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

Violaine Peyronnet, Josiane Warszawski, Jeanne Sibiude, Olivia Dialla, Agnès Bourgeois Moine, Eida Bui, Caroline Simon Toulza, Delphine Peretti, Cécile Brunet-Cartier, Véronique Avettand-Fenoël, et al.

▶ **To cite this version:**

Violaine Peyronnet, Josiane Warszawski, Jeanne Sibiude, Olivia Dialla, Agnès Bourgeois Moine, et al.. Does changing antiretroviral therapy in the first trimester for pregnancy-related concerns have an impact on viral suppression ?: Changing ART in pregnancy and viral suppression ?. Journal of Acquired Immune Deficiency Syndromes - JAIDS, 2019, 80 (5), pp.574-584. 10.1097/QAI.0000000000001954 . inserm-02070251

HAL Id: inserm-02070251

https://inserm.hal.science/inserm-02070251

Submitted on 17 Mar 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Violaine PEYRONNET[1,2], Josiane WARSZAWSKI[1,3,4], Jeanne SIBIUDE[1,2,5], Olivia DIALLA[1], Agnès BOURGEOIS MOINE[6], Eida BUI[7], Caroline SIMON TOULZA[8], Delphine PERETTI[9], Cécile BRUNET-CARTIER[10], Véronique AVETTAND-FENOEL[11,12], Jérôme LE CHENADEC[1], Albert FAYE[5,13], Roland TUBIANA[14], Laurent MANDELBROT[1,2,5] for the ANRS EPF-French Perinatal Cohort Study

[1]CESP INSERM U1018, Le Kremlin-Bicêtre; [2]AP-HP Hôpital L. Mourier, Colombes; [3]Univ Paris Sud, Le Kremlin-Bicêtre; [4]AP-HP Hôpital Bicêtre, le Kremlin-Bicêtre; [5]Univ Paris-Diderot, Paris; [6]AP-HP Hôpital Bichat, Paris; [7]AP-HP Hôpital Trousseau, Paris; [8]CHU de Toulouse, Toulouse ; [9]AP-HP Hôpital de Bicêtre, Le Kremlin-Bicêtre ; [10]CHU de Nantes, Nantes ; [11]AP-HP Hôpital Necker-Enfants Malades, Paris; [12] Univ Paris-Descartes, EA7327 Paris; [13]AP-HP Hôpital R. Debré, Paris; [14]AP-HP Hôpital Pitié Salpétrière, Paris, FRANCE

Corresponding author:

Prof Laurent Mandelbrot, MD

Service de Gynécologie-Obstétrique, Hôpital Louis Mourier, Université Paris-Diderot

178 rue des Renouillers

92700 Colombes, France

+33685127688

laurent.mandelbrot@aphp.fr

Alternate corresponding author :

Violaine Peyronnet, MD

CESP INSERM U1018, Equipe 4 VIH, Cohorte EPF

78 rue du Général Leclerc 9270 Le Kremlin Bicètre

+33675979499
violaine.peyronnet@gmail.com

Word count : manusript 3460, abstract 250 words

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 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, obervational 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 outomes occuring 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 oucomes (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-timester 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 timester 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 timester. 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.

ACKNOWLEDGEMENTS :

Financial support : This work was supported by the French Agence Nationale de Recherche sur le SIDA (ANRS).

Potential conflicts of interest. All authors: no conflicts.Violaine Peyronnet declares herself to be independent of any commercial funder, to have performed the statistical analysis and have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

All authors contributed actively to the manuscript and approved the final version.

We thank all women who agreed to participate and the doctors, midwives, and personnel in the centers participating in the French Perinatal Cohort ANRS: APHP Hôpital Louis Mourier, Colombes, France (Laurent Mandelbrot, Catherine Crenn-Hebert*, Corinne Floch-Tudal*, Fabienne Mazy, Marine Joras, Françoise Meier, Emmanuel Mortier, Catherine Briquet, , Houria Ichou, Laurence Marty, Hélène Jabbarian); APHP Hôpital Beaujon, Clichy, France (Pierre-François Ceccaldi*, Agnès Villemant, Virginie Zarouk, Agnès Lefort, Mariam Ben Salah); Hôpital Sainte Musse, Toulon, France (Gilles Hittinger*, Jean-Marc Chamouilli, Christian Burle, Alain Lafeuillade, Gisèle Philip,Véronique Lambry); CHG Marechal Joffre, Perpignan, France (Marie Medus*, Germaine Bachelard, Martine Malet); CHU Caremeau, Nîmes, France (Joëlle Dendale-Nguyen*); CHD les Oudairies, La Roche sur Yon, France (Thomas Guimard*, Karine Guimard, Jean-Pierre Brossier, Philippe Perré, Jean-Luc Esnault, Olivier Aubry, Sophie Leautez-Nainville, Valerie Bonnenfant, , Laeticia Laine); Centre Hospitalier William Morey, Châlon sur Saone, France (Sandrine-Anne Martha*, Elise Maurel, Michel Françoise, Muriel Barat, Patricia Murger); Centre Hospitalier, Vernon, France (Mahfoud Rouha*, Marc Lévy, Philippe Lumbroso, Alain Checoury, Osseni Sahadatu, Johnson)); Centre Hospitalier Intercommunal de Cornouaille, Quimper, France (Pascale Perfezou*, Gilles Blondin, Jean-Charles Duthé); Centre Hospitalier Universitaire, Brest, France (Séverine Ansart*, Luc De Saint Martin*, Philippe Le Moine, Jean-Charles Duthé); Centre Hospitalier, St Brieuc, France (Corinne Daniel*, Christian Calvez, Emmanuelle Boutaric, Jennifer Rohan); Centre Hospitalier Universitaire, Rennes, France (Cédric Arvieux*, Estelle Bauville, Christelle Dupre, Pascal Lotton, Enora Ouamara-digue); Centre Hospitalier Bretagne Atlantique,

Vannes, France (Yves Poinsignon*, Marie Goussef, Anne Grelier, Gaetane Mousset, Corinne Cudeville, Virginie Mouton-Rioux); Centre Hospitalier de Bretagne Sud, Lorient, France (Mathilde Niault*, Isabelle Belzic, Philippe Moreau, Marie-Françoise Le Coz, Odile Luycx Vaillant, Anne Guerin-Duplessy, Virginie Mouton-Rioux, Philippe De Morel); Centre Hospitalier de la région d'Annecy, Annecy, France (Virginie Vitrat*, Didier Tardif, Jacques Gaillat, Anne Vanderbergh, Suzanne Braig, Gaelle Clavere); Centre Hospitalier Intercommunal, Montfermeil, France (Marion Dehlinger-Paul*, Khaled Mohamed, Marie Echard, Michel Camus, Catherine Mulard, Marie-Agnès Fontelonga); Centre Hospitalier Intercommunal, Montreuil, France (Brigitte Heller-Roussin*, Cécile Winter, Marion Challier, Elise Debruyne); APHP Hôpital Cochin-Port Royal, Paris, France (Valerie Marcou*, Ghislaine Firtion, Emmanuelle Pannier*, Myriam Costa, Odile Launay, Dominique Salmon Ceron, Touria Belkacem, Youcef Bajawi, Valérie Raynal Aubret, Danièle Rivaux); APHP Hôpital Bichat, Paris, France (Sophie Matheron*, Neila Elaoun, Lahcene Allal, Sandrine Djoubou, Djamila Rahli, Agnès Bourgeois Moine, Morgane Valentin, Florence Damond, Virginie Huri, Valérie Vivier, Fatma Ait Yahia); Centre Hospitalier Intercommunal, Créteil, France (Valérie Garrait*, Isabelle Hau*, Claudine Touboul, Lanto Ratsimbazafy, Emilie Boiron, Brigitte Elharrar, Laurent Richier); Hôpital de la Croix Rousse, Lyon, France (Laurent Cotte*, Jean-Marc Labaune, René-Charles Rudigoz, Corinne Brochier, Valérie Galvan, Stanislas Ogoudjobi); Centre Hospitalier Pellegrin, pauchart, Bordeaux, France (Christophe Elleau*, Camille Runel-Belliard*, Thierry Pistone, Hervé Fleury, Jacques Horovitz, Boris Sandler, Denis Roux, Jean-Marie Ragnaud, Pierre Chabanier, Jean-Luc Brun, Sandrine Delveaux); CHU Les Abymes, Pointe à Pître, France (Blandine Muanza*, Mama Doufari Diallo, Isabelle Lamaury, Marie-Thérèse Sow, Ketty Samar); Centre Hospitalier Général, Creil, France (Bénédicte Carpentier*, Zafer Osman, Etienne Dienga); Centre Hospitalier Général, Longjumeau, France (Hervé Seaume*, Sarah Ducrocq, Philippe Bailly-Salin,Christelle Dusart Da Silva, Isabelle Fayolas); Hôpital Paule de Viguier, Toulouse, France (Julie Abbal*, Caroline Simon-Toulza*, Véronique Truillet, Noëlle Bogner, Julie Chiabrando, Evelyne Armand); Centre Hospitalier de la Côte Basque, Bayonne, France (Claudine Cayla*); Centre hospitalier intercommunal, Villeneuve St Georges, France (Anne Chacé*, Isabelle Matheron, Laurent Richier, Joe Miantezila, Sandrine Bry); Centre

Hospitalier Intercommunal, Poissy Saint Germain en Laye, France (Sophie Couderc*, Catherine Narcy); Centre Hospitalier Général, Fontainebleau, France (Corinne Routier*, Rania Nassar); Centre Hospitalier Robert Ballanger, Aulnay, France (Marie-Anne Bouldouyre*, Ahmed Zakaria, Hélène Dauphin, Céline Goissen, Marie Belloy, Jean-Luc Delassus, Véronique Favret, Céline Nemeth); Hôpital Hautepierre, Strasbourg, France (MariaLuisa Partisani*, Natacha Entz-werle, Bruno Langer, Françoise Uettwiller, Myriam Durand) ; Hôpital Civil, Strasbourg, France (MariaLuisa Partizani*, Christine Cheneau, David Rey, Edith Ebel, , Patricia Fischer) ; Centre médico-chirurgical Obstétrique, Strasbourg, France (Eric David, Christophe Vayssiere, Michèle Weil, Marie Paule Schmitt, Israël Nisand) ; Centre Hospitalier Victor Dupouy, Argenteuil, France (Philippe Genet*, Dominique Brault, Christine Allisy, Juliette Gerbe, Virginie Masse, Bouchra Wifaq, Laurence Courdavault, Petra Gabor, Nathalie Tordjeman); APHP Hôpital Tenon, Paris, France (Marie-Gisèle Lebrette*, Lise Selleret, Déborah Samama, Geneviève Vaudre); Centre Hospitalier Général, Saint-Denis, France (Pascal Bolot*, Marie-Aude Khuong-Josses, , Mahdi Amel, Stéphane Bounan, Christelle Nourry, Sabine Andris); APHP Hôpital Necker, Paris, France (Stéphane Blanche*, Marine Driessen*, Pierre Frange, Florence Veber, Alain Fisher, Christine Rouzioux, Véronique Avettand-Fenoel, Nizar Malaoui, Marie-Christine Mourey); Centre Hospitalier Sud Francilien, Evry Corbeil, France (Michèle Granier*, Alain Devidas*, Anne-Claire Donnadieu, , Adrien May, Amélie Chabrol, Pierre Chevojon, Chahrazede Bellahcene, Audrey Sanchez, Claire Malbrunot, Joelle Neizelien, Nouara Agher); Centre Médico-Chirurgical et Obstétrical, Schiltigheim, France; CHR American Memorial Hospital, Reims, France (Claire Pluchart*, Christine Rouger); APHP Groupe Hospitalier Pitié Salpêtrière, Paris, France (Roland Tubiana*, Marc Dommergues, Manuela Bonmarchand, Luminata Shneider, Fabienne Caby, Ruxandra-Oana Calin, Christine Blanc, Catherine Lupin, michèle Pauchard); Centre Hospitalier René Dubos, Pontoise, France (Mohamed Amine Yangui*, Didier Roca, Darina Todorova, Juliette Laurent, A Ferry, Martine Deschaud, Laurent Blum); APHP Hôpital Béclère, Clamart, France (Véronique Chambrin*, Philippe Labrune*, Laure Clech, Mariem Raho-Moussa); Centre Hospitalier Marc Jacquet, Melun, France (Isolde Pauly-Ravelly*, Thierry Jault, Soufiane Bouabdallah, Lydie Sanchez, Anita Sanchez); Centre Hospitalier Général, Evreux, France (Ama Johnson*, Agnès Louchard, Claude Allouche, Jean Paul

Pathe); APHP Hôpital Jean Verdier, Bondy, France (Eric Lachassine*, Laurence Benoist, Vincent Jeantils, Catherine Delannoy, , Amélie Benbara, Lionel Carbillon, Anne Borgne, Laurence Moreau, Fabienne Picard); Centre Hospitalier de Meaux, Meaux, France (Leïla Karaoui*, Véronique Lefevre Elbert, Valérie Balaz); CHU de l'Archet, Nice, France (André Bongain*, Fabrice Monpoux*, Anne Deville, Eliane Galiba); Centre Hospitalier François Quesnay, Mantes La Jolie, France (Ahmed Jabbar*, Martine Joutel); CHU Hôpital Nord, Amiens, France (Jean-Luc Schmidt*, Nathalie Decaux); Hôpital de la Conception, Marseille, France (Ludovic Cravello*, Katia Errichiello); CHU de Brabois-Hôpital des Adultes, Vandoeuvre les Nancy, France (Claire Hubert*); APHP Hôpital Trousseau, Paris, France (Catherine Dollfus*, François Hervé, Marie-Dominique Tabone, Mary-France Courcoux, Guy Leverger, Gilles Kayem, , Aurélie Schnurgier, Aurore Jensen, Geneviève Vaudre); Hôpital Charles Nicolle, Rouen, France (Didier Pinquier*, Alexis Gromez , Gaelle Pinto-Cardoso,); APHP Hôpital Robert Debré, Paris, France (Albert Faye, Constance Borie*, Martine Levine*, Sophie Matheron, Erianna Bellaton Marouts, Christine Boissinot, Marion Caseris, Virginie Pommelet, Geneviève Morau, Sandrine Leveille, Marie Astride Boumediene, Dominique Garion); APHP Hôpital de Bicêtre, Le Kremlin-Bicêtre, France (Delphine Peretti*, Corinne Fourcade*, Marie Houllier, Ikram Jrad, Katia Bourdic, Sylvie Monnier); CHU Hôpital Jean Minjoz, Besançon, France (Catherine Chirouze*, Aurélie Proust, Odile Catteau, Quentin Gardiennet); CHU de Nantes, Nantes, France (Véronique Reliquet*, Cécile Brunet-Cartier*, Norbert Winer, Edouard Vaucel, Audrey Rodallec, Elisabeth Garnier-André); CHRU Hôpital du Bocage, Dijon, France (Claire Briandet*); CHRU Hôpital Clemenceau, Caen, France (Jacques Brouard*, Pascale Goubin, Gaël Beucher, Julia Dina); Centre Hospitalier de Lagny, Lagny, France (Arnaud Chalvon Demersay*, Sylvie Tassi, Gaelle Lavarenne); Hôpital André Mignot, Le Chesnay, France (Mandovi Rajguru*, Fabienne Messaoudi, Nathalie Carre, Mandavi Rajguru, Claire Bobrie-Moyrand, Pierre Foucaud); CHRU de Tours, France (Louis, Bernard*, Zoha Maakroun, Olivier Bourgault); Institut d'Hémato-Oncologie Pédiatrique, Lyon, France (Kamila Kebaïli*, Yves Bertrand, Véronique Alixe, Emeline Boyer); Hôpital Nord, Saint Etienne, France (Kareen Billiemaz*, Cécile Fanget, Véronique Ronat, Catherine Lesauder, Marie Laure Lavastre); Centre Hospitalier Général, Bastia, France (Alice Moulin*, Marie-France Turquini, Dominique

Colombani, Danièle Belgodere); Centre Hospitalier Universitaire, Angers, France (Pascale Fialaire*, Stéphanie Proust, Sami Rehaiem); Centre Hospitalier Régional, Orléans, France (Louis Mesnard, Evelyne Werner*, Nathalie Dukiel, Baya Desmergers, Isabelle Blanc-Ruffat); APHP Hôpital Lariboisière, Paris, France (Barbara Maraux*, Anne Coursol, Julie Castaneda,Lise Etienne); CHR Arnaud de Villeneuve, Montpellier, France (Emmanuelle Vintejoux*, Muriel Lalande, Jacques Reynes, Michel Segondy, Nelly Guigue); Centre Hospitalier Général, Orsay, France (Christiane De Gennes*); Centre Hospitalier de Saint Martin, St Martin, France (Cyril Clavel*, François Cazassus, Véronique Walter); CHR Jeanne de Flandres, Lille , France (Françoise Mazingue*, Yamina Hammou, Marion Lagree, Odile Paquiez, Sophie D'angelo, Faiza Ajana, Laurence Boquet); Centre Hospitalier Dron, Tourcoing, France (Faïza Ajana); CHU - Maison de la Femme et de l'Enfant, Fort de France, France (Yves Hatchuel*, Imad Nahri, Jenny Zebelus); CHU Dupuytren, Limoges, France (Claire Genet*, Sophie Ducroix-Roubertou, Yves Aubrard, Anne Constanty, Pierre Weinbreck); Hôpital Intercommunal Sud Léman Valserine, Saint Julien, France (Emilie Piet*, Françoise Jacquier); Centre Hospitalier Saint Nazaire Cité Sanitaire, Saint Nazaire, France (Christophe Michaud*, Hassan Safwan, Arnaud Boutet, Carole Grand-Courault); Groupe Hospitalier Saint Joseph, Paris, France (Fanny Autret*, Fakher Habibi, Elie Azria); Centre Hospitalier Léon Binet, Provins, France (Mohamed Abdelhadi*); Centre Hositalier Andrée Rosemon, Cayenne, France (Narcisse Elenga*); Hôpital Calmette, Lille, France (Laurence Bocket, Françoise Taillet); Centre Hospitalier de Béziers, France (Gilles Palenzuela*, Redouane Khadly ,Danielle Pierronnet, Emmanuelle Dos-Santos); Centre Hospitalier de Narbonne (Selva David*); Hôpital Edouard Herriot, Lyon, France (Djamila Makhloufi*, Florence Brunel-Dalmas, Elisabeth Carbonnel-Delalande, Pierre Chiarello, Matthieu Godinot, Sylvie Gilbert); Hôpital Femme Mère Enfant, Bron, France (Jérôme Massardier*, Hélène Gauthier-Moulinier) ; Centre Hospitalier de la Basse-Terre, Guadeloupe (Elisabeth Fernandes*, Sata Ranaivojaona, Coralie Chevry). The asterisks indicates the main indicator of each clinical sites.

References

1. Warszawski, J. Tubiana R, Le Chenedec J, Teglas JP, Faye A, Dolfus C et al. Transmission mère enfant du VIH en France: l'impact majeur des stratégies de prévention. Résultats de l'Enquête perinatale française ANRS-EPF. BEH. 2008;14:98–101.
2. Delfraissy J-F. Prise en charge thérapeutique des personnes infectées par le VIH 2004. Recommandations du groupe d'expert. 2004. Edited by Flammarion M-S; 2004.
3. Yeni PG. Prise en charge médicale des personnes infectées par le VIH. Rapports d'experts. 2006.
4. Yéni P. Prise en charge médicale des personnes infectées par le VIH. Rapport d'experts. 2008.
5. Yeni PG. Prise en charge médicale des personnes infectées par le VIH. Rapport d'experts. Vol. 2010, Recherche. 2010. 18-23 p.
6. Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'expert. Rapport 2013. La documentation française. [Internet]. 2013. 478 p. Available from: http://social-sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf
7. Morlat P. CNS et ANRS. Prise en charge médicale des personnes vivant avec le VIH. Actualisation 2015 du rapport 2013. 2015;1–118.
8. Warszawski J, Tubiana R, Le Chenadec J, Blanche S, Teglas J-P, Dollfus C, et al. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS [Internet]. 2008 Jan 11 [cited 2017 Jan 23];22(2). Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-200801110-00015
9. Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr. 2002;29:484–94.
10. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis [Internet].

2005;40((3)):458–65. Available from: http://www.ucl.ac.uk/ich/research-ich/mrc-cech/research/studies/ECS

11. Mandelbrot L, Tubiana R, Le Chenadec J, Dollfus C, Faye A, Pannier E, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. Clin Infect Dis [Internet]. 2015 Dec 1 [cited 2017 Jan 23];61(11):1715–25. Available from: http://cid.oxfordjournals.org/lookup/doi/10.1093/cid/civ578
12. Brogly SB, Abzug MJ, Watts DH, Cunningham CK, Williams PL, Oleske J, et al. Birth defects among children born to HIV-infected women: Pediatric AIDS Clinical Trials Protocols 219 and 219C. Pediatr Infect Dis J. 2010;29(8):721–7.
13. Knapp KM, Brogly SB, Muenz DG, Shapiro DE, Read JS, P FORTHE. Prevalence of Congenital Anomalies in Infants with in Utero Exposure to Antiretrovirals. Pediatr Infect Dis J. 2012;31(2):164–70.
14. Suy A, Martínez E, Coll O, Lonca M, Palacio M, de Lazzari E, et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS [Internet]. 2006 Jan 2 [cited 2017 Jan 23];20(1):59–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16327320
15. Sibiude J, Le Chenadec J, Bonnet D, Tubiana R, Faye A, Dollfus C, et al. In Utero Exposure to Zidovudine and Heart Anomalies in the ANRS French Perinatal Cohort and the Nested PRIMEVA Randomized Trial. Clin Infect Dis [Internet]. 2015 Jul 15 [cited 2017 Jan 23];61(2):270–80. Available from: http://cid.oxfordjournals.org/lookup/doi/10.1093/cid/civ260
16. Sibiude J, Mandelbrot L, Blanche S, Le Chenadec J, Boullag-Bonnet N, Faye A, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). Menéndez C, editor. PLoS Med [Internet]. 2014 Apr 29 [cited 2017 Jan 23];11(4):e1001635. Available from: http://dx.plos.org/10.1371/journal.pmed.1001635
17. Blanche S, Warszawski J. Tolérance pour l'enfant des antirétroviraux durant la grossesse. médecine/sciences [Internet]. 2013 Apr 26 [cited 2017 Jan 23];29(4):383–8. Available from:

http://www.medecinesciences.org/10.1051/medsci/2013294011

18. Heidari S, Mofenson L, Cotton MF, Marlink R, Cahn P, Katabira E. Antiretroviral drugs for preventing mother-to-child transmission of HIV: a review of potential effects on HIV-exposed but uninfected children. J Acquir Immune Defic Syndr [Internet]. 2011 Aug 1 [cited 2017 Jan 23];57(4):290–6. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-201108010-00007
19. Favarato G, Townsend CL, Bailey H, Peters H, Tookey P, Taylor GP, et al. Protease inhibitors and preterm delivery. AIDS [Internet]. 2017 Nov 14 [cited 2018 Apr 29];32(2):1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29135577
20. Ford N, Mofenson L, Kranzer K, Medu L, Frigati L, Mills EJ, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS [Internet]. 2010 Jun 19 [cited 2017 Jan 24];24(10):1461–70. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201006190-00008
21. Tubiana R, Le Chenadec J, Rouzioux C, Mandelbrot L, Hamrene K, Dollfus C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load. Clin Infect Dis [Internet]. 2010 Feb 15 [cited 2017 Jan 23];50(4):585–96. Available from: http://cid.oxfordjournals.org/lookup/doi/10.1086/650005
22. WHO Guidelines Approved by the Guidelines Review Committee. Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Recommendations for a Public Health Approach: 2010 Version. HIV Med [Internet]. 2012 Sep [cited 2017 Nov 7];13:90–90. Available from: http://doi.wiley.com/10.1111/j.1468-1293.2012.01030_2.x
23. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Available from: http:// aidsinfo.nih.gov/contentfiles/lvguidelines/ PerinatalGL.pdf [Accessed 14 November 2014]. [cited 2018 Apr 20]; Available

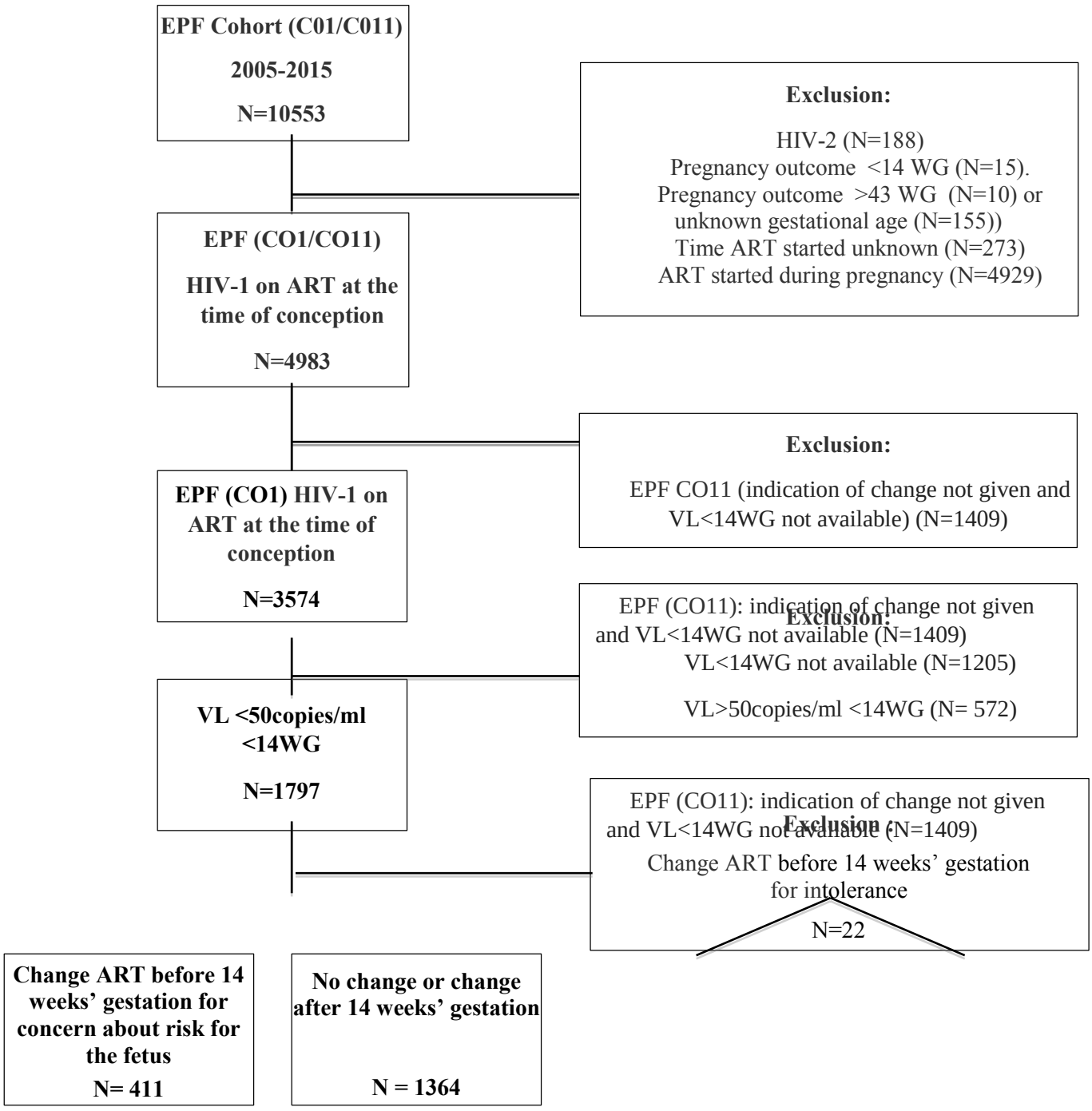
from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/

24. Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, et al. British HIV Association guidelines for the management of HIV infection in pregnant women 2012. HIV Med [Internet]. 2012 Sep [cited 2017 Nov 7];13:90–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22830373
25. Townsend CL, Byrne L, Cortina-Borja M, Thorne C, de Ruiter A, Lyall H, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. AIDS [Internet]. 2014 Apr 24 [cited 2017 Jan 24];28(7):1049–57. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201404240-00014
26. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, et al. Methods for constructing and assessing propensity scores. Health Serv Res. 2014;49(5):1701–20.
27. Momplaisir FM, Brady KA, Fekete T, Thompson DR, Diez Roux A, Yehia BR. Time of HIV Diagnosis and Engagement in Prenatal Care Impact Virologic Outcomes of Pregnant Women with HIV. Ciccozzi M, editor. PLoS One [Internet]. 2015 Jul 1 [cited 2018 Apr 29];10(7):e0132262. Available from: http://dx.plos.org/10.1371/journal.pone.0132262
28. Arribas JR, Girard PM, Landman R, Pich J, Mallolas J, Martínez-Rebollar M, Zamora FX, Estrada V, Crespo M, Podzamczer D, Portilla J, Dronda F, Iribarren JA, Domingo P, Pulido F, Montero M, Knobel H, Cabié A, Weiss L GJO-ESG. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a random. Lancet. 15(7):785–92.
29. Mondi A, Fabbiani M, Ciccarelli N, Colafigli M, D'Avino A, Borghetti A, Gagliardini R, Cauda R, De Luca A DGS. Efficacy and safety of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected patients with virological suppression: 144 week follow-up of the AtLaS pilot study. J Antimicrob Chemother. 2015;70(6):1843–9.
30. Morlat P. CNS et ANRS. Optimisation d ' un traitement antirétroviral en

situation de succès virologique. 2016;(novembre):1–37.

31. Huntington SE, Bansi LK, Thorne C, Anderson J, Newell M-L, Taylor GP, et al. Treatment switches during pregnancy among HIV-positive women on antiretroviral therapy at conception. AIDS [Internet]. 2011 Aug 24 [cited 2017 Jan 23];25(13):1647–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21673558
32. Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults. JAMA [Internet]. 2016 Jul 12 [cited 2017 Nov 7];316(2):191. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27404187
33. Loutfy MR, Wu W, Letchumanan M, Bondy L, Antoniou T, Margolese S, et al. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. Pett S, editor. PLoS One [Internet]. 2013 Feb 13 [cited 2017 Jan 24];8(2):e55747. Available from: http://dx.plos.org/10.1371/journal.pone.0055747
34. Floridia M, Tamburrini E, Ravizza M, Anzidei G, Tibaldi C, Bucceri A, et al. Antiretroviral therapy at conception in pregnant women with HIV in Italy: wide range of variability and frequent exposure to contraindicated drugs. Antivir Ther [Internet]. 2006 [cited 2017 Jan 24];11(7):941–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17302258
35. Bardeguez AD, Lindsey JC, Shannon M, Tuomala RE, Cohn SE, Smith E, et al. Adherence to antiretrovirals among US women during and after pregnancy. J Acquir Immune Defic Syndr [Internet]. 2008 Aug 1 [cited 2017 Jan 24];48(4):408–17. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-200808010-00004
36. Mellins CA, Chu C, Malee K, Allison S, Smith R, Harris L, et al. Adherence to antiretroviral treatment among pregnant and postpartum HIV-infected women. AIDS Care [Internet]. 2008 Sep [cited 2017 Jan 24];20(8):958–68. Available from: http://www.tandfonline.com/doi/abs/10.1080/09540120701767208

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	Change for medical strategy (N= 411)				
	N= 1775	%	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 neonatalogy department)	650	21.1%	13	0.8	[0.7-1.1]	
Level 3 (with a neontatal intensive care unit	1116	24.2%	27	1		
Treatment acccording 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 +/- boost**ed** **No**	682	41.5%	25	1		<0.01
Yes	1093	13.6%	15	0.2	[0.2-0.3]	
PI boost**ed** **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 acccording 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%. [1]Logistic regression, [2]Cox 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.

[1]Logistic regression, [2]Cox 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
Enfurvitide	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

[a]ajustement 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.

[1]Logistic regression, [2]Cox model.