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Comparison of raltegravir-based regimens and three classical PI-based regimens during pregnancy

Jeanne Sibiude[1,2,3], Olivia Dialla[1], Roland Tubiana[4,5], Stéphane Blanche[6,7], Catherine Dollfus[8], Pierre Frange[6,7], Jérôme Le Chenadec[1], Laurent Mandelbrot[1,2,3], and Josiane Warszawski[1,9,10], for the ANRS CO1-French Perinatal Cohort Study

[1]CESP INSERM U1018, Le Kremlin-Bicêtre; [2]AP-HP Hôpital L. Mourier, Colombes; [3]Univ Paris-Diderot, Paris; [4]AP-HP Hôpital Pitié Salpétrière, Paris; [5]Univ Paris-Sorbonne, Paris; [6]AP-HP Hôpital Necker-Enfants Malades, Paris; [7]Univ Paris-Descartes, Paris; [8]AP-HP Hôpital Trousseau, Paris; [9]Univ Paris Sud, Le Kremlin-Bicêtre; [10]AP-HP Hôpital Bicêtre, le Kremlin-Bicêtre; FRANCE

anrs France REcherche Nord & sud Sida-hiv Hépatites — CESP - Inserm U1018
Inserm — Institut national de la santé et de la recherche médicale

EPF
INSERM CESP 1018 - Hôpital de Bicêtre AP-HP
82 rue du Général Leclerc
94276 LE KREMLIN BICETRE Cedex
Tél. : 33 1 49 59 53 05/10 Fax : 33 1 49 59 53 00

Corresponding authors:
J. Sibiude (jeanne.sibiude@aphp.fr)
J. Warszawski (josiane.warszawski@inserm.fr)

OBJECTIVE

To compare maternal and neonatal outcomes between 3 first-line PI-based recommended antiretroviral regimens (ART) in France, and raltegravir-based ART, among women already on treatment at conception.

PATIENTS AND METHODS

The National French Perinatal Cohort (EPF, ANRS CO1/CO11)

Prospective national cohort including all pregnant women with HIV and their children in 90 French centres since 1986.
CO1 component of cohort records detailed information during the pregnancy, including immuno-virological data ; CO11 is simplified and represents 1/3 of the cohort.

Study population:
Inclusion of all HIV-infected women receiving at conception **a 3-drug regimen containing lopinavir/r, atazanavir/r, darunavir/r or raltegravir** associated with 2 NRTIs (xTC+ ZDV, ABC or TDF), included in the cohort 2005-2015.

Statistical analysis: Maternal and neonatal outcomes were compared, in intent-to-treat, according to treatment group using logistic regressions adjusting for NRTIs, maternal age, and geographical origin.

Table 1 – Baseline characteristics according to ART group

Maternal baseline characteristics	Lopinavir/r N=1251 n	%	Atazanavir/r N=942 n	%	Darunavir/r N=541 n	%	Raltegravir N=103 n	%	p
Age (years)									
<25	80	**6.4**	38	**4.0**	30	**5.6**	6	**5.8**	0.03
25-34	709	**56.8**	495	**52.6**	288	**53.4**	53	**51.5**	
≥35	459	**36.8**	408	**43.4**	221	**41.0**	44	**42.7**	
Nulliparous	242	**20.6**	150	**16.2**	108	**20.0**	22	**21.6**	0.06
Geographical origin									
Metropolitan France	120	**9.7**	77	**8.2**	40	**7.5**	14	**13.6**	0.37
Sub-saharan Africa	927	**74.8**	727	**77.3**	411	**76.7**	75	**72.8**	
Other	192	**15.5**	136	**14.5**	85	**15.9**	14	**13.6**	
Years HIV-infected*									
<5	301	**36.2**	186	**28.0**	141	**37.1**	23	**33.3**	<0.01
5-9	358	**43.0**	282	**42.4**	144	**37.9**	23	**33.3**	
≥10	173	**20.8**	197	**29.6**	95	**25.0**	23	**33.3**	
CDC category C*	105	**12.8**	84	**13.0**	52	**14.1**	8	**11.9**	0.92

* Only available for CO1 component, N=1957

Fig 1 – Selection of study population

EPF Cohort (CO1/CO11) 2005-2015 N=11071
→ **ART at conception N=5678**
→ excluded: **NNRTI-based regimens** (N=1417); **NRTI-based regimens** (N=326)
→ N= 3935
→ excluded: **ART with < or > 3 molecules or 2 PIs** (N=413)
→ N=3522
→ excluded: **Other PI or InSTI** (N=407); **Non-boosted ATV** (N=156); **Atypical NTRI** (N=22)
→ **Study Population N=2837**
→ CO1 detailed component N= 1957 | CO11 simplified component N = 880

Fig 2 – Evolution of ART drug use 2005-2015

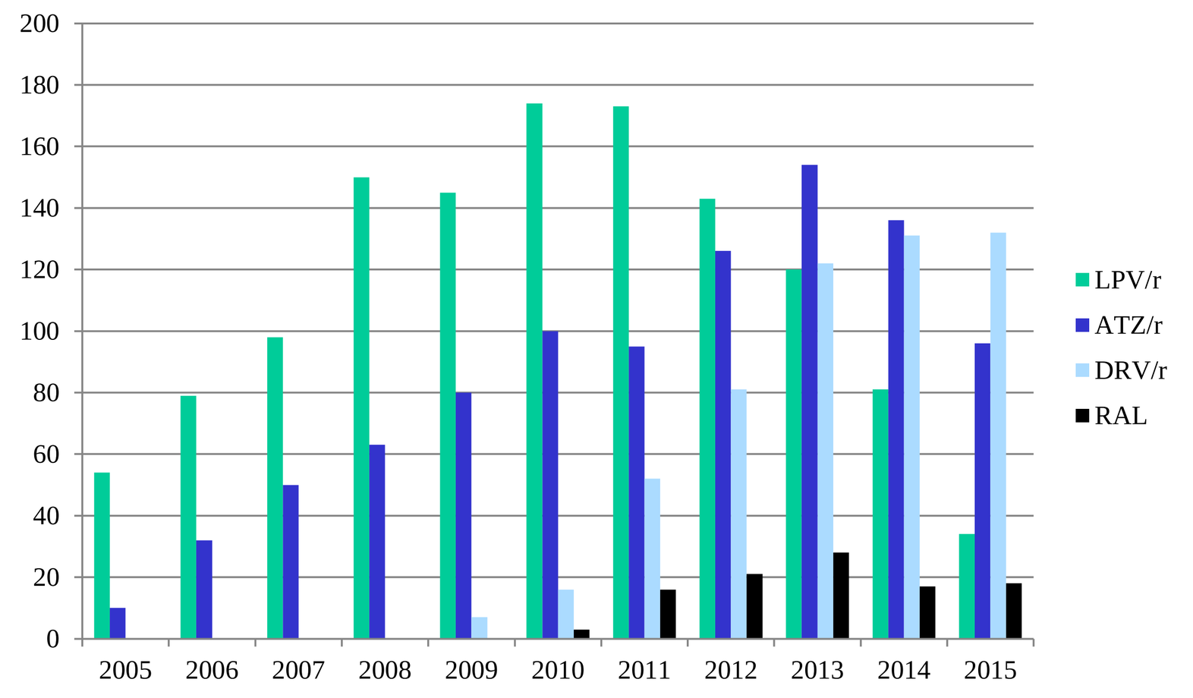

Fig 2a
Evolution of 3rd agent (numbers)

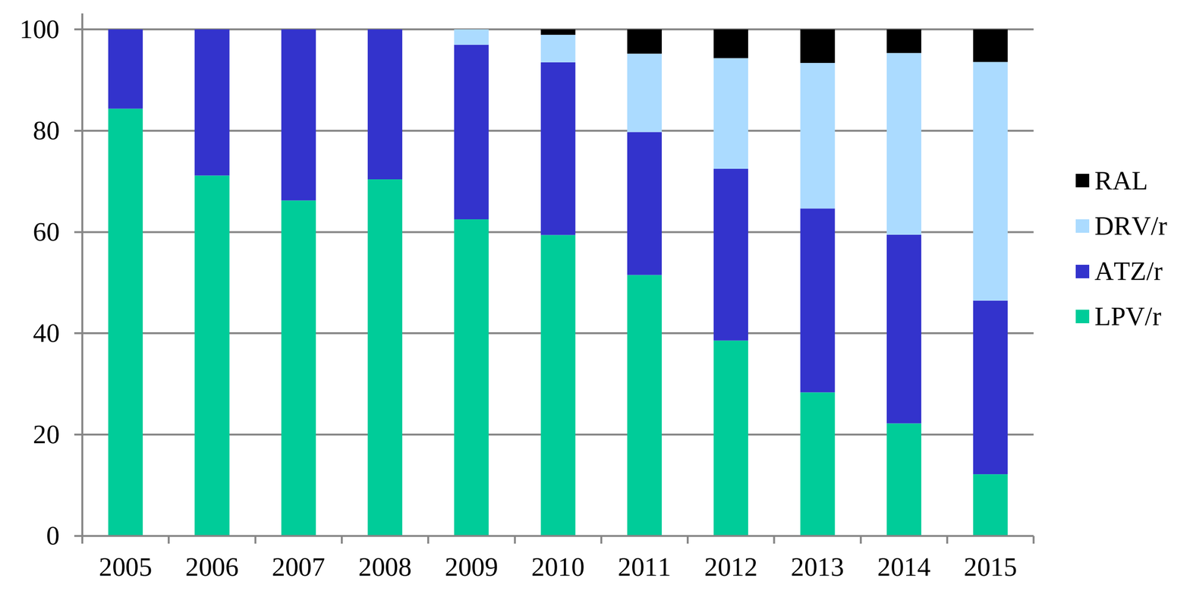

Fig 2b
Evolution of 3rd agent (proportions)

Table 2– Pregnancy outcomes according to ART group

Pregnancy outcomes	Lopinavir Ref group N=1251 %	Atazanavir N=942 %	AOR[a]	[95% CI]	Darunavir N=541 %	AOR[a]	[95% CI]	Raltegravir N=103 %	AOR[a]	[95% CI]	p
Hospitalization*	**30.2**	**28.7**	0.9	[0.7-1.1]	**29.5**	0.9	[0.7-1.2]	**22.7**	0.6	[0.3-1.2]	0.42
Preeclampsia*	**3.0**	**2.4**	0.9	[0.4-1.8]	**2.7**	1.0	[0.4-2.4]	**3.0**	1.1	[0.2-5.0]	0.97
Gestational Diabetes*	**8.1**	**12.1**	1.4	[0.98-2.1]	**7.1**	0.8	[0.5-1.4]	**13.6**	1.7	[0.8-3.7]	0.04
Preterm Birth	**15.9**	**13.4**	0.8	[0.6-1.1]	**14.4**	0.9	[0.7-1.2]	**10.7**	0.6	[0.3-1.2]	0.42

* Only available for CO1 component, N=1957

Table 3 – Immuno-virological characteristics and ART change

	Lopinavir Ref group N=1251 %	Atazanavir N=942 %	AOR[a]	[95% CI]	Darunavir N=541 %	AOR[a]	[95% CI]	Raltegravir N=103 %	AOR[a]	[95% CI]	p
At baseline*											
CD4 < 200/mm3	**8.8**	**6.3**	0.8	[0.5-1.2]	**10.6**	1.4	[0.9-2.2]	**1.5**	0.2	[0.02-1.2]	0.03
Viral Load > 50 c/mL	**25.0**	**19.5**	0.8	[0.6-1.0]	**22.1**	0.8	[0.6-1.1]	**15.9**	0.6	[0.3-1.1]	0.14
At delivery*											
CD4 < 200/mm3	**6.2**	**4.1**	0.7	[0.4-1.3]	**6.3**	1.1	[0.6-2.1]	**0.0**	NA		0.30
Viral Load > 50 c/mL	**11.4**	**9.8**	0.9	[0.6-1.3]	**14.5**	1.3	[0.8-2.0]	**4.7**	0.4	[0.1-1.3]	0.09
Change of ART during pregnancy	**19.5**	**29.4**	1.2	[0.96-1.5]	**18.5**	0.6	[0.5-0.8]	**44.7**	2.3	[1.5-3.6]	0.01

* Only available for CO1 component, N=1957

Table 4 – Neonatal outcomes according to ART group

Neonatal Outcomes	Lopinavir Ref group N=1251 %	Atazanavir N=942 %	AOR[a]	[95% CI]	Darunavir N=541 %	AOR[a]	[95% CI]	Raltegravir N=103 %	AOR[a]	[95% CI]	p
Birth Defect	**2.6**	**2.3**	0.9	[0.5-1.8]	**2.3**	0.9	[0.4-2.0]	**2.2**	1.0	[0.2-4.2]	0.98
Birthweight < 3rd centile	**5.4**	**4.9**	0.9	[0.6-1.4]	**4.8**	0.9	[0.5-1.5]	**1.1**	0.2	[0.1-1.4]	0.41
Birth length < 3rd centile	**5.5**	**5.3**	1.0	[0.6-1.6]	**5.4**	1.0	[0.6-1.8]	**4.7**	0.9	[0.3-2.5]	0.99
Head Circumference < 3rd centile	**2.7**	**3.4**	1.2	[0.6-2.1]	**3.8**	1.3	[0.7-2.7]	**3.5**	1.2	[0.4-4.3]	0.87
HIV infection	**0.2**	**0**	NA		**0.2**	NA		**0**	NA		NA

[a]adjusted on maternal age, geographical origin, and NRTIs

RESULTS

Since 2005, lopinavir/r as 3rd agent received at conception has decreased, and darunavir/r has increased representing 47% of our study population in 2015

Raltegravir-based regimens represent around 6% of ART received at conception

Pregnancy and neonatal outcomes did not differ significantly among treatment groups, although there was a trend toward more gestational diabetes for the raltegravir group. **Immuno-virological characteristics did not differ** significantly between groups.

Change in ART was more frequent in the raltegravir group, tended to be more frequent in the atazanavir/r group, and was less frequent in the darunavir/r group. Among 103 women on Raltegravir at conception, 66% were still receiving raltegravir at delivery. Power was > 80% to detect a 2-fold increase in hospitalization, gestational diabetes, and preterm birth when comparing darunavir and atazanavir to lopinavir

CONCLUSION

We found no significant difference in terms of safety between raltegravir, darunavir/r, atazanavir/r and lopinavir/r-based regimens in a population of women already treated at conception. Larger studies are necessary to evaluate short and long-term safety of raltegravir-based regimens in pregnancy.

ABSTRACT

Background : Antiretroviral therapy (ART) is recommended for all HIV-infected pregnant women as prevention of mother-to-child transmission. A large proportion of women now start pregnancy while already on ART, and more information is needed concerning tolerance of drugs received throughout pregnancy. We sought to compare 3 first-line recommended regimens in France (all of them including one ritonavir-boosted protease inhibitor and two NRTIs), and raltegravir-based ART which has become recently an option for pregnancy.
Methods: All HIV-infected pregnant women included in the national French Perinatal Cohort between 2005 and 2015, receiving at conception a 3-drug regimen containing lopinavir/r, atazanavir/r, darunavir/r or raltegravir associated with 2 NRTIs (xTC+ ZDV, ABC or TDF). Immuno-virological, pregnancy and neonatal outcomes were compared, in intent-to-treat, according to treatment group using univariable and multivariable logistic regressions adjusting for NRTIs, maternal age, and geographical origin.
Results : Among 5678 patients who were on ART at conception, 2837 women responded to selection criteria, among which 44% (N=1251) were receiving at conception a lopinavir-based regimen, 33% (N=942) atazanavir-based, 19% (N=541) a darunavir-based, and 4% (N=103) a raltegravir-based regimen. Change in ART during pregnancy was more frequent for atazanavir- and raltegravir- than for lopinavir-based regimens (AOR=1.2 [95%CI 0.96-1.5 and AOR=2.3 [1.5-3.6] respectively), but less frequent for darunavir-based regimens (AOR=0.6 [0.5-0.8]). In this population, only ‘4 children were HIV-infected. Immuno-virological outcomes, pregnancy and neonatal outcomes did not differ significantly among treatment groups. Power was > 80% to detect a 2-fold increase in hospitalization, gestational diabetes, and preterm birth when comparing darunavir and atazanavir to lopinavir.
Conclusion : Efficacy and tolerance during pregnancy were similar across the 3 groups of PI-based and raltegravir-based regimens. Notably, more recent drugs such as darunavir and raltegravir do not seem to be less safe than lopinavir and atazanavir which have been more largely described in pregnancy. Long term safety for children remains unknown.

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