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

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Introduction: Primate studies and some observational human data have raised concern regarding an association of first-trimester efavirenz exposure with central nervous system congenital anomalies. The objective of this review is to update evidence on efavirenz safety in HIV-infected pregnant women to inform revision of the 2013 WHO guidelines for antiretroviral therapy in low and middle-income countries.

Design: A systematic review and meta-analysis.

Methods: We searched for studies reporting birth outcomes among women exposed to efavirenz during the first trimester of pregnancy up to 10 January 2014. Relative risks of congenital anomalies comparing women exposed to efavirenz and nonefavirenz-based antiretroviral regimens were pooled using random effects meta-analysis.

Results: Twenty-three studies were included in this review, among which 21 reported the birth outcomes of 2026 live births among women exposed to efavirenz during the first trimester of pregnancy. Forty-four congenital anomalies were reported, giving a pooled proportion of 1.63% [95% confidence interval (95% CI) 0.78–2.48], with only one neural tube defect. Twelve studies reported birth outcomes of women exposed to efavirenz or nonefavirenz-containing regimens during the first trimester of pregnancy. Pooled analysis found no differences in overall risks congenital anomalies between these two groups (relative risk 0.78, 95% CI 0.56–1.08). The incidence of neural tube defects was low, 0.05% (95% CI <0.01–0.28), and similar to incidence in the general population.

Discussion: This updated analysis found no evidence of an increased risk of overall or central nervous system congenital anomalies associated with first-trimester exposure to efavirenz, similar to previous systematic reviews. This review contributed to the evidence base for the revised 2013 WHO guidelines on antiretroviral therapy, which recommend that efavirenz can be included as part of first-line therapy in adults regardless of sex, and that it can be used throughout pregnancy, including during the first trimester. However, because of the low incidence of central nervous system anomalies in the overall population and relatively small number of exposures in the current literature, continued birth outcomes prospective surveillance is warranted.

AIDS 2014, **28** (Suppl 2):S123–S131

Keywords: birth defects, congenital anomalies, efavirenz, HIV/AIDS, pregnancy, systematic review, WHO

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DOI:10.1097/QAD.0000000000000231

Introduction

Efavirenz is one of the most widely used nonnucleoside reverse transcriptase inhibitors (NNRTIs) in first-line antiretroviral therapy (ART) and is recommended as a preferred option in adult treatment guidelines [1–3]. However, data from primate studies [4] and some human case reports [4,5] have raised concern regarding a association of first-trimester efavirenz exposure with central nervous system congenital anomalies. These data resulted in a recommendation by the United States Food and Drug Administration (FDA) in 2005 and the European Medicines Agency (EMEA) to avoid using efavirenz-based regimens in the first trimester of pregnancy (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000249/WC500058311.pdf) [6].

Over nearly two decades, an accumulation of data from pregnant women exposed to antiretroviral drugs during the first trimester of pregnancy has allowed for an assessment of the potential association between efavirenz and congenital anomalies. Systematic reviews published in 2010 and 2011 summarized available data at the time and found no evidence of increased risk of congenital anomalies associated with first-trimester exposure to efavirenz [7,8]. On the basis of this evidence, in mid-2012, the WHO released a technical update that highlighted the significant clinical and programmatic benefits of efavirenz use in pregnancy and the potential risks, and recommended that efavirenz can be included as part of preferred first-line therapy in pregnant women and women of childbearing age because the benefits outweighed potential risks [9].

In order to further validate this technical update in the context of the 2013 revised WHO global guidelines for ART in low and middle-income countries, we conducted an updated review to assess the evidence for the safety of efavirenz in pregnancy.

Materials and methods

This systematic review was conducted according to a study protocol following the requirements of the PRISMA Statement [10]. A preliminary version of this analysis was prepared for the WHO guidelines development group in December 2012. This article presents the final, updated analysis, based on updated literature searches up to 10 January 2014.

Search strategy and study selection

We used a compound search strategy to update a previous systematic review of the safety of efavirenz in pregnancy, published in 2011 [7]. The following databases were searched from 01 July 2011 (the date of the last search) up to 30 June 2013: MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, LILACS and Web of Science; this search was updated in MEDLINE via PubMed up to 10 January 2014. We also searched the websites of two major HIV conferences: all International AIDS Society (IAS) conferences (up to Kuala Lumpur, June 2013) and all Conferences on Retroviruses and Opportunistic Infections (CROI, up to Atlanta, March 2013). We also retrieved the latest report of the Antiretroviral Pregnancy Registry (http://www.apregistry.com) (up to January, 2014). Finally, bibliographies of all relevant articles were screened to check for additional publications. No date, language or other restriction was applied. Searches were done in duplicate (N.F., Z.S.).

After preliminary screening of all the titles obtained from our searches, all abstracts were then assessed for eligibility by two reviewers according to the inclusion criteria defined by the protocol. Our primary outcome of interest was any congenital anomaly (birth defect) (http://www.who.int/mediacentre/factsheets/fs370/en [Accessed 26 January 2014]); secondary outcomes included spontaneous abortions, terminations of pregnancy, stillbirths, preterm deliveries and adverse drug reactions. Studies that only reported data on secondary outcomes were included (i.e. they did not have to also report the primary outcome). We sought to compare the risk of congenital anomalies overall, and specifically neural tube defects, among infants born to women receiving efavirenz during the first trimester of pregnancy to the risk among infants born to mothers exposed to other antiretrovirals in the first trimester of pregnancy, and to background reference prevalence. Nonsystematic observations (case series or case reports that did not include denominators to allow for assessment of risk) and data from animal studies were excluded from all analyses.

Data extraction

Data extraction was done independently, in duplicate, using a standardized form. For each study, we gathered information on the study setting, the study population, the sample size, the timing and duration of efavirenz exposure and birth outcomes. Data on patient and study characteristics, and predefined indicators of potential risk of bias were also extracted. The GRADE system was used to assess the overall quality of the evidence [11].

Data analysis

Point estimates and 95% confidence intervals (95% CI) were calculated for the proportion of congenital anomalies reported among live births for each study. We excluded spontaneous and induced abortions as well as stillbirths from the numerator and denominator for the estimate of congenital anomalies, consistent with current reporting conventions [12]. For cohorts that reported and compared birth outcomes of infants born to mothers exposed to efavirenz during the first trimester of pregnancy to outcomes of infants born to mothers

exposed to other antiretroviral drugs, relative risks (RRs) and 95% CIs were calculated. In the case of zero outcome events in one arm, the Haldane method was applied, adding 0.5 to each arm. The variance of the raw proportions was stabilised using a Freeman–Tukey type arcsine square-root transformation [13] and estimates were pooled using a DerSimonian–Laird random effects model [14]. Pooled estimates were subsequently back-transformed to the original scale [15]. Prevalence and 95% CIs were calculated for all secondary outcomes. We did not pool data on our secondary outcomes because the background prevalence of the secondary outcomes is known to vary considerably between study settings. We calculated the τ^2 statistic using DerSimonian and Laird's method of moments estimator [16] to assess between-study heterogeneity [17]. Subgroup analyses were conducted to assess the potential effects of study design, geographical location (low/lower-middle income country versus middle/high-income country, as defined by the World Bank), duration of efavirenz exposure and status of publication (full text article versus conference abstract or unpublished data) on the pooled estimates. Sensitivity analyses were conducted comparing the RR estimates if using fixed-effects rather than random-effect methods, the overall pooled prevalence of congenital anomalies with that reported by the antiretroviral pregnancy registry and by running a 'leave-one-out' analysis to assess the extent to which the overall result might be influenced by any single study. A P value less than 0.05 was considered significant. Publication bias was assessed using the eggers test for small study effects [18]. All analyses were conducted using STATA (version 12, www.stata.com) and GRADE Pro (www.gradeworkinggroup.org).

Results

Our updated search yielded 397 additional titles for screening, in addition to the previous review published in 2011 [7], bringing the total number of study titles screened to 2080 (Fig. 1). Two articles published since the previous review was completed were excluded because they reported outcomes that had previously been reported to the Antiretroviral Pregnancy Registry [19,20]. In total, two updated reports [13,21] from previously published cohorts [22,23], data from one additional published article [24] and one additional conference abstract [25] were included in this updated review. Overall, 23 studies were included in this review, comprising 20 articles and conference abstracts [21,24–42], one unpublished study [43], the Antiretroviral Pregnancy Registry [12] and one unpublished

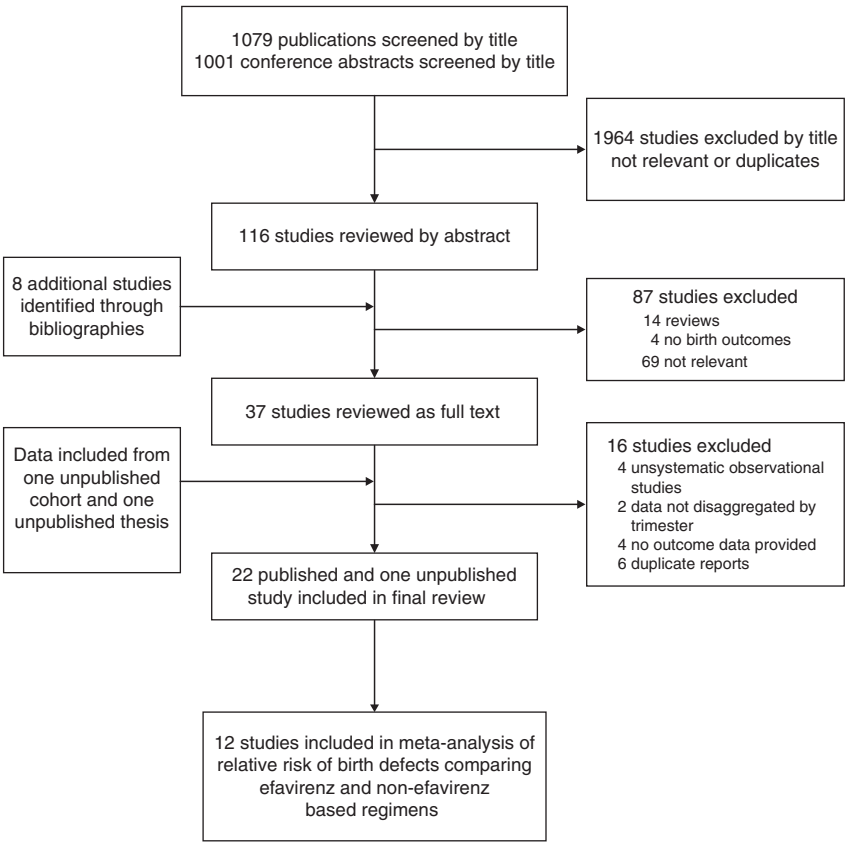

Fig. 1. Flow chart of study selection process.

cohort (the MTCT Plus cohort: E. Abrams, personal communication; data unchanged and carried forward from previous systematic reviews [8]). Additional data on secondary outcomes for one study [35] were provided by a conference abstract [44].

Study characteristics are summarized in Table 1.

Assessment of study quality

Our assessment of the overall risks of bias found that most studies were at a moderate risk of bias. Very few studies considered potential confounders or baseline imbalances between patients receiving efavirenz compared with nonefavirenz regimens (Supplementary Table S1, http://links.lww.com/QAD/A490). Our GRADE review assessed the 12 studies that compared birth outcomes of women exposed to both efavirenz and nonefavirenz containing regimens during the first trimester of pregnancy. We rated the overall evidence base to be of low quality, mainly due to the observational nature of the studies, and due to the limited number of exposures and varying methodologies (Supplementary Table S2, http://links.lww.com/QAD/A490). There was no statistical evidence of publication bias ($P = 0.14$ using Egger's test for funnel plot asymmetry).

Congenital anomalies

Of the 23 studies included in this review, 22 reported the birth outcomes of 2026 live births among women exposed to efavirenz during the first trimester of pregnancy. Details are summarized in Table 2. Forty-four congenital anomalies were reported, yielding a pooled proportion of 1.63% (95% CI 0.78–2.48; $\tau^2 = 0.01$). Of these, one was a neural tube defect. We found no additional cases of neural tube defects compared with previous reviews, thus keeping the overall prevalence of neural tube defects low (0.05%, 95% CI <0.01–0.28).

Results of the overall analysis were not statistically different to the raw proportion of congenital anomalies reported by the Antiretroviral Pregnancy Registry (2.3%, 95% CI 1.3–3.7), and the overall proportion of congenital anomalies in our analysis did not exceed 2% in the 'leave-one-out' sensitivity analysis (Supplementary Table S3, http://links.lww.com/QAD/A490).

Twelve studies reported birth outcomes of women exposed to both efavirenz and nonefavirenz-containing regimens during the first trimester of pregnancy. This analysis found no differences in risk of congenital anomalies between these two groups (RR 0.78, 95% CI 0.56–1.08) (Fig. 2). Heterogeneity between the studies was low ($\tau^2 = 0$), and none of the subgroup analyses assessing the impact of study design, geographical location, duration of efavirenz exposure and publication status were significant (all $P > 0.1$).

Secondary outcomes

The reporting of secondary outcomes varied between the studies. Nine studies reported spontaneous abortions, with prevalence ranging from 0 to 16.1% (95% CI 7.6–28.3). The prevalence of stillbirths, reported by seven studies, ranged from 0 to 7% (95% CI 4.0–11.3). Five studies reported on the prevalence of preterm delivery, with prevalence ranging from 9.1 (95% CI 5.3–15.5) to 18.2% (95% CI 7.0–35.5). These data were not pooled because of differences in background prevalence across populations. The large variation in point estimates and wide CIs resulting from small sample sizes of individual studies make these findings difficult to interpret with respect to any indication of increased risk for these outcomes.

The proportion of medical terminations of pregnancy, reported by 10 studies, ranged from 0 to 34%. Three studies reported data on terminations of pregnancy (terminations not associated with prenatal screening) for women exposed to efavirenz and nonefavirenz-based regimens; pooling these data gave an RR of 2.81 (95% CI 0.94–8.36) for pregnancy terminations compared with women exposed to nonefavirenz-based therapy. A fourth study, from South Africa, reported that 19 of 56 women (34%) who conceived while on efavirenz terminated their pregnancy; data from this study were not included in the pooled analysis, as comparative information for non-EFV regimens was not reported [24]. None of these terminations was due to congenital anomalies detected *in utero* (Sheree Schwartz, personal communication). Data on secondary outcomes are summarized in Supplementary Table S4, http://links.lww.com/QAD/A490.

Adverse drug reactions

Only two studies reported on adverse drug reactions among mothers receiving efavirenz during pregnancy. The first study, reporting data on 25 first-trimester exposures, found no adverse drug reactions resulting from efavirenz treatment [31]. The second study, reporting data on 56 first-trimester exposures, reported one adverse drug reaction resulting from efavirenz therapy (vomiting) [26].

Discussion

This review provides an updated, systematic review of evidence on the safety of efavirenz use during the first trimester of pregnancy and includes information from an additional 589 live births compared with the last review published in 2011 [8], including published data up to January 2014. Nevertheless, the use of efavirenz in pregnancy remains a controversial topic, and this is reflected by varying recommendations in national guidelines: guidelines from the British HIV Association recommend using efavirenz in pregnancy [45] while those issued by the European AIDS Clinical Society [46]

Table 1. Characteristics of included studies.

Study	Setting	Reporting period	Description	Median age (years)	Median $CD4^+$ cell count at pregnancy (cells/μl)	Median gestation at birth	Median birthweight (g)
Antiretroviral Pregnancy Registry	USA and international	January 1989–June 2013	Birth registry	28	NS	NS	NS
Floridia *et al.* [21]	Italy	2001–2012/2011	National surveillance study	32	420	38 weeks	2870
Sibiude [25][a]	France	1994–2010	Prospective cohort	NS	NS	NS	NS
Cressey *et al.* [31]	USA and Thailand	2005–2010	Prospective cohort within a clinical trial	29	413	38.7	3000
Schwartz *et al.* [24]	South Africa	August 2009–January 2012	Prospective cohort	NS	320	NS	NS
Ekouevi *et al.* [32]	Cote d'Ivoire	2003–2009	Prospective cohort within a clinical trial	29	217	NS	2800
Phanupak *et al.* [39][a]	Thailand	April 2004–October 2010	Hospital cohort	28	405	NS	NS
Westreich *et al.* [42][a]	South Africa	April 2004–March 2007	Prospective cohort	NS	NS	NS	NS
MTCT Plus Initiative[b]	Multisite	January 2002–December 2007	Prospective cohort	28	419	NS	NS
Blood *et al.* [29]	USA	2000–2006	Retrospective cohort	29	506	NS	NS
Areechokchai *et al.* [27]	Thailand	2002–2006	Retrospective and Prospective cohort	30	240	NS	NS
Bera *et al.* [28]	Hospital, South Africa	January 2006–December 2008	Prospective cohort	30	275	39	3000
Townsend *et al.* [41]	Birth registry, UK	1990–2007	Population based surveillance	30	400	38	2980
Laher *et al.* [36][a]	Hospital, South Africa	August 2004–March 2008	Retrospective cohort	31	NS	37	NS
Machado *et al.* [37]	Hospital, Brazil	1996–2006	Prospective cohort	29	80% >200	37	NS
Gonzales-Tome *et al.* [33][a]	Hospitals, Spain	2000–2005	Prospective cohort	32	452	38	2815
Oliveira [43][a]	Hospital, Brazil	February 2005–May 2006	Prospective cohort	NS	NS	NS	NS
Rossouw [40]	Hospital, South Africa	2002–2007	Retrospective cohort	32	245	NS	2260
Bussmann *et al.* [30]	Hospital, Botswana	December 2002–January 2006	Prospective cohort	NS	348	NS	2950
Joao *et al.* [35][a]	Hospital, Brazil	January 2001–December 2004	Retrospective cohort	NS	NS	39	2895
Jeantils *et al.* [34]	Four hospitals, France	January 1989–December 2003	Retrospective cohort	33	257	37	3140
Patel *et al.* [38]	European Collaborative Study	1986–December 2003	Prospective cohort	28	420	38	2940
Batallan *et al.* [27][a]	Hospitals, France	January 1999–December 2002	Retrospective cohort	NS	NS	38	3224

NS, not stated.
[a]Abstract, full article not published.
[b]Unpublished cohort; data provided by investigators.

Table 2. Description of reported congenital anomalies in infants born to women with first-trimester efavirenz exposure.

Study	No. with EFV exposure in first trimester	Mean duration of EFV exposure during pregnancy	No. of pregnancies with live births	No. of congenital anomalies (live births)	Description of congenital anomalies
Antiretroviral Pregnancy Registry, 2014	766		766	18[a]	Neural tube defect (Myelomeningocele) (1), anophthalmia with severe oblique facial clefts and amniotic band on arm (1)
Floridia *et al.* [21]	80	NS	80	2	Bilateral clubfoot, undescended testes
Sibiude *et al.* [25]	372		372	4	Neurological defects: pachygyria, agenesis of corpsu callosum, hydrocephaly, cerebral cyst (4) (Preliminary)
Cressey *et al.* [31]	4	NS	4	0	–
Schwartz *et al.* [24]	56	NS	26	0	–
Ekouevi *et al.* [32]	203	59 days	147	0	–
Phanupak *et al.* [39]	7	NS	6	0	–
Westreich *et al.* [42]	60	NS	60	0	–
Blood *et al.* [29]	2	NS	1[b]	0	–
Areechokchai *et al.* [27]	5	NS	5	0	–
Bera *et al.* [28]	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.* [41]	205	NS	204	5	Undescended testes (2), hip dislocation (2), hypertrophic pyloric stenosis
Machado *et al.* [37]	19	Not reported	18	1	Undescended testes
Gonzales-Tome *et al.* [33]	31	2 months	31	7	Renal dilatation (4), angiomatosis, dermoid cyst, acetabular dysplasia, inguinal hernia
Oliveira [43]	17	NS	17	0	–
Rossouw [40]	37	NS	31	0	–
Bussmann *et al.* [30]	38	43 days	22	1	Bone dysplasia
Joao *et al.* [35]	23	15 weeks	21	0	–
Jeantils *et al.* [34]	12	8 weeks	7	1[f]	Right arm angioma
Patel *et al.* [38]	19	40 days	19	0	–
Batallan *et al.* [27]	5	23.7 weeks	5	0	–

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

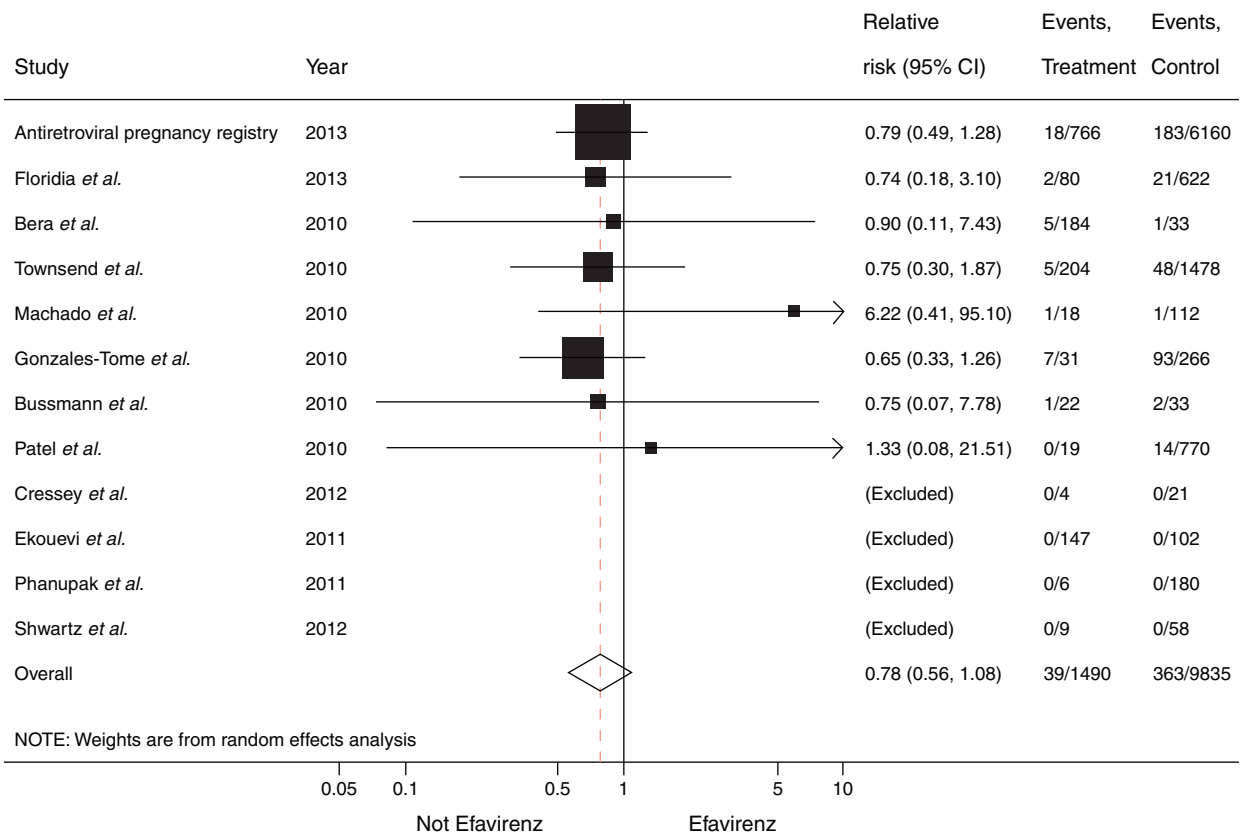

Fig. 2. Forest plot of relative risk of birth defects on efavirenz vs. nonefavirenz regimens. CI, confidence interval; EFV, efavirenz.

recommend avoiding efavirenz during the first 8 weeks of pregnancy. A recent report from France suggested an increased risk of neurologic defects (none of which were neural tube defects) among infants born to women receiving efavirenz during the first trimester of pregnancy [25]. However, when these data were considered together with other available data in our review, we still found no evidence of an increased risk of congenital anomalies associated with first-trimester exposure to efavirenz compared with exposure to other antiretroviral drugs. In the available dataset of published reports, there is only one neural tube defect, giving a prevalence of 0.05%, which is in line with the prevalence of 0.1% reported in the general population [47]. The prevalence of overall congenital anomalies is also in line with that reported in the general population [48]. Although this finding is based on an evidence base that is rated as low quality according to the GRADE approach, randomized trials are unlikely to ever be conducted to address this question.

Strengths of this review include a broad search strategy that identified a number of studies not yet published in the literature and the inclusion of updated data for several cohorts. Results appeared to be consistent across studies, as demonstrated by low statistical heterogeneity and the robustness of the main findings to sensitivity and subgroup analyses. There was no statistical evidence of publication bias, but these tests are less reliable when the number of studies is small [49] and we cannot rule out the possibility of publication bias, but consider that publication bias is likely to favour the reporting of congenital anomalies among women exposed to efavirenz considering prior concerns; such publication bias would be expected to lead to an overestimation of the risk of efavirenz compared with other antiretroviral drugs. Few studies reported on risk of bias or attempted to control for potential confounders, in particular women on efavirenz may differ from those not on efavirenz in ways that were not reported by the studies. For example, the latter group may include more women who planned their pregnancies and so were more likely to be exposed to protective factors (such as folate supplementation) and reduced risk factors (such as smoking and poor nutrition). Consideration of confounding is all the more important given that it would not be ethically acceptable to conduct a randomized trial to assess risk. Nevertheless, such differences are unlikely to affect our results to an important degree and would be expected to result in an overestimation of the risk of congenital anomalies in the efavirenz group. Finally, future studies should be encouraged to provide full descriptions of the types of birth defects that occur.

The variation in the reporting and difficulty in interpreting available evidence on secondary outcomes including spontaneous abortions, terminations

of pregnancy, stillbirths, and preterm deliveries, as well as the still limited prospective data on congenital anomalies compared with larger number of therapeutic exposures confirms the need for better monitoring of these birth outcomes at sentinel sites [50]. The review highlights that medical termination of pregnancy for women exposed to efavirenz has been in the past more frequent than for women not exposed to efavirenz; this is expected to change due to the reassurances provided by recent technical updates and guidelines. The limited reporting of adverse drug reactions means that very little information is available to draw any conclusions regarding potential increased risk of adverse drug reactions associated with efavirenz use in pregnancy, in particular the potential for depression that has been associated with efavirenz use in some [51], but not all [50], studies. Future studies should be encouraged to report data on efavirenz safety and tolerability in pregnancy for both the mother and the child.

In conclusion, this updated review does not find any evidence of an increased risk of congenital anomalies in general, or increased risk of neural tube defects, associated with efavirenz exposure during the first trimester of pregnancy and provides the supporting evidence for WHO's 2013 recommendation that efavirenz should be part of the recommended first-line ART regimen, including for women of child-bearing potential, and can be used during first trimester and throughout pregnancy [3]. As with all drugs used in pregnancy, programmes should be encouraged and supported to collect and report on birth outcome data to further assess any potential risk of adverse outcomes [7–9]. Surveillance planning efforts have recently been established in several countries [52] and such efforts need to be sustained and supported as an increasing number of countries adopt the recommended first-line ART with tenofovir/lamivudine/efavirenz and implement recommendations for provision of ART to all pregnant and breastfeeding women for both prevention of mother-to-child HIV transmission as well as maternal health. The data generated from these efforts to improve data collection and reporting will inform future guidelines on the safety of efavirenz and other antiretrovirals in pregnancy.

Acknowledgements

We would like to thank Martina Penazatto for comments on an earlier draft, and Heather Watts for assisting with access to data from the Antiretroviral Pregnancy Registry. The review was supported by funds from the Bill and Melinda Gates Foundation. This manuscript represents the views of the authors and does not necessarily represent the view of the National Institutes of Health or Department of Health and Human Services.

NF and LM were the lead authors. NF and ZS scrutinized identified studies for eligibility, extracted data and assessed the methodological quality of included studies. NF performed the statistical analysis. All authors critically reviewed the manuscript before submission.

Conflicts of interest

None declared.

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