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TITLE PAGE (120 characters)

Does changing antiretroviral therapy in the first trimester for pregnancy-related concerns have an impact on viral suppression ?

Short Title (40 characters): Changing ART in pregnancy and viral suppression

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ABSTRACT

Objective: To determine whether changing antiretroviral therapy during pregnancy as a medical strategy because of concern about fetal risks led to poorer virological outcomes.

Methods: All pregnancies in women with HIV1 enrolled in the national multicenter prospective French Perinatal cohort (EPF) were included between 01/2005 and 12/2015, at 14 gestational weeks or more and if the mother was on antiretroviral therapy (ART) at conception with a plasma viral load < 50 copies/ml. The reasons for a change in the antiretroviral regimen were analyzed according to treatment guidelines, and defined as for medical strategy in the absence of reported maternal intolerance. Virological and pregnancy outcomes were studied by survival analysis and by logistic regression adjusted for a propensity score established for each patient according to baseline characteristics.

Results: Of 10553 pregnancies in the cohort, 1797 were with with antiretroviral therapy at conception and a documented viral load <50 copies/mL before 14 weeks' gestation. Of these, 411 had a treatment change in the first trimester as medical strategy to follow treatment guidelines. The proportion of change was statistically higher when initial treatment was clearly contraindicated (OR adjusted: 23.1 [14.0-38.2]) or was regarded as an alternative option (ORa: 2.2 [1.3-3.7]), as compared to recommended first-line regimens. Treatment changes for medical strategy did not lead to poorer virological control, compared to pregnancies without such changes (19.3% vs. 15.6%, HRa: 1.0 [0.7-1.4]).

Conclusions: Changing antiretroviral therapy early in pregnancy with the goal of improving fetal and pregnancy outcomes did not appear to have a destabilizing effect on viral suppression.

KEYWORDS

HIV, pregnancy, antiretroviral therapy, preconception care, treatment switch, guidelines, viral suppression.

INTRODUCTION

One of the important benefits of antiretroviral therapy is to prevent perinatal transmission (1–10), virtually to zero in the case of treatment throughout the pregnancy with an undetectable maternal viral load (11). Since recommendations for antiretroviral therapy have been extended to all people with HIV infection (6), an increasing proportion of women are already on antiretroviral treatment at the time of conception, rising from 32% in 2005 to 69% in 2015 in France (ANRS-EPF cohort, unpublished). As the transmission rate declines, safety issues are of crucial importance to decide which antiretrovirals to use in pregnancy. A variety of adverse events have been reported to be related to antiretroviral exposure during pregnancy, regarding the fetus and future infant, the woman herself and also pregnancy outcomes (12–19).

There is large consensus to re-evaluate ART, as for all therapies, when women become or plan to become pregnant. The recommendations on what medications to use change over time according to available data (2–7). The main indications for changing the regimen are poor tolerance or insufficient viral suppression. Many guidelines (7) recognize pregnancy as one of the potential indications for changing an effective ART regimen. However, expert panels diverge about how to take into account the pregnancy-specific safety issues, for several reasons. First, there is debate over the actual risks, in particular for fetal malformations related to use of efavirenz (16,20). Second, there is debate as to whether recent medications should be avoided in pregnancy as long as safety data is lacking. Third, there is concern that switching to a first-line ART may destabilize the woman and lead to an increase in viral load, which is the main risk factor for perinatal transmission (21). In France, as in many other countries, boosted protease inhibitors (PI) associated with two nucleoside reverse transcriptase inhibitors (NRTIs) have been the first-line therapies for pregnant women for two decades, whereas WHO guidelines favor efavirenz with two NRTIs (22). French guidelines suggest that even in case of virological efficacy, consideration should be given to changing an ART in case of concern about potential pregnancy-related risks. In many other countries, it is recommended not to change an effective treatment during pregnancy (23,24),

The objectives of our study were to analyze the factors related to changes in ART in pregnant women under effective therapy at the time of conception and their potential impact on viral load and pregnancy outcomes

METHODS

The French Perinatal Cohort (ANRS EPF CO1/CO11)

The French Perinatal Cohort (ANRS EPF CO1/CO11) is an ongoing since 1985, prospective, observational study involving 90 perinatal centers throughout France (8) and which includes 95% of pregnancies in women with HIV-1 and/or HIV-2 with their informed consent and ethics committee (Comité de Protection des Personnes) approval. Clinicians complete clinical and biological case report forms at the end of pregnancy for maternal and obstetrical data, and pediatric follow-up until the child reaches the age of 2 if not infected or up to 18 years of age if HIV-infected. EPF coverage is estimated at 70% of pregnancies of HIV-positive women in France. More detailed data are collected in the CO1 component performed in selected study sites.

Study population

For the current analysis, we included all pregnancies in EPF, for which the pregnancy outcome occurred at 14 weeks gestation or more, from 01/01/2005 to 31/12/2015. We selected only women who were already on antiretroviral therapy at the time of conception and had a viral load available before 14 WG which was < 50 copies/ml.. Women with HIV type 2, for whom the recommendations are different, were excluded (N = 188).

Exposure

All treatment regimens were collected with the initiation and end dates for each drug. We defined a treatment switch as the change of at least one molecule, ie, the addition, modification or deletion of a molecule in the combination of treatments present at conception. Changes in dose, as well as treatment interruptions, were not considered as switches. The reasons for treatment change were collected and categorized as : poor tolerance, inefficacy/poor compliance or medical strategy in order to comply with treatment guidelines. When several reasons were recorded, the main indication was hierarchically from inefficacy, then to poor tolerance and finally change for medical strategy. The current guidelines for each pregnancy were considered with a margin of 1 year between the date of their publication and the delivery date. Thus, we studied the guideline periods 2005-2006, 2007-2008, 2009-2010, 2011-2013, 2014-2015. The type of treatment at conception was classified into three categories: Indicated as first-line, Alternative or Not Recommended (NR), according to the French national guidelines at

the time of the pregnancy (2–7). In the category of “NR” treatments we included both contraindicated treatments and those with insufficient data in pregnancy to recommend. This classification was made considering for each treatment regimen the individual drugs and their combinations (**Table A- Supplemental data**). Efavirenz was not recommended throughout the study period, as were the other NNRTIs, except for nevirapine started before conception. The integrase inhibitors (raltegravir, dolutegravir) were all in the Not Recommended group until the most recent guidelines. For NRTIs, tenofovir was in the Insufficient Data group until 2011, and throughout the study period it was recommended not to use solely NRTI’s, whether monotherapy, double therapy or a triple NRTI regimen.

We also studied treatment changes after the first trimester, whether or not the ART regimen was switched in the first trimester.

Outcomes

We studied characteristics potentially associated with treatment change, ie. sociodemographic and behavioral characteristics of the mother, clinical and obstetrical factors, HIV infection characteristics and the antiretroviral therapy history.

We studied outcomes following switches in the first trimester of pregnancy (<14 weeks gestation). The main outcome studied was maternal viral load nearest to the time of delivery and also during the pregnancy in order to study the first occurrence of a value above a cut-off of 50 copies /mL (25). Pregnancy outcomes studied were the mode of delivery, preterm delivery (<37 weeks gestation), intrapartum AZT infusion, and adverse outcomes defined as neonatal deaths, medical terminations of pregnancy (TOP), in utero fetal deaths (IUD), mid-trimester abortions. Infant outcomes studied were HIV transmission and mortality at 1 year.

Statistical analysis

We first described the evolution of the percentage of early treatment changes according to the periods (EPF CO1/CO11, N=4983) and then according to the treatment recommendation and the treatment change indications (EPF CO1, N=3574). Percentage comparisons were performed using Chi2 tests.

Then, the main analysis was restricted to first-trimester changes for medical strategy concerns in patients with viral suppression, after exclusion of changes for intolerance

(N= 22) and inefficacy (N=23) (EPF CO1, N=1780). We examined the factors potentially associated with a change in treatment before 14 weeks' gestation. For this, we carried out Chi2 or Fisher tests and logistic regressions. Multivariate models were developed by including the uncollinear variables found associated with univariate $p < 20\%$ after looking for potential interactions. A propensity score was calculated, defined by the probability of early change for medical strategy as a function of the initial characteristics, estimated by the final logistic regression model. Verification steps (analysis of the standardized differences and the disappearance of the association between each variable independently with the change after adjustment on this score (26)) were carried out to verify the good performance of the propensity score.

Finally, we studied the association between these early changes for medical strategy and virological control, complications of pregnancy and neonatal outcomes. For this purpose, we performed univariate and multivariate analysis, using logistic regressions for delivery outcomes or Cox models for outcomes occurring during pregnancy. In case of additional treatment changes, time for survival analysis was censored at the date of the second change.

We performed additional subgroup analyses, for the virological control, according to the treatment recommendations: Indicated as first-line, Alternative or Not Recommended (NR).

Multivariate analysis was performed with adjustment for the propensity score and factors found to be associated with outcomes in the univariate analysis at p-level of 0.20. All analyses were carried out using STATA 14 software.

To account for the effect of enrolling woman more than once for successive pregnancies, we adjusted our analyses on the pregnancy rank in the cohort.

RESULTS

Of a total of 10553 pregnancies (EPF CO1/CO11), in HIV1-infected women with an outcome ≥ 14 SA between 2005 and 2015 (**Figure 1. Flow chart**), about one half (N = 4983) were on antiretroviral therapy at conception. Among these pregnancies, the antiretroviral therapies at conception were recommended as first-line in 27.1% (n=1350), were alternatives in 36.3% (n=1807) and were not recommended in 36.6% (n=1826). Over time, the proportion receiving recommended first-line treatment increased. Overall, there was at least one treatment change during pregnancy in 35.9% (N = 1789) of which 20% (N = 1019) occurred in the first trimester of pregnancy. The proportion of first trimester switches declined from 23.4% (95%CI [20.3-26.4]) in 2005-2006 to 18.7% [15.7-21.7] in 2014-2015 ($p < 0.01$).

In the component of the cohort with detailed information (EPF CO1, N= 3574), the reason for change in the first trimester, when available, was poor tolerance for 5.1% of cases (N = 52) of which the majority (53.8%) were gastro-intestinal disorders, virological inefficiency or/and poor compliance in 7.3% (N = 75) and medical strategy in 66.4% (N = 677). The reasons for treatment changes remained stable over time.

The proportion of early change for medical strategy appeared to decrease over time from 20.6% (N=733/3558) [17.3-23.9] in 2005-2006 to 18.2% [14.5-21.9] in 2014-15 (p global < 0.01). This decrease mainly concerned patients treated with a possible alternative combination, from 10.2% in 2005-2006 to 2.6% in 2014-2015 (overall $p < 0.001$), while the proportion of changes tended to increase from 1.6% to 7.0% for those treated with a recommended first-line combination and especially for women whose initial treatment was not recommended, from 28.3% in 2005-2006 to 52.2% in 2014-2015 (overall $p < 0.001$) (**Table B-Supplemental data**).

Among women with a viral load < 50 copies/mL in the first trimester who changed only for medical strategy (N = 411), as expected, the incidence of ART switch was higher when their regimen was NR (not recommended) or A (alternative) compared with those receiving R (recommended) first-line treatment (respectively: 48.7% (315/647), 9.9% (71/720) and 6.1% (25/408); $p < 0.01$). Other factors associated with ART switch were younger maternal age, being unmarried and living alone vs married/cohabiting, inactive vs working, increasing time between HIV diagnosis and pregnancy, geographic origin sub-Saharan Africa compared to those born in France, primiparous, living in the Paris

area, a low CD4 count. Change for medical strategy was not significantly associated with the time of the first prenatal visit, the type of perinatal center, BMI, tobacco use or alcohol use, singleton vs twin pregnancy, mode of HIV acquisition, assisted reproduction vs spontaneous conception. (**Tables 1a and 1b**)

In multivariate analysis, change for medical strategy remained significantly associated with the type of treatment according to guideline (adjusted ORs of 2.2 [1.3-3.7] for alternate ARTs and 23.1 [14.0-38.2] for not recommended ARTs, vs first-line therapy; $p < 0.01$) (**Table 2**). Geographical region of maternity, delivery period, marital status, time since diagnosis of HIV, and pregnancy rank of inclusion in EPF remained significantly associated with the probability of early change for medical strategy.

We established a propensity score for each patient from the final multivariate model to study association between ART change for medical strategy and virological and pregnancy outcomes. (**Table 2**).

In women initially well controlled for viral load on ART at conception, first-trimester ART change for medical strategy was not associated with time to virological escape during pregnancy (Kaplan-Meier estimates: 19.3% in the switch group vs 15.6%, HRa: 1.0 [0.7-1.4]) or with proportion of virological failure near delivery ($CV > 50cp / mL$: 6.5% vs. 4.6% ORa : 1.1 [0.6-2.0]) (**Table 3**)

First-trimester ART change was not associated with any adverse pregnancy outcomes (1.9% vs. 2.9%), mode of delivery, perinatal deaths or HIV transmission to the child (**Table 3**).

The probabilities of ART change for any reason beyond 14 gestational weeks did not differ statistically between women who changed or not for medical strategy at first trimester (23.1% vs 14.0% ; $p = .4$). The reason for subsequent change did not differ ($p = .9$). In the case of an early change for medical strategy, subsequent change occurred for intolerance in 30.6%, for inefficacy in 25.8% and for other pregnancy-related concerns in 43.6%. The respective proportion for those who did not change before 14 weeks gestation for medical strategy, were respectively 36%, 20% and 44%.

In subgroup analyses, virological failure was not associated with early change for medical strategy when the initial ART was not recommended (**Table 4**). However, viral load escape tended to be twice higher after initial change for medical strategy when the

initial treatment was considered as an alternative treatment (27.5% vs. 14.3%, HRa: 1.6 [0.9-2.9]) though the difference was not statistically significant ($p = .2$).

We performed the same analyses for women on efavirenz who had a first-trimester switch, in line with French guidelines throughout the study period. There was no significant difference in the proportion of VL > 50 copies/mL (16.8% in 143 pregnancies with a first-trimester switch from efavirenz vs 15.6% in the overall group of 1364 pregnancies without a first-trimester switch, HRa : 1.1 [0.7-1.8], $p = .7$) (**Table C-Supplemental data**).

DISCUSSION

Our findings are reassuring regarding the decision to change antiretroviral therapy in the first trimester in pregnant women with well controlled viral load in order to avoid exposure to medications with potential fetal risks. Indeed, there was no increase in the incidence of virological escape above 50 copies/mL compared to pregnancies in which the initial ART regimen was maintained. In all cases, the ART regimen could be changed again later in pregnancy for poor tolerance or inefficacy. Of concern, whatever the treatment group, the proportion of women who failed to maintain viral suppression throughout their pregnancy was on the average 15.6%. The proportion is, however, much lower than in some other high-resource settings (27). The incidence of virological escape in all groups was quite similar to that reported in non-pregnancy literature (28–30).

Regarding other pregnancy outcomes, there was a trend towards a lower incidence of adverse outcomes (fetal demise, termination of pregnancy, neonatal death) in pregnancies with first-trimester switches, however the difference was not statistically significant. There was no difference in the incidence of congenital malformations, however many of the first-trimester switches occurred after embryogenesis was completed.

Overall, the proportion of ART switches during pregnancy was quite high in our cohort, reaching 35%, of which more than one half occurred in the first trimester. This was comparable to findings from a British study conducted in an earlier period (31). The main indication for first-trimester switches in our population was not for efficacy or maternal tolerance, but as a medical strategy.

We found a strong association between treatment guidelines and actual clinical practice. Women were 23 times more likely to switch ART when it was not recommended compared with patients with a recommended first-line treatment. Decisions regarding ART regimens classified as alternative were less clear-cut, with a twofold increase in first-trimester ART switches. This is consistent with variations in perceptions by the clinician and the woman of available risk/benefice data. The proportion of first-trimester ART switches decreased over the decade for the alternative ART regimens, whereas it increased for regimens which were not recommended. The reasons for first-

trimester ART changes were not available for the small group of pregnancies where a first-line regimen was changed despite recorded efficacy and no reported intolerance. Overall, the main reason for switching ART in the first trimester was to conform to the guidelines. We specifically looked at outcomes following first-trimester switches from efavirenz because, contrary to French guidelines, as well as US guidelines until recently, some other international guidelines have recommended efavirenz-based ART in women of childbearing age and throughout pregnancy (22,24,32). We did not observe a higher proportion of viral load escape in women who changed from efavirenz.

Nevertheless, nearly one half of women with ART regimens which were not recommended at the time of their pregnancy did not change their therapy in the first trimester. This may be due to prior resistance or tolerance issues, differences in the frequency and timing of clinic visits for HIV care, lack of knowledge regarding the latest pregnancy guidelines among some clinicians and concern about potentially destabilizing treatment compliance. In pregnancies where the switch for medical strategy was not done during the first trimester, there was a high proportion where the switch ended up occurring later in the pregnancy.

This highlights the need for multidisciplinary care (1), particularly preconceptionally, in order to choose an ART regimen taking into account the plan for pregnancy with an optimal control of viral load, adherence, and tolerance, which in addition to the benefit/risks for the pregnancy is important for long-term health and in order to protect the partner (33). In an Italian study (34) among women on ART before their pregnancy (n=334), there was a large number of different regimens (80) and less than one half had received specific preconceptional care.

In our analysis, some markers of social and personal vulnerability or deprivation were associated with changes in ART regimen later in pregnancy, which may reflect poorer engagement in care including family planning and treatment adaptation prior to conception.

The short delay since diagnosis of HIV was also significantly associated with early change. The possible mechanism is a better virological equilibrium of patients who have been followed for a longer period of time, also having histories of failures or intolerance

limiting the therapeutic options. In addition, we found an association with parity that also went in this direction.

The main strengths of the study are the large, multicenter enrollment and the prospective collection of detailed data, especially for indications of treatment change. For the main variable of interest, we carefully classified antiretroviral prescriptions and changes with regards to successive changes in guidelines.

The main limitation is the extent to which our results concerning French recommendations and practices are applicable in other settings. In most resource-limited settings, close follow-up and viral load monitoring are not available.

We chose to perform some of the survival analyses to account for the delay between first-trimester change and the possible occurrence of a complication or subsequent change in ART because the gestational age may have an influence on the decisions as well as later outcomes.

In the decade we studied, the principal ART regimens which were discouraged in the French guidelines were efavirenz and triple NRTIs, as well as several antiretrovirals which are no longer in use, for instance didanosine and stavudine. Also, we defined a change in ART to include any addition, deletion or change of at least one drug in the combination. Today, the main issue is whether to switch from single-tablet regimens without pregnancy safety data to regimens with several tablets. Since efavirenz-based therapy was usually a single-tablet regimen, switching to a boosted PI-based regimen meant increasing the pill burden, and this did not lead to poorer virological outcomes. Some studies (35,36) have shown that compliance is improved during pregnancy, which may suggest that women are willing to make special efforts in order to improve their chance of having a healthy child.

When recommending to avoid certain antiretrovirals, a fundamental issue is whether the potential risks justify this precaution. For most recent medications, there is simply not enough pregnancy data to conclude about their safety. Few antiretrovirals have documented risks for the fetus. This was the case for efavirenz, with preclinical primate data showing an increased risk of neural tube defects, as well as clinical data from some cohort studies including the French cohort EPF (16). This led in the French guidelines to discourage efavirenz in the first trimester of pregnancy. The WHO guidelines (22)

were on the contrary to continue efavirenz in pregnant women, based on reassuring data from the Antiviral Pregnancy Registry and some meta-analyses. In case of such controversy, approaches may differ between expert guidelines because of different analyses of the data, and also because of great differences in populations, health systems and resources.

CONCLUSION

When antiretroviral therapy at conception is changed early during pregnancy with the goal of improving fetal and pregnancy outcomes, this does not appear to have a destabilizing effect on viral suppression. These findings highlight the need for multidisciplinary care and a discussion between the physicians and each woman. In order to avoid exposing the fetus to potentially harmful medications, the optimal treatment should be chosen as early as possible in pregnancy, and if possible preconceptionally. As guidelines evolve, it is also important to inform clinicians. Since a large number of effective antiretroviral regimens are now available, the choice of which ones to use requires adequate data on their risks. This requires ongoing research, including follow-up in cohort studies, biological investigations, randomized controlled trials.

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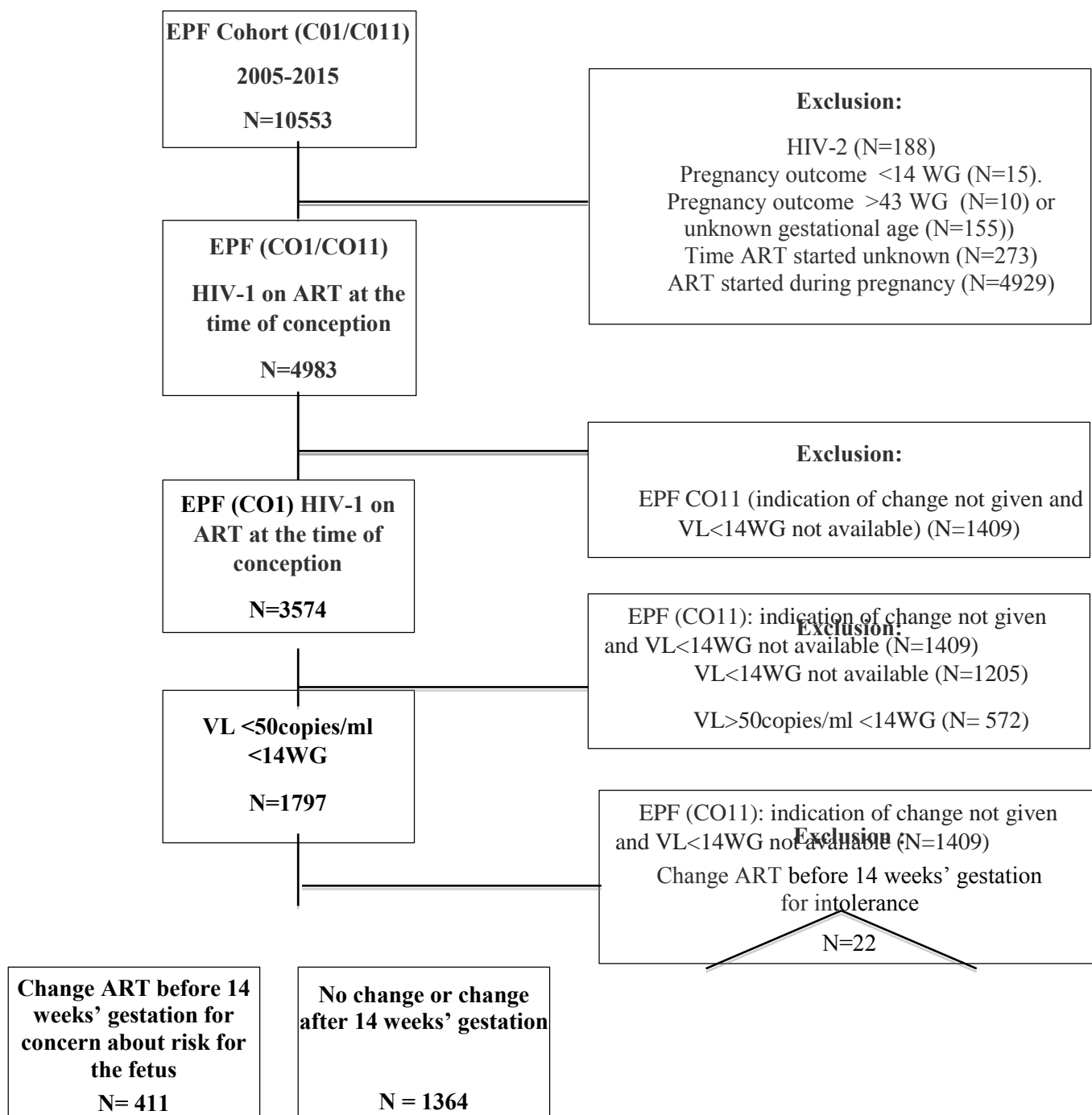
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Figure 1 : Flow chart



ART : antiretroviral therapy, WG : weeks of gestation, VL : viral load.

Legend for figure**Figure 1 : Flow chart**

ART : antiretroviral therapy, WG : weeks of gestation, VL : viral load.

Table 1a : Pregnancies started under antiretroviral therapy with viral load < 50 copies/mL in the first trimester, univariate analysis (EPF-CO1, 2005-2015).

Maternal characteristics.

	Total N= 1775	Change for medical strategy (N= 411)				
		%	n	OR	IC95%	p
Delivery period						
2005-2006	201	22.9%	46	1.3	[0.9-1.9]	.02
2007-2008	316	25.9%	82	1.5	[1.1-2.1]	
2009-2010	401	26.9%	108	1.6	[1.2-2.1]	
2011-2013	644	18.8%	121	1		
2014-2015	213	25.4%	54	1.5	[1.0-2.1]	
Maternal age						
<=24 years	65	33.8%	22	1		.05
25-34 years	1037	23.9%	248	0.6	[0.4-1.0]	
>=35 years	671	21.0%	141	0.5	[0.3-0.9]	
Geographical origin						
France	218	19.7%	43	1		.03
Sub-saharan Africa	1336	24.6%	329	1.3	[0.9-1.8]	
Others	216	17.6%	38	0.9	[0.5-1.4]	
BMI (kg/m2)						
<18.5	66	27.3%	18	1		.8
18.5-24.9	834	22.5%	188	0.8	[0.4-1.4]	
25-29.9	527	23.5%	124	0.8	[0.5-1.5]	
>=30	272	22.1%	60	0.7	[0.4-1.4]	
Tobacco use						
No	1708	23.4%	399	1		.4
Yes	55	18.2%	10	0.7	[0.4-1.5]	
Alcohol use						
No	1744	23.2%	404	1		.6
Yes	10	30.0%	3	1.4	[0.4-5.5]	
Occupational status						
Inactive	548	26.3%	144	1		.04
Working or student	1171	21.8%	255	0.8	[0.6-1.0]	
Marital status						
Married or	1177	20.2%	238	1		<0.01
Single	524	30.2%	158	1.7	[1.3-2.1]	
Parity						
Primipare	803	25.7%	206	1		.02
Multiparous	972	21.1%	205	0.8	[0.6-1.0]	
Previous pregnancies in EPF						
None	803	25.7%	206	1		<0.01
One or two	895	20.0%	179	0.7	[0.6-0.9]	
Three or more	77	33.8%	26	1.5	[0.9-2.4]	
Time since HIV diagnosis						
<5 years	534	28.7%	153	1		<0.01
5- <10 years	714	22.0%	157	0.7	[0.5-0.9]	
10- <15 years	332	20.5%	68	0.6	[0.5-0.9]	
>=15 years	182	17.6%	32	0.5	[0.3-0.8]	
Mode of transmission of HIV						
Sexual	1178	24.5%	288	1		.2
Others	85	18.8%	16	0.7	[0.4-1.2]	
Multiple pregnancy						
Singleton	1723	23.2%	400	1		.7
Multiple	52	21.1%	11	0.9	[0.4-1.7]	
Mode of conception						
Spontaneous	1758	23.3%	409	1		.2
Medically assisted	17	11.8%	2	0.4	[0.1-1.9]	

OR : crude odd ratio, IC95% : confidence interval 95%, BMI : body mass index

Table 1b: Pregnancies started under antiretroviral therapy with viral load < 50 copies/mL in the first trimester, univariate analysis (EPF-CO1, 2005-2015). Management characteristics

	N= 1775	Changes for medical strategy (N= 411)				
		%	n	OR	IC95%	p
Gestational age at booking in maternity						
1st trimester <14WG	1170	23.8%	27	1		.3
14 -20WG	437	23.3%	10	1.0	[0.7-1.3]	
>=21WG	168	18.5%	31	0.7	[0.5-1.1]	
Geographical region of maternity						
Paris	846	20.2%	17	1		.02
Paris region	512	26.4%	13	1.4	[1.1-1.8]	
Other regions	417	25.2%	10	1.3	[1.0-1.7]	
Level of maternity						
Level 1	9	44.4%	4	2.5	[0.7-9.4]	.1
Level 2 (with neonatology department)	650	21.1%	13	0.8	[0.7-1.1]	
Level 3 (with a neonatal intensive care unit)	1116	24.2%	27	1		
Treatment according to guidelines						
Recommended	408	6.1%	25	1		<0.01
Alternative	720	9.9%	71	1.7	[1.0-2.6]	
Not recommended	647	48.7%	31	14.5	[9.4-22.4]	
Type of initial ART regimen						
PI+/- NRTI	1115	13.3%	14	1		<0.01
NNRTI + NRTI	469	41.6%	19	4.6	[3.6-6.0]	
PI+NNRTI+/-NRTI	20	25%	5	2.2	[0.8-6.1]	
1 NRTI ou 2 NRTIs	8	12.5%	1	0.9	[0.1-7.6]	
3 NRTIs	82	43.9%	36	5.1	[3.2-7.6]	
Others	81	32.1%	26	3.1	[1.9-5.1]	
Type of initial drug class						
NRTI:	No	61	21.3%	13	1	.7
	Yes	1714	23.2%	39	1.1	[0.6-2.1]
NNRTI:	No	1276	16.4%	20	1	<0.01
	Yes	499	40.5%	20	3.5	[2.7-4.4]
PI +/- boosted	No	682	41.5%	25	1	<0.01
	Yes	1093	13.6%	15	0.2	[0.2-0.3]
PI boosted	No	608	39.2%	26	1	<0.01
	Yes	1167	13.2%	14	0.2	[0.2-0.3]
Integrase inh ibitor:	No	1702	22.9%	38	1	.2
	Yes	73	30.1%	22	1.5	[0.9-2.4]
Others :	No	1767	23.0%	40	1	.1
	Yes	8	50%	4	3.3	[0.8-13.4]
First CD4 cell count during pregnancy (/mm3)						
<200	59	37.3%	22	1		.01
200- <350	269	23.9%	66	0.5	[0.3-1.0]	
350- <500	523	24.6%	13	0.6	[0.3-1.0]	
>=500	917	20.2%	19	0.4	[0.2-0.8]	

OR : crude odd ratio, IC95% : confidence interval 95%, WG : weeks of gestation, ART : antiretroviral therapy, PI : protease inhibitors NRTI : nucleoside reverse transcriptase inhibitors, NNRTI : non nucleoside reverse transcriptase inhibitor

Table 2 : Factors associated with an ART change for medical strategy in the first trimester in HIV+ pregnant women on ART with viral suppression at the conception. Final multivariate logistic model. (EPF- CO1 2005-2015)

	Univariate analysis (N=1775)			Multivariate analysis (N=1655)		
	Crude OR	IC95%	p	Adjusted OR	IC95%	p
Treatment according to guidelines						
Recommended	1		<0.01	1		<0.01
Alternative	1.7	[1.0-2.6]		2.2	[1.3-3.7]	
Not recommended	14.5	[9.4-22.4]		23.1	[14.0-38.2]	
Previous pregnancies in EPF						
None	1		<0.01	1		.03
One or two	0.7	[0.6-0.9]		0.8	[0.6-1.1]	
Three or more	1.5	[0.9-2.4]		1.9	[1.0-3.6]	
Geographical region of						
Paris	1		.02	1		<0.01
Paris region	1.4	[1.1-1.8]		1.4	[1.1-2.0]	
Other regions	1.3	[1.0-1.7]		1.6	[1.1-2.3]	
Delivery period						
2005-2006	1.3	[0.9-1.9]	.02	0.5	[0.3-0.7]	<0.01
2007-2008	1.5	[1.1-2.1]		0.6	[0.4-0.9]	
2009-2010	1.6	[1.2-2.1]		1.1	[0.8-1.6]	
2011-2013	1			1		
2014-2015	1.5	[1.0-2.1]		1.7	[1.1-2.8]	
Marital status						
Married or cohabitating	1		<0.01	1		.01
Single	1.7	[1.3-2.1]		1.4	[1.0-1.9]	
Time since HIV diagnosis						
<5 years	1		<0.01	1		<0.01
5- <10 years	0.7	[0.5-0.9]		0.7	[0.5-1.0]	
10- <15 years	0.6	[0.5-0.9]		0.5	[0.4-0.8]	
>=15 years	0.5	[0.3-0.8]		0.3	[0.2-0.6]	
Occupational status						
Inactive	1		.04	1		.3
Working or student	0.8	[0.6-1.0]		0.8	[0.6-1.1]	

OR : odd ratio, IC95% : confidence interval 95%

Table 3 : Virological and obstetrical outcomes according to change for medical strategy in HIV+ pregnant women on ART with viral suppression at the conception. Univariate and multivariate analysis by survival analysis and logistic regression. (EPF-CO1. 2005-2015)

	Change for medical strategy				Univariate Analysis			Multivariate Analysis		
	No (N=1364)		Yes (N=411)		OR ¹ /HR ²	IC 95%	p	ORa ¹ /HRa ²	IC 95%	p
	n	%	n	%						
Virological failure (VL > 50 cp/mL)										
During the pregnancy	212	15.6	79	19.3	1.2 ²	[0.9-1.6]	.2	1.0 ^{2a}	[0.7-1.4]	.9
Near delivery	58	4.6	25	6.5	1.4 ¹	[0.9-2.3]	.2	1.1 ^{1a}	[0.6-2.0]	.7
Pregnancy complications										
Hospitalization <28 WG	418	29.9	111	27.5	0.9 ²	[0.7-1.1]	.3	0.9 ^{2a}	[0.7-1.1]	.3
Adverse pregnancy outcomes*	39	2.9	8	1.9	0.7 ¹	[0.3-1.4]	.3	0.7 ^{1b}	[0.3-1.7]	.4
Change in ART regimen >14 WG										
Yes	191	14.0	95	23.1	1.3 ²	[1.0-1.7]	.06	0.9 ^{2a}	[0.6-1.2]	.4
Pregnancy outcome										
Cesarean section**	664	49.1	182	44.5	0.8 ¹	[0.7-1.0]	.1	0.8 ^{1c}	[0.6-1.1]	.2
Preterm birth <37 WG	177	14.5	49	15.3	1.0 ²	[0.8-1.4]	.7	1.1 ^{2a}	[0.8-1.6]	.6
Neonatal outcome										
Death in the first year	6	0.4	0	0	.	.	.3	.	.	.
HIV infection	0	0	0	0

*fetal demise, termination of pregnancy, neonatal death; **compared to vaginal delivery

^a adjusted on propensity score (PS); ^b adjusted on PS, gestational age at outcome; ^c adjusted on PS, BMI (body mass index), gestational age at outcome

ART : antiretroviral therapy, WG: weeks gestation, VL: viral load, OR : crude odd ratio, ORa: odd ratio adjusted, HR: crude hazard ratio, HRa: hazard ratio adjusted, IC95% : confidence interval 95%. ¹Logistic regression, ²Cox model;

Table 4: Univariate and multivariate associations between virological failure and the type of treatment according to guidelines in HIV+ pregnant women on ART viral suppression at the conception who changed ART in the first trimester for medical strategy (EPF-CO1. 2005-2015)

		Virological failure (VL > 50 cp/mL)														
		During the pregnancy							Near delivery							
N	%	Univariate Analysis			Multivariate Analysis				%	Univariate Analysis			Multivariate Analysis			
		HR	IC 95%	p	HRa ²	IC 95%	p	OR		IC 95%	p	ORa	IC 95%	p		
Type of treatment according to the guidelines																
Recommended																
Change	25	8	0.4	[0.0-2.7]	.3	0.4	[0.0-2.9]	.4	4.0	1.0	[0.1-8.1]	1	1.2	[0.1-9.4]	.9	
No change	387	15.3	1			1			3.9	1			1			
Alternative																
Change	71	27.5	1.7	[0.9-3.1]	.1	1.6	[0.9-2.9]	.2	4.5	1.1	[0.3-3.8]	.8	1.1	[0.3-3.7]	.9	
No change	667	14.3	1			1			4.0	1			1			
Not recommended																
Change	315	18.4	0.9	[0.6-1.3]	.5	0.9	[0.6-1.4]	.6	7.1	1.1	[0.6-2.0]	.8	1.1	[0.6-2.1]	.8	
No change	355	18.7	1			1			6.7	1			1			

OR: crude odd ratio, ORa: odd ratio adjusted on the propensity score , HR: crude hazard ratio, HRa: hazard ratio adjusted on the propensity score.

¹Logistic regression, ²Cox model

SUPPLEMENTAL DATA

Table A : Recommendations for antiretrovirals in pregnancy according to successive French national guidelines. 1: Treatment indicated as first-line; 2: Alternative; 3: Not recommended: contraindicated or insufficient data in pregnancy to recommend

	2004	2006	2008	2010	2013
NRTI^a					
Zidovudine	1	1	1	1	1
Didanosine	2*	1*	2*	2	3
Lamivudine	1	1	1	1	1
Stavudine	2*	2*	2*	3	3
Abacavir	2	2	2	2	1
Tenofovir	3	3	3	2	1
Emtricitabine	3	3	3	2	1
NNRTI^b					
Nevirapine	3	2**	2**	2**	2**
Delavirdine	3	3	3	3	3
Efavirenz	3	3	3	3	3
Etravirine	3	3	3	3	3
Rilpivirine	3	3	3	3	3
Protease inhibitors					
Amprenavir	3	3	3	3	3
Ritonavir	1	1	1	1	1
Saquinavir	1	1	1	1	2
Nelfinavir	1	1	3	3	3
Indinavir	3	2	2	2	3
Lopinavir	3	1	1	1	1
Atazanavir	3	3	3	2	1
Fosamprenavir	3	2	2	2	3
Tipranavir	3	3	3	3	3
Darunavir	3	3	3	2	1

Integrase inhibitors					
Raltegravir	-	-	3	2***	2***
Elvitegravir	-	-	-	-	-
Dolutegravir	-	-	-	-	-
Others					
Maraviroc	3	3	3	3	3
Enfuvirtide	3	3	2***	2***	2***

^a NRTI : Nucleoside reverse transcriptase inhibitors

^b NNRTI : Non nucleoside reverse transcriptase inhibitors

* contra-indicated in association with D4T

**acceptable if started before the pregnancy

*** recommended in case of virologic escape or late presenter

Table B: Proportions of early change of treatment (<14WG) for medical strategy according to the guidelines period and type of the initial treatment. (EPF-CO1.2005-2015)

Periods	Overall N= 3558			Type of initial ART								
				Recommended N= 821			Alternative N= 1378			Not recommended N= 1359		
	switch			switch			switch			switch		
	%	IC95%	p	%	IC95%	p	%	IC95%	p	%	IC95%	p
2005-2006	20.6	17.3-	<0.01	1.6	-1.6-4.9	0.07	10.2	5.4-15.0	<0.0	28.3	23.7-33.0	<0.01
2007-2008	22.1	18.8-		1.2	-1.2-3.6		5.7	2.2-9.2		34.5	29.6-39.3	
2009-2010	22.0	19.1-		1.8	-0.7-4.3		12.1	8.8-15.4		43.3	37.4-49.1	
2011-2013	14.9	12.9-		4.5	2.2-6.7		7.1	5.0-9.1		49.4	42.9-55.8	
2014-2015	18.2	14.5-		7.0	3.6-10.3		2.6	-1.0-6.2		52.2	42.8-61.7	

Table C : Associations between switch and virologic failure in women with a viral load <50 copies/mL who changed Efavirenz in the first trimester as a medical strategy to follow guidelines patients. Uni and multivariate analysis by survival analysis or logistic regression (EPF-CO1. 2005-2015)

	Switch EFV				Univariate analysis			Multivariate analysis		
	No (N=1364)		Yes (N=143)		OR ¹ /HR ²	IC 95%	p	ORa ¹ /HRa ²	IC 95%	p
	n	%	n	%						
Virological failure (VL > 50 cp/mL)										
During the pregnancy	212	15.6	24	16.8	1.3 ²	[0.8-2.0]	0.3	1.1 ^{2a}	[0.7-1.8]	0.7
Near delivery	58	4.6	11	8.3	1.9 ¹	[0.9-3.6]	0.07	1.8 ^{1a}	[0.9-3.6]	0.1

^aajustement on the propensity score

VL : viral load,

OR: crude odd ratio, ORa: odd ratio adjusted on the propensity score , HR: crude hazard ratio, HRa: hazard ratio adjusted on the propensity score.

¹Logistic regression, ²Cox model.

