Risk of birth defects and perinatal outcomes in HIV-infected women exposed to integrase strand inhibitors during pregnancy

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Running head: INSTI exposure and risk of birth defects

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Word count : 2804

Abstract

Objectives. Following an alert on neural tube defects and dolutegravir, we sought to evaluate if the exposure integrase strand transfer inhibitors (INSTIs) at conception was associated with birth defects or other adverse pregnancy outcomes.

Methods : In the prospective national French Perinatal Cohort (EPF), we studied birth defects and other perinatal outcomes by matching each pregnant woman exposed to INSTIs with a pregnant woman exposed to darunavir/ritonavir receiving the same backbone of nucleoside reverse transcriptase inhibitors and matched for other characteristics such as age, geographic origin, center and year of delivery.

Results : Among 808 women exposed to INSTIs during pregnancy (raltegravir=703, dolutegravir=57 and elvitegravir=48), we reported a slightly higher rate of birth defects in infants exposed at conception to raltegravir (6.7%) vs infants exposed to raltegravir later in pregnancy: 2.9% if initiated during pregnancy as first-line, and 2.5% as second-line treatment, p=0.04. When compared to matched controls, raltegravir exposure at conception was not significantly associated with birth defects: 6.4% vs 2.3%, p=0.08. There was no cluster of birth defect type and no neural tube defects were observed. Other perinatal outcomes, such as preterm birth and stillbirths, did not differ significantly between raltegravir-exposed women and matched counterparts. No difference in any outcome was observed for elvitegravir/cobicistat or dolutegravir.

Conclusion : We found a non-significant trend for an association between exposure to raltegravir at conception and birth defects which needs to be evaluated by larger prospective surveillance data, as these drugs are increasingly prescribed in women living with HIV.

Introduction

In women living with HIV, the wide use of antiretroviral therapy (ART) has led to a spectacular decrease in the rate of mother-to-child transmission, from about 20% to less than 1% currently in high-income countries and less than 5% in low to middle-income countries [1–3]. Many women are now taking ART before the occurrence of pregnancy and are thus exposed to ART from conception. Concern has been raised about the potential toxicity of these drugs on fetal development, and the risk of birth defects associated with ART has been regularly evaluated in cohorts and registries [4,5].

An association between dolutegravir, an integrase strand transfer inhibitor (INSTI), administered from the time of conception and neural tube defects [6,7] was observed in a prospective cohort in Botswana. Nonetheless, INSTIs are widely used because of their high antiretroviral potency, low resistance, and good tolerance profile. Dolutegravir is now recommended by the World Health Organization (WHO) as first-line treatment in countries implementing option B+ (lifelong treatment for all pregnant women diagnosed with HIV infection). WHO concluded that the benefit/risk was favorable in comparison with the previous standard efavirenz-based treatment, while stating that reproductive-age women prescribed dolutegravir should receive information on the malformation risk and also be informed about efficient contraception [8]. In contrast, guidelines in most high-resource countries are to consider other options for women wishing to be pregnant [9].

Raltegravir-based regimens are among these options and are progressively replacing non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens and protease inhibitors (PI)-based regimens in high-resource countries. In France, the use of INSTIs has regularly increased since 2008, with raltegravir being the most used of the drugs in this class during pregnancy. No signal for birth defects or adverse pregnancy outcomes have been reported in humans yet but the data are scarce and an increase in supernumerary ribs had been described in rats [10–12]. Thus, following the alert on dolutegravir, questions have been raised on a potential class effect for INSTIs.

We sought to evaluate if the exposure to raltegravir and other INSTIs at conception was associated with birth defects or other adverse pregnancy outcomes.

Methods

In the large national prospective French Perinatal Cohort (EPF) (Agence Nationale de Recherche sur le Sida et les Hepatites [ANRS] CO1/CO11), we compared birth defects and other perinatal outcomes according to the timing of exposure to INSTI during the pregnancy. We also matched each mother-infant pair exposed to INSTI with a mother-infant pair exposed to darunavir/ritonavir receiving the same backbone of nucleoside reverse transcriptase inhibitors and matched for other characteristics detailed below.

The French Perinatal Cohort, Enquête Périnatale Française (EPF)

EPF (ANRS CO1/CO11**)** is a national multicenter cohort, prospectively enrolling pregnant HIV-infected women delivering in 90 centers throughout France [1]. No specific recommendations are made for women included in the cohort, but clinicians are encouraged to follow the most recent French national guidelines. These recommendations include prenatal ultrasound at each trimester of pregnancy and pediatric clinical examinations at birth, 1, 3, 6, 12 and 18-24 months [9]. Standardized questionnaires were filled out by clinicians, after delivery for pregnancy, and at each visit for children. Variables collected are described below. The EPF coverage is estimated to be around 70% of HIV-infected women in metropolitan France. In each participating maternity around 95% of pregnant women living with HIV are included, with informed consent. The study was approved by the Hôpital Cochin IRB and the French computer database watchdog commission (Comission Nationale Informatique et Libertés).

Study population

Integrase Strand Transfer Inhibitors-exposed mother-infant pairs. All ART combinations administered during pregnancy were recorded with the dates when started and stopped. We included all pregnant women who received an INSTI-based ART during pregnancy between January 2008 (first prescription of an INSTI in the cohort) and December 2017 and for whom pregnancy outcome was available. Terminations of pregnancy (TOP) for fetal abnormalities and stillbirths were included in the analysis. We classified mother-infant pairs in three groups: (Group 1) ongoing INSTI-based ART at conception; (Group 2) not receiving any ART at conception, and initiating an INSTI-based treatment during pregnancy; and (Group 3) starting with another ART-combination and switching to an INSTI-based treatment during pregnancy, whatever the timing of initiation of the first ART.

Matched mother-infant pairs. Each INSTI–exposed mother infant pair was matched 1:1 with an INSTI-unexposed mother-infant pair according to the type of associated ART drugs in the combination (ART backbone), age (< 35years vs ≥ 35 years), geographic origin, center, year of delivery, gestational age at ART-initiation, and number of fetuses (singleton vs twins). INSTI-exposed women who did not receive PI or NNRTI were matched to women who received darunavir/ritonavir, with the same other drugs, as this is currently the first-line recommended regimen and has not yet been associated with birth defects [9]. For example, a woman receiving a combination of raltegravir/tenofovir/emtricitabine was matched with a woman receiving a combination of darunavir/ritonavir/tenofovir/emtricitabine; a woman receiving both an INSTI and a PI as in this regimen: raltegravir/darunavir/ritonavir/abacavir/emtricitabine was matched with a woman receiving darunavir/ritonavir/abacavir/emtricitabine. Women in INSTI-exposed group 3 were matched according to timing of first ART (trimester of pregnancy). In case of twins, the first-born twin was retained for analysis, we also conducted a sensitivity analysis for birth defect considering the outcome if at least one of the twins was affected. This analysis did not change the numbers.

Variables.

Birth defects. All clinical events in infants were recorded at each visit (at birth, and at 1, 3, 6, 12 and 18-24 months). We first coded the birth defects with the International Classification of Diseases (ICD) 10 codes. We then used EUROCAT inclusion criteria and guidelines in order to assess the overall prevalence of abnormalities and to classify them in different organ systems [13,14]. When comparing the overall rates of birth defect, each child was only counted once, even if several defects were present. Clusters of defects were studied by comparing the rates of birth defects by organ system.

Perinatal outcomes. Other perinatal outcomes studied included: stillbirths; preterm birth, defined as gestational age < 37 weeks' gestation (WG); small for gestational age (SGA) as birthweight < 3rd centile, length and head circumference at birth < 3rd centile according to French references [15].

Maternal variables included age, geographic origin (France, sub-Saharan Africa, other), parity, timing of HIV diagnosis (number of years since diagnosis), viral load and CD4 count

at delivery. Neonatal variables used for analysis included gender, gestational age, birthweight and HIV infection status.

Statistical analysis

Maternal characteristics and perinatal outcomes were compared between the 3 groups of exposure with Chi 2 tests. Associations between birth defect and group of exposure was then studied with univariate and multivariate logistic regression, adjusting on potential confounders.

In the matched analysis, the prevalence of birth defects and other perinatal outcomes was compared between INSTI exposed mother-infant pairs and matched unexposed pairs, according to specific INSTI drugs (raltegravir, dolutegravir, or elvitegravir/cobicistat) and by grouping all INSTI-based ART together. For the comparison of outcomes according to matched pairs, Mc Nemar tests were used whenever the discordant pairs were $\geq$ 10, allowing the use of this test.

A two-sided $P < 0.05$ was taken as indicating statistical significance. Data were analyzed using Stata 14.0 software (Stata Corp., College Station, Texas, USA)[16].

Results

Between 2008 and 2017, we identified 808 women exposed to INSTI-based ART during pregnancy. Among these, 37% (N=301) were exposed at conception, 23% (N=183) started INSTI-based ART during pregnancy as first-line ART, and 40% (N=324) switched during pregnancy from a non-INSTI-based ART to a INSTI-based ART. Raltegravir was most often received (N=703), followed by dolutegravir (N=57) and elvitegravir (N=48).

Characteristics of patients differed significantly among the three groups of timing of INSTI exposure (Table 1). Women receiving INSTI at conception were older, more often from metropolitan France, and over 40% were living with HIV for over 10 years. They had a lower viral load and a higher CD4 count at delivery than the two other groups ($p<0.01$ for all differences).

Perinatal outcomes did not differ significantly among the three groups (Table 2a), however, when restricting to raltegravir, there was a slightly higher rate of birth defects in infants exposed at conception vs infants exposed later in pregnancy (6.7% vs 2.9% and 2.5%

respectively, p=0.04, Table 2b). The OR for raltegravir exposure at conception vs started as first-line ART during pregnancy was 2.4 [95%CI 0.8-6.7, p=0.09]. After adjusting on maternal age, ethnic origin and multiple pregnancy, the magnitude of the effect was decreased: aOR = 1.6 [95%CI 0.5-4.8], p=0.37.

When compared to matched controls, INSTI exposure at conception was not significantly associated with a higher risk of birth defects (5.7% vs 2.9, p=0.13, Table 3a). When restricting to raltegravir exposure, there was a trend towards more birth defects, but it did not reach significance: 6.4% vs 2.3%, p=0.08 (Table 3b). There was no cluster of birth defect type among raltegravir-exposed children and no neural tube defects were observed in this population (Table 4). In order to evaluate the potential role of other drugs and to allow comparison with the literature, we described NRTI-backbone-exposure: in the group exposed to raltegravir at conception, and their matched counterparts: the backbone included zidovudine in 10 cases (6%). Most NRTI-backbones included tenofovir disoproxil fumarate (102 cases, 60%).

Other perinatal outcomes, such as preterm birth and stillbirths, did not differ significantly between INSTI-exposed women and their darunavir-exposed matched counterparts, or when restricting the comparison to raltegravir-exposed women, whatever the timing of ART initiation (Table 3a and b). Among stillbirths, two were associated with birth defects : one complex heart defect (exposed to darunavir at conception) and one trisomy 18 (exposed to raltegravir at conception). Other stillbirths were unexplained according to the database.

Preterm birth and stillbirth rates were not different when comparing dolutegravir or elvitegravir-exposed women to matched INSTI unexposed women (data not shown).
A small number of women could not be matched exactly (N=55 Group1, N=58 Group 2, and N = 19 Group 3). Outcomes did not differ between INSTI-exposed mother-infant pairs that could be matched and those that could not be matched.

Discussion

The incidence of birth defects was not significantly higher in pregnancies with exposure to INSTI at conception, in comparison with darunavir-exposed pregnancies. We did actually observe a higher rate of birth defects in children exposed to raltegravir at conception when compared to later exposure to raltegravir (p=0.04) and a trend when compared to the

darunavir-exposed matched controls (p=0.08). However, due to the small number of women and children included, the absence of significant difference may be due to insufficient statistical power. The number of pregnancies with exposure to dolutegravir as well as to elvitegravir was small, in accordance with French perinatal guidelines, which were to avoid their use in pregnancy.

However, the absence of cluster of malformation by organ and the absence of neural tube defects is reassuring, pleading against a causal class effect. Our study is the first to compare raltegravir-exposed women with matched controls receiving the same NRTIs at the same moment of pregnancy, differing thus only by the raltegravir exposure. The absence of increased birth defects is consistent with published data from the United Kingdom, from a comprehensive prospective cohort, with comparable numbers [10], that compared birth defect rates among women exposed at conception (2.25%) to those exposed later in pregnancy (2.8%). As in our study, birth defects reported were mostly heart or limb abnormalities. Other data on birth defects and raltegravir are from non-comprehensive reports, where reporting of pregnancy may be done individually on a voluntary basis and thus not systematically, assembling various databases and data collection. The largest to date has described no increase in the risk of neural tube defects among 456 women exposed at conception but unlike our study, other birth defects were not reported [17]. Finally, a study using the French National Health system database also did not find significant differences in birth defect rates [18]. However, the diagnoses were extracted only from coding at birth, which is propitious to underreporting. Indeed only 3 birth defects (1.3%) were reported among raltegravir-exposed women, which excluded all diagnoses made after discharge. In contrast, in our study, children were followed by pediatricians until the age of 2 years, which made accurate and comprehensive diagnoses of birth defects possible.

The birth defect rate among women exposed to darunavir at conception was 2.9% which is lower than the rate we reported previously in EPF (4.4%) [5]. However, in that previous study, most women were exposed to zidovudine containing combinations, found to be associated with congenital defects. Overtime the zidovudine backbone has been progressively replaced by tenofovir. In the present study, most women were exposed to tenofovir at conception, rather than zidovudine, and the birth defect rate we report here is close to the rate of 3.6% that was reported in women exposed to tenofovir in the first trimester in our previous study. The results are thus consistent in terms of birth defect rates.

Regarding preterm delivery, there was no difference in our population between raltegravir-exposed women and matched women, whatever the timing of initiation of ART. We expected a possible inferior rate of preterm birth in raltegravir-exposed vs darunavir-exposed pregnancies, because boosted-PIs have been shown to be associated with preterm birth [19–21]. However, all studies that showed a difference between PI-based ART and other regimens were comparing lopinavir-based ART to either NRTI monotherapy [21] or 3 NRTIs [20], or non-boosted PIs [19]. It is possible that darunavir might be less associated with preterm birth than lopinavir in a specific drug-effect. The preterm birth rate in women starting raltegravir or darunavir during pregnancy (12.8% and 11.2% respectively) was lower than the rate reported among women starting lopinavir during pregnancy in our earlier publication on PI-containing ART regimen started during pregnancy (14.4%) [19]. This rate remains higher than the preterm birth rate in the French general population which is 7% [22], but this may be due to other non-measured factors particular to the population of women living with HIV and not solely to ART. There is no published data to date on the risk of preterm birth associated with raltegravir.

We found no difference in stillbirth rates nor in birth weight, length or head circumference according to INSTI exposure, which is reassuring.

Our study presents many strengths. It is the first to match INSTI-exposed pregnancies according to co-exposure to other antiretroviral drugs and timing of ART initiation, as well as other factors potentially associated with birth defects, such as geographic origin and twins. Most studies compare women exposed at conception to women exposed later but we showed that these groups differ with many characteristics that may be confounding factors. Women on raltegravir at conception usually received this treatment before the wish to be pregnant was known, and then it was decided not to switch an effective treatment during pregnancy; whereas women for whom raltegravir was prescribed during pregnancy were generally either late-presenters or women for whom the first ART was ineffective, as shown by the high rate of detectable viral-load in these two groups. We also matched according to center and year of delivery to eliminate possible biases related to local differences in diagnosis of malformations or a time-effect. It is a prospective study with high quality data collection filled out by the clinicians. Our data is comprehensive with over 95% inclusion in the participating centers. The major limitation is the small number of INSTI-exposed pregnancies, in accordance with French national guidelines that favor PI-based therapy for women wishing to become pregnant, thus limiting the power of our analyses. This highlights the importance on

maintaining an active research on the possible side effects of any ART given during pregnancy and especially those that have a high placental transfer ratio such as INSTIs [23,24]. Another limitation is that we cannot exclude possible confounding factors that may have not been taken into account, such as viral load and CD4 count at conception, or pre-existing conditions and concurrent drugs potentially associated to birth defects as these were not available in our study.

In conclusion, in our study we were not able to find a significant difference in the risk of birth defect between women exposed to raltegravir at conception and women matched on ART backbone, and factors that could be associated with birth defects, but this may be due to limited power. There was no cluster of birth defects and no neural tube defects. No other signal was observed for stillbirth, preterm birth or neonatal measurements. French current guidelines state that raltegravir is a possible alternate treatment when the first-intention treatment, which is PI-based ART, is not suitable. However, these guidelines also state that the data on raltegravir and pregnancy is mostly on late-pregnancy prescription and that the quality of the data available is limited. Our results need to be re-evaluated by larger prospective surveillance data, as these drugs are increasingly prescribed in women living with HIV.

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Tables.

Table 1: Maternal characteristics according to timing of INSTI-based ART - French Perinatal Cohort ANRS EPF CO1/CO11- 2008-2017

Maternal Characteristics	**INSTI at conception (Group 1)** N=301		**INSTI as 1st line during pregnancy (Group 2)** N=183		**INSTI as 2nd line during pregnancy (Group 3)** N=324		
	n	%	n	%	n	%	p[a]
Age (years)							
<25	21	7.0	33	18.0	32	9.9	<0.01
25-34	156	52.0	114	62.3	195	60.2	
>35	123	41.0	36	19.7	97	29.9	
Geographical origin							
Metropolitan France	50	16.6	11	6.0	18	5.3	<0.01
Sub-saharan Africa	198	65.8	133	72.7	242	75.6	
Other	53	17.6	39	21.3	60	18.8	
Nulliparous (vs parous)	79	26.3	45	25.1	66	20.6	0.21
HIV diagnosis during the current pregnancy[b]	0	0.0	75	41.9	251	77.9	<0.01
Living with HIV > 10 years (vs ≤ 10y)	76	40.4	8	8.6	52	23.1	<0.01
Viral load at delivery > 50 cp/mL (vs ≤ 50 cp/mL)	28	11.0	61	35.9	105	34.7	<0.01
CD4 at delivery < 200/µL (vs ≥ 200/µmL)	9	4.3	24	16.3	38	14.0	<0.01

[a:] Chi2 test ; [b]Only available for ~~CO1 component~~2/3 of women included. N=506. Missing data was < 1% for all variables except viral load at delivery (9%) and CD4 count at delivery (22%).

Table 2: Perinatal outcomes according to timing of INSTI-based ART. French Perinatal Cohort ANRS EPF CO1/CO11- 2008-2017

Perinatal outcomes	**INSTI at conception (Group 1)** N=301		**INSTI as 1st line during pregnancy (Group 2)** N=183		**INSTI as 2nd line during pregnancy (Group 3)** N=324		
	n	%	n	%	n	%	p[a]
Birth defect	18	5.8	5	2.7	9	2.7	0.09
Stillbirth	7	2.3	2	1.1	1	0.3	0.06
Preterm Birth	50	16.8	22	12.1	47	14.6	0.36
Birthweight < 3rd centile[b]	9	3.0	6	3.4	20	6.2	0.13
Length < 3rd centile[b]	12	4.4	9	5.5	14	4.5	0.86
Head circumference <3rd centile[b]	8	2.9	8	4.8	11	3.5	0.56

[a:] Chi2 test or Fisher exact test as appropriate [b:] Outcomes for children are reported to number of children exposed (G1, n= 312, G2, n = 184, G3, n = 333)

Table 2b : Perinatal outcomes according to timing of raltegravir-based ART ANRS EPF CO1/CO11- 2008-2017

Perinatal outcomes	**raltegravir at conception (Group 1)** N=218		**raltegravir as 1st line during pregnancy (Group 2)** N=170		**raltegravir as 2nd line during pregnancy (Group 3)** N=309		
	n	%	n	%	n	%	p[a]
Birth defect	15	6.7	5	2.9	8	2.5	0.04
Stillbirths	4	1.8	2	1.2	1	0.3	0.20
Preterm Birth	36	16.7	19	11.2	43	14.0	0.32
Birthweight < 3rd centile [b]	8	3.7	6	3.7	19	6.2	0.33
Length < 3rd centile [b]	9	4.5	9	5.9	13	4.4	0.76
Head circumference <3rd centile [b]	6	3.0	7	4.5	10	3.3	0.71

[a:] Chi2 test or Fisher exact test as appropriate [b:] Outcomes for children are reported to number of children exposed (G1, n= 224, G2, n = 171, G3, n = 318)

Table 3a : Comparison of perinatal outcomes between INSTI-exposed and -unexposed matched mother-infant pairs.
French Perinatal Cohort ANRS EPF CO1/CO11- 2008-2017

Perinatal outcomes	**INSTI-exposed** matched		**INSTI-unexposed** m~~M~~atched[a]		
	n	%	n	%	~~p~~[a]p[b]
	Exposed at conception (Group 1)				
	N=246		N=246		
Birth defect	14	5.7	7	2.9	0.13
Stillbirth	6	2.4	6	2.4	1.0
Preterm birth	41	16.8	39	16.1	0.71
	Unexposed to any ART at conception. INSTI as 1st line during pregnancy (Group 2)				
	N=125		N=125		
Birth defect	4	3.2	10	8.0	0.12
Stillbirth	2	1.6	1	0.8	~~0.57~~NA
Preterm birth	16	12.8	14	11.2	0.70
	INSTI as 2nd line during pregnancy (Group 3)				
	N=305		N=305		
Birth defect	8	2.6	14	4.6	0.21
Stillbirth	0	0.0	0	0.0	~~1.0~~NA
Preterm birth	45	14.8	41	13.5	0.63

Mis en forme : Exposant

Table 3b : Comparison of perinatal outcomes between raltegravir-exposed and -unexposed matched mother-infant pairs.
French Perinatal Cohort ANRS EPF CO1/CO11- 2008-2017

Perinatal outcomes	**raltegravir-exposed** matched		**raltegravir-unexposed** matched[a]		
	n	%	n	%	p[b]
	Exposed at conception (Group 1)				
	N=171		N=171		
Birth defect	11	6.4	4	2.3	0.08
Stillbirth	4	2.3	4	2.3	1
Preterm birth	28	16.5	25	14.9	0.66
	Unexposed to any ART at conception. INSTI as 1st line during pregnancy (Group 2)				
	N=114		N=114		
Birth defect	4	3.5	9	7.9	0.18
Stillbirth	2	1.8	1	0.9	0.56
Preterm birth	14	12.3	12	10.5	0.68
	INSTI as 2nd line during pregnancy (Group 3)				
	N=290		N=290		
Birth defect	7	2.4	14	4.8	0.13
Stillbirth	0	0.0	0	0.0	
Preterm birth	41	14.2	39	13.5	0.80

Exposure numbers differ between Tables 2 and Tables 3 because of the small number of women who could not be matched (G1,n=55, G2, n=58, and G3, n = 19). Outcomes did not differ between INSTI-exposed mother-infant pairs that could be matched and those that could not be matched.
a : matched mother-infant pairs were exposed to darunavir/ritonavir-based ART b: p-value for McNemar test.

Mis en forme : Exposant

Table 4 Birth defects among infants exposed to raltegravir at conception and matched infants exposed to darunavir at conception

Children exposed to raltegravir at conception, N= 218		Matched children exposed to darunavir at conception, N= 171	
Birth defect	n	Birth defect	n
Chromosomal abnormalities (T21 N=1, T18 N=2)	3	Hydronephrosis	1
Polydactyly	3+1*	Polydactyly	2
Patent ductus arteriosus in children born ≥37 WG	2	Complex congenital heart defect	1
Anomalous pulmonary venous drainage*	1		
Coarctation of the aorta*	1		
Corpus callosum agenesis	1		
VACTERL syndrome	1		
Hip dislocation*	1		
Posterior urethral valves	1		
Total birth defects	**15**	**Total birth defects**	**4**

* birth defects in children who could not be matched to darunavir-exposed children. T21: trisomy 21; T18 : Trisomy 18. No child presented with several defects other than those for whom chromosomal abnormalities of VACTERL syndrome were diagnosed. Each child is thus counted only once in this table.