%), but the difference with atazanavir was not statistically significant. Overall, atazanavir might represent a preferable choice in particular situations if there is an indication that suggests clinical benefits for maintaining lower levels of triglycerides and cholesterol during pregnancy.

In terms of strengths and limitations, our study has the advantage of providing new information on a particular population commonly excluded from clinical trials, with a sample size of more than 400 cases. We were also able to analyse an array of different measures that included maternal and infant outcomes, HIV-related parameters and metabolic indexes, allowing a broad evaluation of the profiles of the two drugs in pregnancy. The limitations of this study include a non-randomized attribution of treatment and a potential selection bias due to the exclusion of cases who switched to and from these two protease inhibitors in pregnancy. However, randomized studies are very difficult to perform in pregnancy, and the reason for switching during pregnancy may represent a combination of toxicity, confidence in older drugs and alignment with international HIV perinatal guidelines. Other study limitations include availability of some measures (insulin and HOMA–IR) only for a minority of cases and imbalance between the two groups for some characteristics, which was, however, corrected in a multivariable analysis. Finally, the sample size did not have enough statistical power to detect significant differences in more infrequent outcomes, such as delivery complications and large-by-gestational-age infants.

Overall, the study findings show that the two HIV protease inhibitors currently recommended by HIV perinatal guidelines appear to have similar safety and activity in pregnancy, likely representing equally valid alternative options. Physicians prescribing lopinavir or atazanavir to pregnant women should be aware of the different risks of hyperlipidaemia and hyperbilirubinaemia, respectively, for the two drugs, and evaluate their potential clinical implications.

Acknowledgements

We thank Cosimo Polizzi and Alessandra Mattei of the Istituto Superiore di Sanità in Rome, Italy, for providing technical secretarial assistance for this study. No compensation was paid for this assistance.

The Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy

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Funding

This work was supported by a public research grant (ref.: H85E08000200005) from the Italian Medicines Agency (AIFA).

Transparency declarations

None to declare. None of the authors has a commercial or other association, financial interest, activity, relationship or association that might pose a conflict of interest. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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