Pregnancy outcomes following exposure to efavirenz-based antiretroviral therapy in the Republic of Congo

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SUMMARY

WHO recently recommended efavirenz (EFV) use for HIV infection through pregnancy, breastfeeding and childbearing age. However the use of EFV during pregnancy remains of concern and not all national guidelines reflect WHO advice. Few data are available concerning pregnancy outcomes. The objective of our study was to evaluate pregnancy outcomes in a cohort of women who conceived on EFV. A retrospective, multicenter cohort study was conducted in Pointe Noire, Republic of Congo (September 2005- June 2012). The following adverse pregnancy outcomes were considered: births defects, low birth weight, premature delivery, stillbirth and abortion, stratified by antiretroviral exposure at the time of conception. During the study period, 188 women conceived on antiretrovirals: 35 (18.6%) on EFV-based regimens and 153 (81.4%) on nevirapine-based regimens. Adverse pregnancy outcomes were observed in 17/35 (48.6%, 95% CI 33.0-64.4%) women in the EFV group and in 43/153 (28.1%, 95% CI 21.6-35.7%) in the non-EFV group (p=0.019). No birth defect was observed in either group. An increased incidence of adverse pregnancy outcomes was observed in the EFV group. As WHO is promoting a widespread use of EFV also for women in childbearing age, our study emphasizes the importance of launching large prospective cohort studies investigating pregnancy outcomes in exposed women.

KEY WORDS: Efavirenz, Pregnancy, Birth defects, Pregnancy outcome, Africa.

INTRODUCTION

In sub-Saharan Africa, non-nucleoside reverse transcriptase inhibitor (NNRTIs) - based combined antiretroviral treatments (cART) are the

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preferred first-line regimens for the treatment of HIV infection. Among the NNRTIs available in low- and middle-income countries, efavirenz (EFV) has a more favorable side-effects profile (Shubber et al., 2013) and a lower pill burden than nevirapine (NVP) and is significantly less likely to lead to virologic failure compared to NVP (Pillay et al., 2013). Therefore, EFV is becoming the NNRTI of choice. Moreover, the increase in the prescription of EFV, associated with the increasing numbers of reproductive-aged women accessing cART services, will lead to an increase in the number of women

who will conceive on EFV-based cART. In recent decades, this possibility always frightened clinicians because of its possible association with congenital abnormalities, in particular neural tube defects (Nightingale, 1998; Fundarò et al., 2002; De Santis et al., 2002; Saitoh et al., 2005; Gudu et al., 2013). However, data on the association between EFV and birth defects are limited and their interpretation controversial (Patel et al., 2005; Bussmann et al., 2007; Watts, 2007; Townsend et al., 2009; Bera et al., 2010; Brogly et al., 2010; Ekouevi et al., 2011; Knapp et al., 2012; Shanske, 2012; Floridia et al., 2013; Watts, 2007; Phiri et al., 2014; Sibiude et al., 2014; Ford et al., 2014). In addition, little evidence is available on the impact of EFV on pregnancy (Ekouevi et al., 2011). Thus, the use of EFV during pregnancy remains of concern and conflicting recommendations are proposed by different countries both in resource-limited and resource-rich settings (Chersich et al., 2006; Giles, 2013), balancing clinical benefits and perceived risks (Ouattara et al., 2012; Uthman et al., 2012). For this reason, WHO reviewed the safety of EFV during pregnancy (WHO. Technical update on treatment optimization: use of efavirenz during pregnancy: a public health perspective. 2012) and recently recommended EFV use as first line regimen also for the prevention of HIV vertical transmission (p-MTCT), including the first trimester of pregnancy, breastfeeding and child-bearing age (WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013).

The objective of our study was to evaluate pregnancy outcomes in a cohort of women who conceived during an EFV-based cART.

METHODS

Study design, participants and setting

A retrospective multicenter cohort study was conducted in the Republic of Congo from September 2005 to June 2012 among all women enrolled in the p-MTCT Kento-Muana (phase I: 2005-2008) and Kento-Mwana (phase II: 2009-2012) projects in the city of Pointe Noire. Both phases of the project were carried out in peripheral local care units, as previously described (Bisio et al., 2013). Briefly, the project offered voluntary counseling and testing to all pregnant women attending the antenatal care units included in the project sites. A complete preventive protocol was offered to HIV-positive pregnant women and their children, including cART prophylaxis/therapy, serological, immunological and virological test, assisted vaginal delivery and appropriate feeding choice. Especially during phase II, not only women who discovered their HIV positivity status during pregnancy but also those who were already aware of their HIV positive status were included in the project. Only HIV-infected pregnant women who conceived on cART and were followed until the end of pregnancy (miscarriage, stillbirth or delivery) are included in the present study. According to the recommendations for cART prescription in the Republic of Congo, the first line regimen for all adults, including women in childbearing age, was zidovudine (AZT) + lamivudine (3TC) + NVP. The reasons why EFV was prescribed instead of NVP were previous hepatic or skin toxicity to NVP or concomitant tuberculosis (TB) treatment. In case of severe anemia (Hb <7 g/dl) stavudine (d4T) or tenofovir (TDF) were prescribed instead of AZT, before and after the year 2010, respectively. As per protocol, only pregnant women receiving an EFV-based regimen who presented during the first trimester of pregnancy (gestational age <14 weeks) were switched to a non-EFV containing regimen (NVP, PI or dual NRTIs therapy, according to year of prescription and drug availability). Baseline demographic characteristics (age, CD4 cell count, plasma HIV-RNA viral load, CDC stage, and gestational age), co-morbidities, duration of cART and of EFV or non-EFV regimen prior to conception, compliance with cART, switch to another drug during pregnancy, outcome of pregnancy and newborn anthropometric characteristics were obtained from all pregnancies. The gestational age was estimated by the history of last menstruation or, if available, by an ultrasound examination. The clinical status of each newborn was evaluated at birth and the age of one, four and six weeks of life by a physician of the Paediatric Services of the Army Hospital and of the Tié-Tié Hospital in Pointe Noire. The presence of internal birth defects was investigated by ultrasound tomography only if clin-

ically suspected. All data were retrospectively collected from clinical records and analyzed in order to compare outcomes in women exposed and nonexposed to an EFV-based regimen. Primary analyses classified women according to their exposure at the time of conception. However, in a set of secondary, explanatory analyses, women who changed therapy during pregnancy were excluded.

Outcomes

The following outcomes were considered for both EFV and non-EFV group: miscarriage after first observation (unwanted termination of pregnancy <24 weeks of amenorrhea); stillbirth (unwanted termination of pregnancy ≥24 weeks of amenorrhea); premature delivery (live birth occurring <37 weeks of amenorrhea); birth weight (low birth weight infant defined as live born occurring ≥37 weeks of amenorrhea and weighing <2,500 g); births defects observed in the first six weeks of life.

Ethical approval

The project was conducted in accordance with the Declaration of Helsinki and in partnership with the Congolese Ministry of Health and the Congolese Council against AIDS. All participants provided written informed consent at the time they agreed to be taken in charge by the project. Confidentiality was maintained throughout all phases of the study, as previously described (Bisio *et al.*, 2013).

Statistical analysis

Group comparisons were performed using non-parametric Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test, as appropriate, for categorical variables. Continuous variables are presented as medians with interquartile ranges (IQRs) and dichotomous data as proportions with 95% confidence intervals (CIs). All analyses were performed with Epi-info software, version 3.5.4.

RESULTS

Baseline characteristics

During the study period, a total of 188 women conceived on cART: 35 (18.6%) on EFV-based regimens and 153 (81.4%) on non-EFV based regimens. All non-EFV based regimens were NVP-based. Baseline demographic characteristics, type and duration of cART prior to conception are reported in Table 1. As expected, the two groups differed in several respects. The median gestational age at the first visit was 22 weeks and 19 weeks (IQR:16-23), respectively, and only a minority of women presented during the first trimester: 4/35 (11.4%) and 37/153 (24.2%) in EFV and non-EFV group, respectively. The duration of any cART before conception, as well as the duration of the specific regimen taken at the time of conception, were 693 (IQR 351-1059) and 672 days (IQR 350-1050), respectively, and did not differ between EFV and non-EFV groups. The two-nucleoside drug combination associated with EFV or NVP was AZT+3TC in the majority of women of both groups; d4T was more frequently prescribed in the EFV group (5/35, 14.3%) as compared to non-EFV one (6/153, 3.9%). At the first visit, the median lymphocyte T CD4+ cell count was 227 (IQR 102-364) and 299 (206-399) in the EFV and non-EFV groups, respectively. A baseline viral load determination was performed only in 120 women: 17/24 (70.8%) and 59/96 (61.5%) presented with HIV-RNA values <50 cp/ml in EFV and non-EFV group, respectively. A higher proportion of women in the EFV group had a history of an AIDS defining event (17/35, 48.6% vs. 38/153, 24.8% in EFV and non-EFV group, respectively).

Follow-up during pregnancy

During pregnancy, 30 (16.0%) women switched their initial treatment: 12/35 (34.3%) and 18/153 (11.8%) of those who conceived on EFV and non-EFV based regimen, respectively (p=0.001) (Table 1). The reason for switching differed between the two groups. Women who conceived on EFV mainly switched because the physician was worried about the potential teratogenicity (7/12, 58.0%), but only in one case was the switch done during the first trimester. Other causes of switch were virological failure in 4/12 (33.3%) cases and intolerance in one woman (8.3%). The antiretroviral used instead of EFV was a protease inhibitor (for the four cases of virological failure) or NVP (for the remaining eight cases). Women who conceived on NVP

TABLE 1 - *Baseline characteristics and treatment during pregnancy among 188 women included in the study.*

	EFV group (n:35)	Non-EFV group (n:153)	p
Age (years) Mean+SD	32±5	32±4	0.553*
Gestational age (weeks) - Median (IQR)	22 (18-24)	19 (16-23)	0.053*
First visit during the I trimester - Number (%)	4/35	37/153	0.191***
CDC stage at presentation - Number A/B/C	11/4/17	84/31/38	0.006**
Stavudine in NRTIs back-bone - Number (%)	5/35 (14.3)	6/153 (3.9)	0.067***
Days of cART at conception - Median (IQR)	517 (238-988)	725 (371-1061)	0.154*
Days of cART conception regimen - Median (IQR)	510 (184-988)	706 (370-1057)	0.143*
CD4+ T cell count at presentation - Median (IQR)	227 (102-364)	292 (206-399)	0.030*
HIV-RNA at presentation - Number <50 cp/ml (%)	17/24 (70.8)	59/96 (61.5)	0.394**
Full adherence to cART - Number (%)	20/33 (60.6)	118/151 (78.2)	0.035**
Switch of cART regimen - Number (%)	12/35 (34.3)	18/153 (11.8)	0.001**

*Mann-Withney U-test; **Chi square test. ***Fisher exact test.

primarily switched to a PI-based regimen because of virological failure (17/18, 94.4%); only one woman (5.6%) switched from NVP to EFV because she started an anti-TB treatment. The adherence to the treatment during pregnancy, as defined by pill count and self-reporting, was better in the non-EFV group (p=0.035), with 118/151 (78.1%) women who fully adhered to the cART prescribed, compared with 20/33 (60.6%) in the EFV group. Lymphocyte T CD4+ cell count and the percentage of women with HIV-RNA values <50 cp/ml at delivery was significantly higher in non-EFV group, as compared to EFV (p<0.01).

Outcomes

Among all 35 women in the EFV group, four (11.4%) had a stillbirth, while no miscarriage was observed. In the non-EFV group 4/135 (2.6%) women had a stillbirth and 3/135 (2.0%) a miscarriage. Because of the small numbers observed and in consideration of the probable under-reporting of miscarriage due to delayed presentation during pregnancy, miscarriage and stillbirth were considered cumulatively and no difference was observed between the two groups. The remaining 177 women (31 who conceived on EFV and 146 on NVP) gave birth to 184 live newborns (seven couples of twin). Among live births, premature delivery was reported in 19/177 women (10.7%, 95% CI: 6.6-16.3), with no difference when considering drug exposure at conception. Considering term deliveries, the occurrence of low birth weight infants was higher in the EFV group (9/27, 33.3% 95% CI: 16.5-54.0) when compared to the non-EFV regimen (21/131, 16% 95% CI: 10.2-23.5) (p=0.037). As shown in table 2, the frequency of each adverse pregnancy outcome was higher in the EFV group, achieving statistical significance for the most frequent one (low birth weight infants) and when globally consid-

TABLE 2 - *Outcomes in women, according to cART exposure at the conception.*

	EFV group	Non-EFV group	p
Pregnant women - Number	35	153	
Miscarriage + stillbirths - Number (%)	4/35 (11.4)	7/153 (4.6)	0.251**
Miscarriage - Number (%)	0/35 (0)	3/153 (2.0)	1**
Stillbirths - Number (%)	4/35 (11.4)	4/153 (2.6)	0.082**
Women who gave birth to a live-born infant - Number	31	146	
Preterm delivery - Number (%)	4/31 (12.9)	15/146 (10.3)	0.869**
Term deliveries - Number	27	131	
Low birth weight - Number (%)	9/27 (33.3)	21/131 (16.0)	0.037*
Cumulative negative pregnancy outcomes*** - Number (%)	17/35 (48.6)	43/153 (28.1)	0.019*

*Chi square test. **Fisher exact test. ***Computed as: miscarriages + stillbirths + preterm deliveries + low birth weight.

TABLE 3 - *Outcomes in women who subsequently do not switch cART regimen.*

	EFV group	*Non-EFV group*	*p*
Pregnant women - Number	23	133	
Miscarriage + stillbirths - Number (%)	3/23 (13.0)	7/133 (5.3)	0.335**
Miscarriage - Number (%)	0/23 (0)	3/133 (2.3)	1**
Stillbirths - Number (%)	3/23 (13.0)	4/133 (3.0)	0.132**
Women who gave birth to a live-born infant - Number	20	126	
Preterm delivery - Number (%)	2/20 (10.1)	12/126 (9.5)	1**
Term deliveries - Number	18	114	
Low birth weight - Number (%)	5/18 (27.8)	20/114 (17.5)	0.465**
Cumulative negative pregnancy outcomes*** - Number (%)	10/23 (43.5)	39/133 (29.3)	0.177*

*Chi square test. **Fisher exact test. ***Computed as: miscarriages + stillbirths + preterm deliveries + low birth weight.

ered. Overall, the incidence of negative pregnancy outcome was almost doubled, occurring in 17/35 (48.6%, 95% CI 33.0-64.4%) and 43/153 (28.1%, 95% CI 21.6-35.7%) in the EFV and non-EFV groups, respectively (p=0.019). When women who switched therapy during pregnancy are excluded from the analysis (Table 3), the difference between the two groups in the occurrence of the negative outcomes is similar but no longer significant: 10/23 (43.5%, 95% CI 25.6-63.2%) and 39/133 (29.3%, 95% CI 22.3-37.6%) in the EFV and non-EFV groups, respectively (p=0.177). No birth defect was observed among all cART-exposed live born infants (0/31, 95% CI 0-11.9% and 0/146, 95% CI 0-2.5% in the EFV and non-EFV groups).

Additional reports

One case of omphalocele was reported in a stillbirth from an HIV-infected pregnant woman who conceived on an EFV-based regimen. The case was not included in the analysis because the attending physician diagnosed an intrauterine death at the first visit and, for this reason, did not include the woman in the project. Therefore we report this case separately to minimize bias as other case of stillbirths at presentation without evident birth defects or with different drug exposure at the conception may not have been reported.

DISCUSSION

In this study, a higher proportion of low birth weight infants and of cumulative negative pregnancy outcomes were observed in the EFV-exposed pregnancies. This finding is in contrast with previous experiences showing no increased risk of adverse pregnancy outcomes following EFV exposure compared to NVP exposure during the first trimester, except for voluntary termination of pregnancy (Ekouevi *et al.,* 2011) (which was not considered in our study, because it is allowed in the Republic of Congo only if evident malformations are diagnosed by ultrasound examination).

No birth defects were observed among women exposed to cART at conception. Given the low underlying incidence of birth defects in the overall population (2-3%), in particular of neural tube defects (0.1-0.4%), and the small size of our cohort, our results do not allow us to exclude a teratogenic risk linked to the exposure to EFV or NVP. In a recent updated systematic review including 2026 first trimester EFV exposures, the incidence of neural tube defects remained low, 0.05% (95% CI <0.01-0.28) and similar to the incidence in the general population. (Ford *et al.,* 2014). However, because of the low incidence of central nervous system anomalies in the general population and relatively small number of exposed women in the current literature, continued prospective surveillance is warranted. Our data may enhance the power of future meta-analyses, contributing to assemble the sample size needed to reach definitive conclusions on EFV safety in pregnancy.

The group of women on EFV at conception differed from those on NVP in several aspects, including a more advanced CDC stage and a lower CD4 cell count at presentation. As a consequence, the different frequency in adverse pregnancy outcomes between the EFV and

non-EFV group might be attributable to these baseline differences and be independent of any negative effect of EFV. These clinical differences at presentation between EFV and NVP exposed women are not surprising and reflect the reality on the field. In fact, EFV is routinely prescribed in case of concomitant TB infection and in women who had already undergone NVP-related adverse events and in case of more severe immune-virological impairment, as a better virological response follows EFV administration (Pillay *et al.,* 2013). The small numbers of women in both groups preclude the use of multivariate analyses to adjust for imbalances in baseline factors.

A second major limitation of our study, beside sample size, is that all data were obtained through a retrospective survey, and we could only focus on the visible and external congenital abnormalities during the first six weeks of age. In addition, no specific box was provided in clinical records concerning the presence or absence of birth defects. For this reason, minor birth defects and internal birth defects that take time to show complications may be underreported.

Another important limitation of this study stems from the fact that the observation of many women started late during pregnancy. Only a minority of women (41/188, 14.3%) presented during the first trimester, with a mean gestational age at presentation of 19 weeks of gestation. For this reason the rate of miscarriage is assumed to be strongly underestimated in both groups, as women who had an early miscarriage did not present to a Project health care unit. As a consequence, no definitive inferences concerning this pregnancy outcome can be drawn. However, presenting late during pregnancy is a common feature in the real word of low-resource settings. Furthermore, this limitation does not affect the analysis of the other outcomes (stillbirth, premature delivery, weight at birth).

One might also argue that the events observed with EFV- and NVP-based regimens may be attributable to companion drugs (ie d4T and. AZT); in this regard, no association was found between d4T exposure and pregnancy outcome (data not shown). In addition, no reliable data were available concerning the use of cotrimoxazole (CTX) at the time of conception. As CTX prophylaxis is prescribed in the Republic of Congo according to WHO recommendation, to all patients with CD4+ cell count <500 mm³, we can assume that the majority of woman included in the study were exposed to CTX at conception, but no inferences can be drawn in this regard.

In our study, the analysis on all pregnant women by cART at the time of conception supports the hypothesis of a detrimental effect of EFV on pregnancy outcome, with a rather homogeneous effect on all outcomes. Yet, this analysis has to take into account the significant proportion of women who switched cART regimen during pregnancy, usually during the second trimester. This may be particularly relevant since low birth weight in term deliveries was the most frequent adverse pregnancy outcome, and intra-uterine growth occurs mainly during the last trimester of pregnancy. When the analysis was restricted to women who stayed on the same therapy throughout their pregnancies the differences in adverse pregnancy outcomes were still present and of a comparable order of magnitude, even though no longer statistically significant. This finding might be interpreted as supporting the hypothesis of a possible detrimental effect of EFV on pregnancy outcomes.

Among the seven women who changed EFV because the physician was worried about its potential teratogenicity, only one switched during the first trimester, at 10 weeks of gestation. The remaining six women switched during the second or the third trimester, regardless of the protocol indications which recommended stopping EFV only if the women presented before the 14 week of pregnancy. This is in line with previous experiences (Floridia *et al.,* 2006; Hungtington, 2011) and reflects the reality in the field, where physicians are worried about the use of EFV throughout all pregnancy. As the lack of clear evidence and univocal recommendations leads to uncertainty in clinical practice (Chersich *et al.,* 2006, Giles, 2011), in 2012 WHO published a technical update reviewing the evidence on the safety, tolerability and efficacy of EFV (WHO. Technical update on treatment optimization: use of efavirenz during pregnancy: a public health perspective. 2012). More recently, the consolidated WHO guidelines (WHO.

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013) clearly stated that providing an optimized, fixed-dose combination first-line regimen of TDF + 3TC (or FTC) + EFV to all pregnant and breastfeeding HIV-infected women gives important programmatic and clinical advantages, including ease of implementation, harmonization of the regimen with non-pregnant adults, better acceptability and increased coverage of cART, with consequent benefits on vertical transmission, maternal health and sexual prevention.

In conclusion, our results are not fully reassuring, as they suggest an increased frequency of adverse pregnancy outcomes, and in particular of low birth weight infants, in association with exposure to EFV. Whether this is due to the exposure to the treatment or to the differences in baseline clinical characteristics remains to be established. Since the consolidated WHO guidelines are likely to promote a widespread use of EFV also for women in childbearing age, a considerable number of women will conceive on EFV. This will allow us to investigative the occurrence of birth defects on a significant number of pregnancies by the mean of large prospective cohort studies. Our experience emphasizes that not only the prevalence and type of birth defects but pregnancy outcomes globally considered should be considered and evaluated.

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