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Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the leDEA West Africa and ANRS databases, Abidjan, Côte d'Ivoire

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Abstract

Background—An increasing number of HIV-infected women become pregnant while receiving efavirenz (EFV). We compared the pregnancy outcomes of women exposed to EFV and to nevirapine (NVP) during the first trimester.

Methods—A retrospective study in four HIV care centers participating to clinical trials and international cohort collaboration. All HIV-infected pregnant women who conceived on EFV or NVP-based antiretroviral therapy (ART) between 2003 and 2009 were included. Pregnancy outcomes were: abortion (voluntary termination), miscarriage (unwanted termination <20 weeks of amenorrhea [WA]), stillborn (death ≥20 WA), preterm delivery [PTD] (live-birth <37 WA) and low birth weight [LBW] (<2,500 grams).

Results—Overall, 344 HIV-infected pregnant women conceived on ART (213 on EFV and 131 on NVP). Median age was 29 years and median CD4 count 217 cells/μl at ART initiation. The overall proportion was 11.7% for abortion, 5.2% for miscarriage, 6.7% for stillborn, 10.8% for PTD and 20.2% for LBW. There was no difference between EFV and NVP exposure, except for

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abortion (14.3% vs 7.3%; $p=0.05$). No external and visible congenital malformation was observed neither in women exposed to EFV nor in women exposed to NVP.

Conclusion—Among women exposed to EFV, no significant increased risk of unfavorable pregnancy outcome was reported except for abortion.

Keywords

Efavirenz; HIV infection; congenital abnormalities; pregnancy outcomes; Africa

INTRODUCTION

In resource-limited settings, non-nucleoside reverse transcriptase inhibitors (NNRTI) are recommended for first-line antiretroviral therapy (ART) (1). Efavirenz (EFV) is the preferred NNRTI because of its lower toxicity compared to nevirapine (NVP), its possible use in case of co-infection of HIV with tuberculosis and in women with CD4 count above 250 cells/ μ l. However these benefits need to be carefully weighed against its potential risk of birth defects, especially in the settings where contraceptive and family planning services are limited. Indeed, EFV was classified by the US Food and Drug Administration (FDA) in category D (positive evidence of risk of teratogenicity) after birth defects were reported in some infants exposed to EFV during the first trimester of pregnancy (2-4).

In sub-Saharan Africa, 60% of HIV-infected patients are women, most of them of childbearing age (5-7). Thus, an increasing number of pregnancies is occurring in women initiating ART. An incidence of 9.0 new pregnancies per 100 women on ART was recently reported in the MTCT-Plus network (8). In Côte d'Ivoire, in the ANRS Ditrane-Plus cohort where the contraceptive methods were "free of charge", the risk of a new pregnancy was 16.5% at 24 months (9). In Botswana, this probability was 7.9 per 100 person-years among women on EFV-based ART (10).

To date, few data are available on the pregnancy outcomes of women exposed to EFV during the first trimester. Data from the international Antiretroviral Pregnancy Registry (APR) (11) and cohort studies (12,13) have found no evidence of increased prevalence of overall congenital abnormalities after first-trimester EFV exposure (2.8/100 live births), compared to second or third-trimester EFV exposure (3.6/100 live births), to first-trimester NVP exposure (2.1/100 live births) or to the general population (2.7/100 live births). Detailed data on these pregnancy outcomes with a breakdown by miscarriage, preterm delivery (PTD), stillbirth and low birth weight (LBW) are hardly reported (10,12,14,15). Our objective was to describe and compare the pregnancy outcomes between women who were exposed to EFV and those exposed to NVP during the first trimester in Côte d'Ivoire, West Africa.

METHODS

Study design and setting

A retrospective survey was conducted in Abidjan within four adult HIV clinical centers that are participating in the IeDEA (International epidemiological Databases to Evaluate AIDS) West Africa collaboration (<http://www.iedeawestafrika.org>) and in two Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS) randomized trials, ANRS 1269 Trivacan (16) (registered number NCT 00158405) and ANRS 12136 Temprano (registered number NCT 00495651).

Inclusion and follow-up of pregnant women

The occurrence of new pregnancy was based on the last menstruation date at each follow-up visit and/or the urine test. New pregnancy was systematically recorded in the standardized forms (for the two trials) or in the clinical forms.

We searched information on all women on EFV who became pregnant in the data base of the two trials and in the computerized information system of the participating clinics. Therefore all HIV-infected pregnancy women who conceived on EFV or NVP-based ART between January 2003 and July 2009 were eligible for this study. Only the first recorded pregnancy in the given period was taken into account for each woman. The gestational age was estimated by the history of last menstruation or an ultrasound examination. Standardized forms were developed to collect information on age, pretreatment CD4 count, date of starting ART (NVP or EFV), drug regimen, switch and reason of switching to other ARV drugs than NVP or EFV, gestational age at diagnosis of pregnancy, last menstruation date, outcome of pregnancy and newborn anthropometric characteristics. Women exposed to EFV were advised by the physicians about the potential risk of congenital abnormalities and received free of charge the contraceptive methods available.

Outcomes

Five outcomes were considered: (1) abortion defined as a voluntary termination of pregnancy (not based on the detection of congenital abnormality by obstetrical ultrasound), (2) miscarriage as an unwanted termination of pregnancy <20 weeks of amenorrhea, (3) stillborn as any death reported in children between 20 weeks of amenorrhea and delivery, (4) PTD as any live birth occurring <37 weeks of amenorrhea, LBW as a live born child weighing <2,500 grams, and (5) congenital abnormalities as all visible and external abnormalities observed or diagnosed in the first six weeks of age.

Ethical aspects

The protocol of the IeDEA West Africa collaboration and of the ANRS 1269 and 12136 trials were approved by the national ethics committees of Côte d'Ivoire. Each IeDEA-affiliated clinical center has a federal-wide assurance number identification.

Statistical analysis

Group comparisons were performed using Student's t test or non-parametric Mann-Whitney U test for continuous variables, Chi-square test or Fisher's exact test when appropriate for categorical variables. The proportion of birth outcomes was reported with its 95% confidence interval (95% CI). All analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

From January 2003 to July 2009, a total of 344 HIV-infected women conceived while receiving ART: 213 (61.9%) conceived on EFV-based ART and 131 (38.1%) on NVP-based ART. Overall, the median age at ART initiation was 29 years (inter-quartile range [IQR], 26-32), the median CD4 count was 217 cells/ μ l (IQR, 146-280) and 193 (56.1%) women were at WHO stage 3 or 4. The two nucleoside drug combinations associated with EFV or NVP were zidovudine-lamivudine (59.9%), stavudine-lamivudine (37.2%), tenofovir-emtricitabine (2.3%), and didanosine-stavudine (0.6%). The baseline characteristics of women were comparable in the EFV and NVP-based ART groups, except for the ART regimen, with more women receiving ZDV-lamivudine with EFV than with NVP (Table 1).

Follow-up

During pregnancy, 18 (5.2%) women were lost to follow-up and 192 (55.8%) switched their initial treatment. The proportion of women who were lost to follow-up before delivery and whose pregnancy outcome could not be ascertained was not statistically different between women exposed to EFV and those exposed to NVP (4.7% vs 6.1%; $p=0.57$) (Table 2). As for the treatment modification, 190 (89.2%) of the 213 women exposed to EFV switched to either a protease inhibitor (PI) ($n=25$) or to a NVP-based regimen ($n=165$) because of the diagnosis of pregnancy. In those exposed to NVP, two women switched to a PI-based regimen because of severe adverse events. The median duration of ART exposure after conception was 52 days [IQR, 37-75] in the EFV group and 264 days [IQR, 222-285] in the NVP group ($p < 0.001$).

Outcomes of pregnancy

Overall, the pregnancy outcomes were known in 94.8% of women: 203 exposed to EFV and 123 to NVP. Of these 326 women, 11.7% had an abortion (95% CI: 8.4-15.7), 5.2% had a miscarriage (95% CI: 3.1-8.2) and 6.7% experienced a stillbirth (95% CI: 4.3%-10.0%). The proportion of abortion was higher in the EFV group than in the NVP group (14.3% vs 7.3%; $p=0.05$). The proportion of miscarriages and stillbirths was similar in both groups (Table 2). A total of 249 live births (76.4%) were reported, including 30 (12.0%) via caesarean section (Table 2). Data on birth weight were available for 223 infants (89.6%) and median birth weight was 2800 grams [IQR 2500-3250]. PTD was reported in 27 (10.8%) live born infants, with no statistical difference between those exposed to EFV and to NVP (9.5% vs. 12.7%; $p=0.76$). A LBW was measured in 45 infants (20.2%), without any statistical difference between those exposed to EFV and to NVP (17.2% vs. 24.2%; $p=0.20$). No external congenital malformation was reported in the clinical charts of the 249 live born infants, neither those exposed to EFV (upper limit of the 95% confidence interval: 2.5%) nor those exposed to NVP (upper limit of the 95% confidence interval: 3.6%) (Table 2).

DISCUSSION

Our study conducted in Côte d'Ivoire is the largest single study to-date evaluating HIV-infected women exposed to EFV during the first trimester of pregnancy. In this survey, no increased risk of pregnancy outcomes was reported following EFV exposure compared to NVP exposure during the first trimester, except for induced abortion. In general, our results are comparable to those observed in previous studies in terms of frequency of pregnancy outcomes after exposure to EFV during the first trimester. For abortion, the frequency was higher after EFV exposure (14.3%) compared to NVP exposure (7.3%). Similar results were found in two studies conducted in Africa. The first report included 37 women and 15% of these chose to have an early termination of pregnancy (17). The second study included 117 women and the frequency of abortion was 33.7% (28/83) after EFV-based ART exposure and 5.9% (2/34) after a non EFV-ART (18). This high frequency of abortion after early exposure to EFV could be related by the fear of warning given by clinicians about the potential risk of congenital abnormalities. Another explanation is, at enrolment; the women did not want children and therefore were eligible for EFV

In our sample of women who became pregnant while receiving ART, no case of congenital abnormalities was reported in infants exposed to EFV (upper limit of the 95% confidence interval: 2.5%) or to NVP (upper limit of the 95% confidence interval: 3.6%), although the median time of exposure covered the critical period of organogenesis (52 days with EFV and 264 days with NVP). These results should be taken with caution, as they were obtained through a retrospective survey, with moderate sample size, and we could only focus on the visible and external congenital abnormalities during the first six weeks of age. However, our

findings are compatible with data already reported where the frequency of congenital abnormalities ranged between 0.0% and 4.5% and where no increased risk of congenital abnormalities was found with EFV-based ART compared to a non-EFV-based ART (10-13,19). In the US-based prospective antiretroviral pregnancy registry, congenital abnormalities had been observed as of July 2009 in 14 of 501 (2.8%, 95% CI: 1.5%-4.7%) live born infants following first-trimester exposure to EFV and in two of 55 (3.6%, 95% CI: 0.4%-12.5%) live births with second-or third-trimester EFV exposure (11). A similar observation was made in a study in South Africa where the proportion of congenital abnormalities was not significantly different between live births exposed to EFV during the first trimester (3.3%) and second/third trimester (2.6%). In this report, the proportion of congenital abnormalities was 3.0% in live births exposed to NVP-based ART during the first trimester (12).

For the other pregnancy outcomes, miscarriage, stillborn, PTD and LBW, the frequencies following first trimester EFV exposure found in our study were also comparable to other studies reported in Africa (10,12,18) or in Europe (13-15). As reported also in our study, there was no increased risk of these pregnancy outcomes after EFV exposure during the first trimester, compared to second/third trimester exposure with EFV or to a non-EFV-based ART (12,18).

We also found that approximately 90% of HIV-infected women exposed to EFV during the first trimester switched to NVP or to LPV/r once pregnancy was diagnosed (median time of exposure of 52 days after conception). In South Africa, EFV was substituted with NVP in all the women, once the diagnosis of pregnancy was made (median time of exposure of 43 days) (10). However, in another study in the same country, EFV was substituted with NVP or PI in 32% only (63/195) of women who conceived on EFV-based ART with no increased risk of congenital abnormalities compared to second/third EFV exposure (12). It is thus likely that in EFV-treated HIV-infected women, EFV switches is only necessary if the diagnosis of pregnancy is made before the complete closure of the neural tube. This event occurs approximately 28 days in median after conception. This situation will thus be rarely encountered in Africa where antenatal care is usually initiated much later in pregnancy. In conclusion, our study is the largest evaluation made in a single setting to date on EFV exposure during the first trimester of pregnancy. It provides important additional information to the EFV teratogenicity debate and has already been integrated in the recently published meta-analysis (20). Indeed, Ford et al concluded that there was no increased risk of overall birth defects between 35/1132 EFV-exposed women with live births compared to 289/7163 women with live births exposed to other antiretroviral drugs in the first trimester of pregnancy (20). Although our data seem reassuring as the previous reports and the meta-analysis, it is clear that the limited sample size remains a weakness. The 2009 revision of the World Health Organization guidelines recommends that EFV be avoided during the first trimester of pregnancy or that it should not be used by women of childbearing age in the absence of an effective contraceptive method (21). In addition, it states that if a woman already on EFV is diagnosed as pregnant before 28 days of gestation, EFV should be stopped and substituted with NVP or a PI. If a woman is diagnosed as pregnant after 28 days of gestation, EFV should be continued. Finally, there is no indication for abortion in women exposed to EFV in the first trimester of pregnancy (21). More collaborative studies and pharmacovigilance systems capturing routine data should be put in place especially in sub-Saharan Africa to improve the evidence informing public health guidelines. In between, models may investigate the cost-benefit ratio between a small additional risk of severe malformations in the infants and an improvement in survival for a small number of mothers receiving ART using EFV compared to NVP.

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APPENDIX

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REFERENCES

1. World Health Organization. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. [Accessed 27 April 2010]. Nov2009 Available at: http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf
2. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med* 2002;162(3):355. [PubMed: 11822930]
3. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002;16(2):299–300. [PubMed: 11807320]
4. Saitoh A, Hull AD, Franklin P, Spector SA. Myelomeningocele in an infant with intrauterine exposure to efavirenz. *J Perinatol* 2005;25(8):555–6. [PubMed: 16047034]
5. Bashi J, Balestre E, Messou E, Maiga M, Coffie PA, Zannou DM, et al. Time trends in demographic and clinical characteristics of adult patients on HAART initiation in West Africa. *Med Mal Infect*. 2009 [Epub ahead of print] [French].
6. Calmy A, Pinoges L, Szumilin E, Zachariah R, Ford N, Ferradini L. Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. *AIDS* 2006;20(8):1163–9. [PubMed: 16691068]
7. Toure S, Kouadio B, Seyler C, Traore M, Dakoury-Dogbo N, Duvignac J, et al. Rapid scaling-up of antiretroviral therapy in 10,000 adults in Cote d'Ivoire: 2-year outcomes and determinants. *AIDS* 2008;22(7):873–82. [PubMed: 18427206]
8. Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med* 2010;7(2):e1000229. [PubMed: 20161723]
9. Viho, I.; Becquet, R.; Ekouevi, DK.; Brou, H.; Yao, A.; Dabis, F., et al. Alternatives to prolonged breastfeeding and incidence of pregnancies among HIV-infected women: The ANRS 1201-1202 Ditrane Plus Cohort in Abidjan, Côte d'Ivoire, 2001 to 2005. 15th Conference on Retroviruses and Opportunistic Infections; Boston, USA. 3-6 February 2008; [Abstract 73]
10. Bussmann H, Wester CW, Wester CN, Lekoko B, Okezie O, Thomas AM, et al. Pregnancy rates and birth outcomes among women on efavirenz-containing highly active antiretroviral therapy in Botswana. *J Acquir Immune Defic Syndr* 2007;45(3):269–73. [PubMed: 17450102]
11. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2009. Registry Coordinating Center; Wilmington, NC: [Accessed 27 April 2010]. 2009 Available at: www.APREgistry.com
12. Bera E, McCausland K, Nonkwelo R, Mgudlwa B, Chacko S, Majeke B. Birth defects following exposure to efavirenz-based antiretroviral therapy during pregnancy: a study at a regional South African hospital. *AIDS* 2010;24(2):283–9. [PubMed: 19864931]
13. Townsend CL, Willey BA, Cortina-Borja M, Peckham CS, Tookey PA. Antiretroviral therapy and congenital abnormalities in infants born to HIV-infected women in the UK and Ireland, 1990-2007. *AIDS* 2009;23(4):519–24. [PubMed: 19165088]
14. Floridia M, Tamburrini E, Bucceri A, Tibaldi C, Anzidei G, Guaraldi G, et al. Pregnancy outcomes and antiretroviral treatment in a national cohort of pregnant women with HIV: overall rates and differences according to nationality. *Bjog* 2007;114(7):896–900. [PubMed: 17501959]
15. Jeantils V, Khuong MA, Delassus JL, Honore P, Taverne B, Uzan M, et al. Efavirenz (Sustiva) in pregnancy: a study about 12 HIV patients. *Gynecol Obstet Fertil* 2006;34(7-8):593–6. [PubMed: 16814587]
16. Danel C, Moh R, Anzian A, Abo Y, Chenal H, Guehi C, et al. Tolerance and acceptability of an efavirenz-based regimen in 740 adults (predominantly women) in West Africa. *J Acquir Immune Defic Syndr* 2006;42(1):29–35. [PubMed: 16763490]
17. Rossouw T. Quantifying antiretroviral risk in pregnancy. *S Afr Med J* 2007;97(11):1014–6. [PubMed: 18250904]
18. Laher, F.; Forrest, J.; Mohapi, L.; Gray, G. Efavirenz conceptions in Soweto, South Africa. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Cape Town, South Africa. 19-22 July 2009; [Abstract TUPEC047]

19. Patel D, Thorne C, Fiore S, Newell ML. Does highly active antiretroviral therapy increase the risk of congenital abnormalities in HIV-infected women? *J Acquir Immune Defic Syndr* 2005;40(1): 116–8. [PubMed: 16123696]
20. Ford N, Mofenson L, Kranzer K, Medu L, Frigati L, Mills E, Calmy A. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. *AIDS*. 2010 [Epub ahead of print].
21. World Health Organization. Rapid advice. Use of antiretroviral drug for treating pregnant women and preventing HIV infection in infants. [Accessed: May 30, 2010]. Nov2009 http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf

TABLE 1

Demographics and procedure type by group

	Control Group 22 patients	ONDS Group 24 patients
Mean age, years	55	49
Ethnicity, % of group		
White, non-Hispanic	88%	84%
Hispanic	8%	4%
Native American	0%	12%
Asian	4%	0%
Fitzpatrick Score, median	3	3
Smoking history		
Current	0%	4.2%
Previous	4.5%	4.2%
Procedure Type		
1% croton oil/phenol	5%	4%
TCA peel (20-25%)	9%	8%
TCA peel (30-35%)	13%	13%
Erbium laser	73%	75%

TABLE 2

Obagi Nu Derm System regimen

	Weeks 1 to 4		Procedure (Week 4)		Re-epithelialization to Week 8		Weeks 8 to 14	
	AM	PM			AM	PM	AM	PM
<i>Foaming Gel Cleanser</i>	X	X			X	X	X	X
<i>Toner</i> (adjusts skin pH)	X	X					X	X
<i>Clear</i> (4% hydroquinone)	X	X					X	X
<i>Exfolerm Forte</i> (alpha-hydroxy acids)	X							
<i>Healthy Skin Protection</i> (SPF-35)	X				X	X		
<i>Blender</i>		X						X
0.05% tretinoin		X						X
<i>Sun Fader</i> (SPF-15)							X	

* Italicized name indicates a trademarked component of the ONDS

TABLE 3

Standard care regimen

	Weeks 1 to 4		Procedure (Week 4)		Re-epithelialization to Week 8		Weeks 8 to 14	
	AM	PM			AM	PM	AM	PM
Cetaphil wash	X	X			X	X	X	X
Neutrogena Moisturizing Sunscreen	X				X	X	X	
4% hydroquinone	X						X	
0.05% tretinoin		X						X

TABLE 4

Data Collection Schedule

	Visit 1 Baseline 30 Days Before OR	Visit 2 Day of Procedure	Visit 3 4 Days After OR	Visit 4 7 Days After OR	Visit 5 10 Days After OR	Visit 6 2 Weeks After OR	Visit 7 6 Weeks After OR	Visit 8 10 Weeks After OR
Photo	X	X	X	X	X	X	X	X
Survey	X	X				X	X	X
Photo Evaluation	X	X	X	X	X	X	X	X

* Re-epithelialization defined as "the disappearance of all crusting or scabs from the face, when the facial skin appears smooth and pink."

TABLE 5

Median patient satisfaction scores after skin product use (Visit 8 data, 10 weeks after surgery).

	ONDS Group 18 patients	Control Group 19 patients	p value
Easy to use	5	5	0.393
Too time consuming	1	1	0.666
Instructions were clear	5	5	0.803
Products caused discomfort	1	1	0.661

Self-reported compliance with skin product regimen	1	1	0.556
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1=Strongly Disagree, 2=Disagree, 3=Neutral, 4=Agree, 5=Strongly Agree

1=Always, 2=Most of the Time, 3=Sometimes, 4=Not Very Often, 5=Never

TABLE 6

Median erythema score by visit number

Visit Number	ONDS Group	Control Group	p value
2	1 (n=21)	0 (n=18)	p = .009
3	2 (n=16)	2 (n=14)	p = .405
4	2 (n=14)	2 (n=9)	p = .895
5	2 (n=13)	2 (n=8)	p = .319
6	2 (n=10)	2 (n=11)	p = .818
7	1 (n=11)	1 (n=11)	p = .104
8	1 (n=10)	1 (n=8)	p = .349

*
Score range: 0-3 (none, mild, moderate, severe)

TABLE 7**Levels of Evidence for Therapeutic Studies ⁹**

Level	Description of evidence
I	High-quality, multi-centered or single-centered, randomized controlled trial with adequate power; or systematic review of these studies
II	Lesser-quality, randomized controlled trial; prospective cohort study; or systematic review of these studies
III	Retrospective comparative study; case-control study; or systematic review of these studies
IV	Case series
V	Expert opinion; case report or clinical example; or evidence based on physiology, bench research or “first principles”