Research Letter

AIDS 2011, **25**:2301–2304

Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

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Evidence of the risk of birth defects with efavirenz use is limited. We updated a meta-analysis of birth defects in infants with first trimester efavirenz exposure up to July 2011. In 21 studies, there were 39 defects among live births in 1437 women receiving first trimester efavirenz [2.0%, 95% confidence interval (CI) 0.82–3.18]. The relative risk of defects comparing women on efavirenz-based (1290 live births) and nonefavirenz-based regimens (8122 live births) was 0.85 (95% CI 0.61–1.20). One neural tube defect was observed (myelomeningocele), giving an incidence of 0.07% (95% CI 0.002–0.39).

Current antiretroviral treatment guidelines in resource-limited settings recommend efavirenz or nevirapine as first-line drugs [1]. Efavirenz is widely used because it is well tolerated, easy to monitor, conveniently coformulated as a once-daily pill and shows similar virologic suppression to nevirapine. However, efavirenz use during the first trimester of pregnancy is contraindicated due to animal data and case reports indicating a potential association with neural tube defects [2]. We previously published a systematic review and meta-analysis that found no increase in overall birth defects comparing first trimester receipt of efavirenz-based and nonefavirenz-based regimens, although the limited number of reports prevented a definitive conclusion regarding the risk of rare outcomes such as neural tube defects [3]. We updated our systematic review to include data up to July 2011.

Using a predefined protocol (http://tinyurl.com/3hzz5wo), we combined terms for efavirenz, pregnancy and birth outcomes and searched the following databases up to 1 July 2011 without language restrictions: *MEDLINE* via *PubMed*; *EMBASE*; *CINAHL* and *PsycInfo*; *Cochrane CENTRAL*; *LILACS*; *Current Controlled Trials*; *BioMedCentral* and *Public Library of Science*; and websites of major HIV conferences such as International AIDS Society conferences up to July 2011 and Conferences on Retroviruses and Opportunistic Infections up to February 2011. Data were abstracted from the latest Antiretroviral Pregnancy Registry (http://www.apregistry.com), and the following treatment cohorts were contacted: the MTCT Plus Initiative; Médecins Sans Frontières; the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDA-SA); and the Reproductive Health Research Unit (RHRU).

The primary endpoint was birth defects of any kind. Unsystematic observations (case series or case reports) were excluded. Point estimates and 95% confidence intervals (CIs) were calculated for birth defects reported among live births for each study (spontaneous and induced abortions and stillbirths were excluded). Proportions were summarized using random effects meta-analysis using a Freeman–Tukey arcsine transformation of the raw proportions. The τ^2-statistic was calculated to assess between-study heterogeneity. For cohorts reporting birth outcomes of infants exposed to efavirenz vs. other antiretrovirals during the first trimester, relative risks (RRs) and CIs were calculated and data pooled using random effects method. Subgroup analyses assessed potential effects on the pooled estimates of study design, location, exposure duration and publication status. All analyses were conducted using Stata, version 11 (StataCorp LP, College Station, Texas, USA).

The initial search yielded 798 publications and 885 conference abstracts, from which 32 studies were reviewed as full text. Twenty-one studies were included for analysis (among which 19 reported our primary outcome), including 13 prospective studies. This updated review found 181 additional live births with first trimester efavirenz exposure and birth defect data from five additional cohorts [4–8], one updated study [9] of a previous report [10], and the updated Antiretroviral Pregnancy Registry [11].

Across the 19 studies reporting birth defects among 1437 live-born infants born to women receiving efavirenz in the first trimester, birth defect prevalence ranged from 0% [12] to 22.6% [13], with a 2.0% pooled prevalence (CI 0.82–3.18); heterogeneity between studies was low ($\tau^2 = 1.89$). One neural tube defect was observed (myelomeningocele) [11], giving an incidence proportion of 0.07% (CI 0.002–0.39) (Table 1) [4–9, 11–23]. In a subgroup analysis, there was no difference according to publication status ($P = 0.58$), study design ($P = 0.19$) or exposure duration ($P = 0.96$); prevalence appeared higher in developed countries compared with developing countries ($P = 0.015$).

Eleven studies reported birth defects among infants born to women receiving first trimester efavirenz-containing regimens (38 defects among 1290 live births) and

DOI:10.1097/QAD.0b013e32834cdb71

Table 1. Description of reported birth defects in infants born to women with first trimester efavirenz exposure.

Study	Number of with EFV exposure in first trimester	Mean duration of EFV exposure during pregnancy	Number of pregnancies with live births	Number of birth defects (live births)	Description of birth defects
Antiretroviral Pregnancy Registry, [11]	623		623	17[a]	Myelomeningocele ($n=1$), anophthalmia with severe oblique facial clefts and amniotic band on arm
Ekouevi *et al.* [9]	203	59 days	147	0	NR
Phanuphak *et al.* [4]	7	NS	6	0	NR
Cressey *et al.* [5]	4	NS	4	0	NR
Westreich *et al.* [14]	60	NS	60	0	NR
Blood *et al.* [7]	2	NS	1[b]	0	NS
Areechokchai [6]	5	NS	5	0	NR
Bera *et al.* [15]	195	39 weeks	184	5[c]	Arthrogryposis multiplex congenital[d], oesophageal atresia with trachea oesophageal fistula, polysyndactyly[e], postaxial polydactyly, central lower incisor
Townsend *et al.* [16]	205	NS	204	5	undescended testes ($n=2$), hip dislocation ($n=2$), hypertrophic pyloric stenosis
Machado *et al.* [17]	19	Not reported	18	1	Undescended testes
Gonzalez-Tome *et al.* [13]	31	2 months	31	7	Renal dilatation ($n=4$), angiomatosis, dermoid cyst, acetabular dysplasia, inguinal hernia
Oliveira [8]	17	NS	17	0	NR
Rossouw *et al.* [18]	37	NS	31	0	NR
Bussmann *et al.* [19]	38	43 days	22	1	Bone dysplasia
Floridia *et al.* [20]	39	NS	32	2	Bilateral clubfoot, undescended testes
Joao *et al.* [12]	23	15 weeks (median)	21	0	NR
Jeantils *et al.* [21]	12	8 weeks	7	1[f]	Right arm angioma
Patel *et al.* [22]	19	40 days	19	0	NR
Batallan *et al.* [23]	5	23.7 weeks	5	0	NR

EFV, efavirenz; NS, not specified; NR, not reported.
[a]Detailed information on type of birth defects in the Antiretroviral Pregnancy Registry only provided for the two central nervous system defects.
[b]One woman defaulted.
[c]One additional birth defect was noted in stillbirth (trisomy 18).
[d]Arthrogryposis multiplex congenita: birth defects included joint contractures, webbed limbs, pulmonary hypoplasia, absent sacrum and unilateral cleft lip and palate.
[e]Polysyndactyly, polysyndactyly with syndactyly: extra digits fully formed with phanges and nail, fingers were postaxial and toes were pre-axial fused with big toe.
[f]One additional birth defect was noted on autopsy of medically aborted fetus (multiple malformations including pulmonary segmentation, bicuspid pulmonary value and accelerated skeletal maturation without genetic abnormalities).

nonefavirenz-containing regimens (316 defects among 8122 live births), giving a nonsignificant RR of 0.85 (CI 0.61–1.20); heterogeneity was low ($\tau^2=0$) (Fig. 1). The pooled estimate was not affected by subgroup analyses that compared study setting ($P=0.47$), duration of efavirenz exposure ($P=0.78$) or publication status ($P=0.50$).

The reporting of secondary outcomes varied across studies. Eight studies reported spontaneous abortions, with prevalence raging from 0% [6] to 16.05% [14]. The prevalence of stillbirths, reported by eight studies, ranged from 0% [19] to 13.3% (MTCT-Plus). The prevalence for termination of pregnancy, reported by 10 studies ranged from 0% [6] to 33.7% [24]. Three studies reported data on termination of pregnancy (none based on prenatal screening) for women exposed to efavirenz-containing and nonefavirenz-containing regimens [9,19,24], giving a RR of 2.81 (95% CI 0.94–8.36) for efavirenz-exposed women. Finally, five studies reported on preterm delivery, with prevalence ranging from 9.1% [19] to 18.2% [20].

The methodological quality of included studies was judged to be moderate. The vast majority of reports were from prospective cohorts (1364 live births), and only four studies were composed of less than 10 patients with first trimester efavirenz use. Ascertainment of birth defects among stillborn/terminated births was only reported by two studies (the prevalence of birth defects was consistent with data reported for live births).

This expanded review confirms the previous meta-analysis findings of no increased risk of overall birth

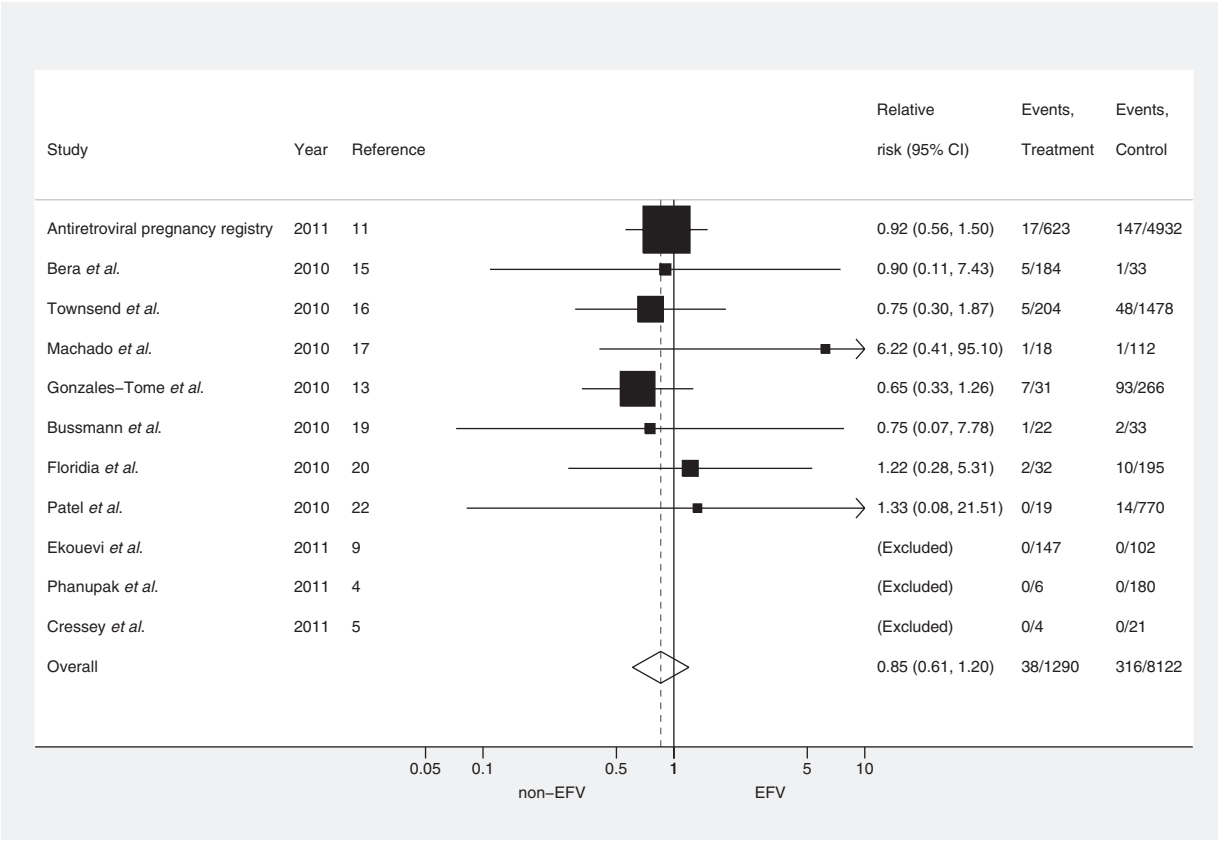

Fig. 1. Relative risk of birth defects on efavirenz vs. nonefavirenz regimens. CI, confidence interval; EFV, efavirenz.

defects among women receiving first trimester efavirenz. The pooled prevalence of birth defects for women exposed to first trimester efavirenz (2.0%) is similar to that for women exposed to nonefavirenz-based regimens in the antiretroviral pregnancy registry (2.9%) [11], and in the general population (6%) [25]. Incidence of neural tube defects remains low (0.07%), but this estimate is derived from a small sample.

Strengths of this review include a broad search strategy that identified data from the grey literature and unpublished cohorts, and the inclusion of updated data for several cohorts. Limitations include the inconsistent reporting of secondary outcomes and the potential for bias associated with selective abortion as a result of prenatal screening that could result in a reduction of birth prevalence. We consider such bias unlikely, given that none of the studies reporting rates of termination of pregnancy among women exposed to efavirenz used prenatal screening to guide termination decisions and note that in the Antiretroviral Pregnancy Registry the reported prevalence of birth defects among induced abortuses of women exposed to antiretroviral therapy in the first-trimester (2.5%) is consistent with the background prevalence [11]. The main limitation of this review is the small sample size. It is notable that more than 80% of data come from just four studies in which prospective reporting of birth outcomes has been established [9,11,15,16]. The lack of systematic recording of birth outcomes from women receiving antiretroviral drugs during pregnancy persists, with reports of birth outcome data for only 181 live births found by this review in the last 18 months. Prospective surveillance systems particularly in developing countries are needed to improve data reporting and inform the assessment of risk of rare defects.

Acknowledgements

The authors would like to thank Tim Cressey, Nittaya Phanuphak and D. Heather Watts for providing additional data, and Stephanie Bartlett and Catherine Kirby for assistance with the preparation of the final report.

Conflicts of interest

There are no conflicts of interest.

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Received: 5 August 2011; revised: 26 August 2011; accepted: 7 September 2011.

References

1. WHO. Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach 2010 revision. Geneva: World Health Organization; 2010.
2. Lewis-Hall F. Important change in SUSTIVA (efavirenz) package insert: change from category C to D. 2005. Bristol-Myers Squibb Company.
3. 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* 2010; **24**:1461–1470.
4. Phanuphak N, Teeratakulpisarn S, Chinmahun A, Ooprasithiwong J, Mathajittiphun P, Jittarach K, *et al*. **Efficacy and safety of maternal triple-drug ARV regimens: Thai Red Cross PMTCT Program, 2004 to 2010**. *18th Conference on Retroviruses and Opportunistic Infections*; February 2011; Boston, Massachusetts. Abstract 742.
5. Cressey T, Stek A, Capparelli E, Bowonwatanunwong C, Prommas S, Huo Y, Read J, Smith E, Best B, Morichnick M, IMPAACT P1026 s team. **Efavirenz pharmacokinetics during the 3rd trimester of pregnancy and postpartum**. *18th Conference on Retroviruses and Opportunistic Infections*; February 2011; Boston, Massachusetts. Abstract 754.
6. Areechokchai D, Bowonwatanuwong C, Phonrat B, Pitisuttithum P, Maek ANW. **Pregnancy outcomes among HIV-infected women undergoing antiretroviral therapy.** *Open AIDS J* 2009; **3**:8–13.
7. Blood E, Beckwith C, Bazerman L, Cu-Uvin S, Mitty J. **Pregnancy among HIV-infected refugees in Rhode Island.** *AIDS Care* 2009; **21**:207–211.
8. Oliveira M. **Pharmacovigilance of antiretroviral drugs in carrying pregnant women of HIV and children displayed to the HIV during the gestation in use of prophylaxis of the vertical transmission: study incidence pilot** [masters thesis]. Instituto de Pesquisa Clínica Evandro Chagas: Rio de Janeiro, Brazil; 2007. pp. 123.
9. Ekouevi DK, Coffie PA, Ouattara E, Moh R, Amani-Bosse C, Messou E, *et al*. **Pregnancy outcomes in women exposed to efavirenz and nevirapine: an appraisal of the IeDEA West Africa and ANRS Databases, Abidjan, Cote d'Ivoire.** *J Acquir Immune Defic Syndr* 2011; **56**:183–187.
10. Coffie P, Moh P, Tonwe-Gold B, Amani-Bosse C, Messou E, Gabillard D, *et al.* Birth outcomes among women exposed to efavirenz in Abidjan, Ivory Coast. 5th Francophone Conference on HIV/AIDS, Casablanca, Morocco, 28–31 March 2010: Abstract 448/73P.
11. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 January 2011. Wilmington, NC: Registry Coordinating Center; 2011. http://www.APRegistry.com. [Accessed 1 July 2011].
12. Joao E, Calvet G, Cunha C, Menezes J, Martins E, Medeiros A, *et al.* **Pregnancy outcome in women exposed to efavirenz,** XVI *International AIDS Conference*; 13–18 August 2006; Toronto, Canada. Abstract CDB0698.
13. Gonzalez-Tome M, Fernandez-Ibieta M, Ramos AJ, Munoz-Galligo E, Rojo C, Nieto O, *et al.* **The Spanish cohort of HIV-infected mother -infant pairs. Efavirenz in pregnancy: maternal characteristics of women who become pregnant on EFV-containing regimen and neonatal effects**. *XVII International AIDS Conference 3-8 August 2008*, Mexico City, Mexico. Abstract CDB0207.
14. Westreich D, Robel D, MacDonald P, Majuba P, Maskew M, Nagar S, Jaffray I, MacPhail Abstract P, Cole S, Sanne I. **Pregnancy, efavirenz, and birth outcomes in Johannesburg** *17th Conference on Retroviruses and Opportunistic Infections, San Francisco*; 2010. Abstract 922.
15. 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**:283–289.
16. 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, 1999–2007.** *AIDS* 2009; **23**:519–524.
17. Machado ES, Hofer CB, Costa TT, Nogueira SA, Oliveira RH, Abreu TF, *et al*. **Pregnancy outcome in women infected with HIV-1 receiving combination antiretroviral therapy before versus after conception.** *Sex Transm Infect* 2009; **85**:82–87.
18. Rossouw T. **Quantifying antiretroviral risk in pregnancy.** *S Afr Med J* 2007; **97**:1014–1016.
19. 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**:269–273.
20. 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* 2006; **11**:941–946.
21. Jeantils V, Khuong MA, Delassus JL, Honore P, Taverne B, Uzan M, Tassi S. **Efavirenz (Sustiva) in pregnancy: a study about 12 HIV patients [in French].** *Gynecol Obstet Fertil* 2006; **34**:593–596.
22. 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**:116–118.
23. Batallan A MG, Levine M, Longuet P, Bodard M, Legac S, *et al.* **In utero exposure to efavirenz: evaluation in children born alive**. *2nd IAS Conference on HIV Pathogenesis and Treatment*; 13–16 July 2003; Paris, France. Abstract 1100.
24. Laher F FJ, Mohapi L, Gray G. **Efavirenz Conceptions in Soweto, South Africa.** *5th IAS Conference on HIV Pathogenesis, Treatment and Prevention*; 19–22 July 2009; Cape Town, South Africa. Abstract TUPEC047.
25. Global report on birth defects. March of Dimes Birth Defects Foundation White Plains: New York; 2006. http://wwwmarchofdimescom/downloads/Birth_Defects_Report-PFpdf.