Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts

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Introduction: Data on efavirenz safety in first trimester pregnancy are conflicting. We conducted a systematic review and meta-analysis of the available evidence from observational cohorts.

Methods: We ran duplicate searches of databases (up to 02 January, 2010) and searchable websites of major HIV conferences (up to February, 2010) to identify observational cohorts reporting birth outcomes among women exposed to efavirenz during the first trimester of pregnancy. Our primary endpoint was birth defects of any kind; secondary outcomes were spontaneous abortions, termination of pregnancy, stillbirths, and preterm delivery.

Results: Sixteen studies met our inclusion criteria, comprising 11 prospective cohorts and five retrospective reviews. Nine prospective studies reported on rates for birth defects both among women exposed to efavirenz-containing regimens (1132 live births) and non-efavirenz-containing regimens (7163 live births) during first trimester, giving a pooled, nonsignificant relative risk of 0.87 [95% confidence interval (CI) 0.61–1.24%, $P = 0.45$]. Low heterogeneity was observed between studies ($I^2 = 0$, 95% CI 0–56.3%, $P = 0.85$). Across all studies (1256 live births), one neural tube defect (meningomyelocele) was observed with first trimester efavirenz exposure, giving a prevalence of 0.08% (95% CI 0.002–0.44%).

Conclusion: We found no increased risk of overall birth defects among women exposed to efavirenz during the first trimester of pregnancy compared with exposure to other antiretroviral drugs. Prevalence of overall birth defects with first trimester efavirenz exposure was similar to the ranges reported in the general population. However, the limited sample size for detection of rare outcomes such as neural tube defects prevents a definitive conclusion.

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Introduction

Current guidelines for the use of antiretroviral therapy (ART) during pregnancy recommend that women be offered the same drugs that are prescribed to nonpregnant HIV-infected individuals. The exception is efavirenz, which has been associated with a potential increase in the risk of central nervous system birth defects. Initial reports

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from animal studies led to a classification of efavirenz as a Class C drug ('risk cannot be ruled out') by the United States Food and Drug Administration (FDA); in cynomolgus monkeys treated with efavirenz at a dose resulting in plasma concentrations comparable to systemic human therapeutic exposure, significant central nervous system defects (anencephaly, microphthalmia and anophthalmia, and cleft palate) were observed in three of 20 infant monkeys. Subsequent retrospective case reports of several human infants with first trimester exposure to efavirenz who were born with neural tube defects (myelomeningocele) [1,2], led the FDA to reclassify efavirenz as a Class D drug ('evidence of human fetal risk') in 2005 and recommend against its use during first trimester pregnancy [3].

Prospective reports from the Antiretroviral Pregnancy Registry [4] and cohort studies [5] have found no evidence of an increased incidence of overall congenital abnormalities among infants born to pregnant women who received efavirenz in the first trimester compared with rates among the general population. However, the relatively small sample size of these cohorts provides insufficient power to rule out an increased risk of a specific and rare congenital abnormality such as a neural tube defect. The latest WHO guidelines for resource-limited settings acknowledge the low quality of evidence but recommend against using efavirenz in first-trimester given the potential seriousness of the adverse event (but also do note that use after the first trimester can be considered) [6]. The United States guidelines issued in April 2009 recommend avoidance of efavirenz in the first trimester of pregnancy but note that use after the first trimester can be considered if it is the best choice in individual cases, and that if it is continued postpartum adequate contraception must be assured [7]. European guidelines issued at the end of 2009 recommend against using efavirenz in pregnancy altogether [8]. These safety concerns have led to a decline in efavirenz use in pregnancy in developed countries. One study from Europe found that although approximately 10% of women were reported to be receiving efavirenz at the time of conception, virtually all had switched by the third trimester [9]. This move away from efavirenz use during pregnancy in developed countries is facilitated by the availability of a wide drug formulary and widespread access to prenatal care [10].

In developing countries, ART options are far more limited. Current WHO guidelines for resource-limited settings recommend efavirenz or nevirapine as core first-line drugs [6], and around one-fifth of people on ART in resource-limited countries are receiving an efavirenz-based regimen. In South Africa, efavirenz is prescribed more frequently than nevirapine [11]. Efavirenz is widely used because it is relatively well tolerated (psychiatric symptoms being the predominant toxicity, with rash and hepatic toxicity less frequent than seen with nevirapine), easy to monitor, and shows similar virological suppression compared with nevirapine [12]. Efavirenz is one of the antiretrovirals of choice for patients coinfected with tuberculosis because it has fewer interactions with rifampicin compared with nevirapine [13]. In addition, as emerging evidence increasingly supports a move towards earlier initiation of antiretroviral therapy [6], use of efavirenz in women of childbearing age will likely increase, given the risk of hypersensitivity reactions associated with nevirapine use at higher CD4 cell counts. This is of particular relevance to pregnant women, who are generally diagnosed earlier in their disease than the general population.

These issues, together with the practical constraints associated with regimen changes in large treatment programmes with limited resources, call for an assessment of the evidence regarding the safety of efavirenz in pregnancy. We conducted a systematic review to assess the available evidence from observational cohorts on efavirenz safety in first-trimester pregnancy.

Methods

Search strategy

We developed a highly sensitive search strategy combining key terms that may indicate birth defects (e.g. anencephaly, myelomeningocele, microophthalmia, anophthalmia, cleft palate, neural tube defect, birth defect, abnormality) with the MeSH headings 'HIV' or 'AIDS'. Initial searches were developed (N.F.) for the following databases from inception to 02 January, 2010): MEDLINE via PubMed, EMBASE, Cochrane CENTRAL, CINAHL, PsycInfo, LILACS, Current Controlled Trials (www.controlled-trials.com) and the United States National Institutes of Health (www.clinicaltrials.gov); and the searchable websites of major HIV conferences: all International AIDS Society conferences (up to Cape Town, July 2009) and all Conferences on Retroviruses and Opportunitistic Infections (up to San Francisco, February 2010). We also searched the Antiretroviral Pregnancy Registry (http://www.apregistry.com). Our search was complemented by reviewing bibliographies of relevant papers and contacting individual clinical researchers and large treatment cohorts: the Antiretroviral Treatment in Lower Income Countries (ART-LINC) Collaboration, the Antiretroviral Cohort Collaboration (ART-CC), the European Collaborative Study (ECS), the International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA), Médecins Sans Frontières, the MTCT Plus Initiative, the National Institute of Child Health and Human Development International Site Development Initiative (NISDI), the Paediatric European Network for Treatment of AIDS (PENTA), the Perinatal Health Research Unit (PHRU) and the Reproductive Health Research Unit (RHRU).

Study selection

One of us (N.F.) did a preliminary search scanning all titles for eligibility according to predefined inclusion criteria. After obtaining full abstracts for potentially eligible studies two reviewers (N.F., K.K.) worked independently to assess eligibility. Once all potentially relevant full-text articles and abstracts were identified, we consulted as a team (N.F., K.K., L.M.) to achieve consensus regarding eligibility.

Data extraction

Data extraction was conducted independently, in duplicate, using a standardized form (N.F., K.K.), and once tabulated was subsequently verified by a third investigator (L.M.). Data abstractors collected information about the study setting, study populations, sample size, duration of exposure, and birth outcomes. Our primary endpoint was birth defects of any kind; secondary outcomes were spontaneous abortions, termination of pregnancy, stillbirths, and preterm delivery. We sought to compare the risk of birth defects among infants born to women receiving efavirenz during the first trimester of pregnancy with the risk associated with exposure to other antiretrovirals also in the first trimester. Unsystematic observations (case series or case reports) were excluded from all analyses. We applied the GRADE system to assess the quality of evidence [14].

Data analysis

In order to assess interrater reliability on inclusion of articles, we calculated the ϕ statistic, which provides a measure of interobserver agreement independent of chance [15]. N.F. and E.M. conducted all statistical analyses. We calculated the relative risk (RR) and 95% confidence intervals (95% CI) of the primary outcomes within cohorts by comparing birth defects in infants exposed to efavirenz during the first trimester vs. infants exposed to other antiretroviral drugs, according to the number of events reported in the original studies. Spontaneous and induced abortions and stillbirths were excluded from the denominator of birth defects, consistent with reporting norms. We pooled data using the DerSimonian-Laird random effects method, which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability [16]. In the event of zero outcome events in one arm, we prepared to apply the Haldane method and add 0.5 to each arm [17]. We calculated the I^2 statistic for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity, and calculated the appropriate I^2 confidence intervals. We conducted univariate sensitivity analysis assessing study location, duration of exposure, and status of publication. Prevalence rates were calculated for secondary outcomes. All *P*-values are two-sided. We considered a *P*-value less than 0.05 to be significant. Analyses were conducted using StatsDirect (version 2.5.2, www.statsdirect.com), Stata (version 11, www.stata.com), and GRADE Pro (www.gradeworkinggroup.org).

Results

Figure 1 shows the flow diagram of study selection for analysis. Ninety studies passed the first screening of articles from titles and abstracts; agreement between reviewers on inclusion of abstracts for further analysis was strong ($\phi = 0.87$). A further eight studies were included from article bibliographies and conference abstracts, and 72 were excluded because they did not meet our inclusion criteria. Of the remaining 26 studies considered eligible for inclusion, two studies were excluded because data were not disaggregated by trimester and authors were unable to provide clarification [18,19], and three did not have outcome data available; additional data on secondary outcomes from one unpublished cohort (MTCT-Plus, communication with Dr Elaine Abrams March 5 2010) were included. Of the 21 studies that remained eligible for inclusion, three unsystematic retrospective reports identified at initial screening, including one case series [2] and two case reports [1,20], were excluded from analysis. Individual studies were cross-checked against the Antiretroviral Pregnancy Registry to avoid duplicate reporting and two studies were excluded from analysis for this reason [21,22]. Overall, 16 studies were included for analysis (Table 1), including 11 prospective cohorts (including the MTCT-Plus cohort) [4,5,11,23–29], and five retrospective cohorts [30–34]. Nine studies were done in resource-limited settings (South Africa [11,29–31], Botswana [23], Ivory Coast [24], Brazil [26,32] and one multisite study: the MTCT-Plus Initiative), six in Europe [5,25,27,28,33,34] and one primarily in the United States [4]. Eight were journal articles [5,11,23,25,26,28,31,34], six were conference abstracts [24,27,29,30,32,33], one was an unpublished cohort (MTCT Plus), and one was the Antiretroviral Pregnancy Registry report [4]. (Table 1) Two studies were published in French [24,34] and the remainder published in English. Additional data on secondary outcomes from one study [32] were reported in a separate abstract [35]. Authors provided additional birth outcome data for six studies and the MTCT-Plus cohort [5,11,24,26,28,31].

Birth defects among infants born to women who received efavirenz in the first trimester in the 14 studies with reports of defects by trimester of exposure are summarized in Table 2. (Autopsy reports of birth defects from abortuses were reported by two studies [11,34] but these are not included as reporting across cohorts was inconsistent). Overall, nine of the prospective studies [4,5,11,23–28] reported on rates for birth defects for both infants born to women receiving efavirenz-containing regimens (35 defects in 1132 women with live births) and non-efavirenz-containing regimens (289 defects in 7163

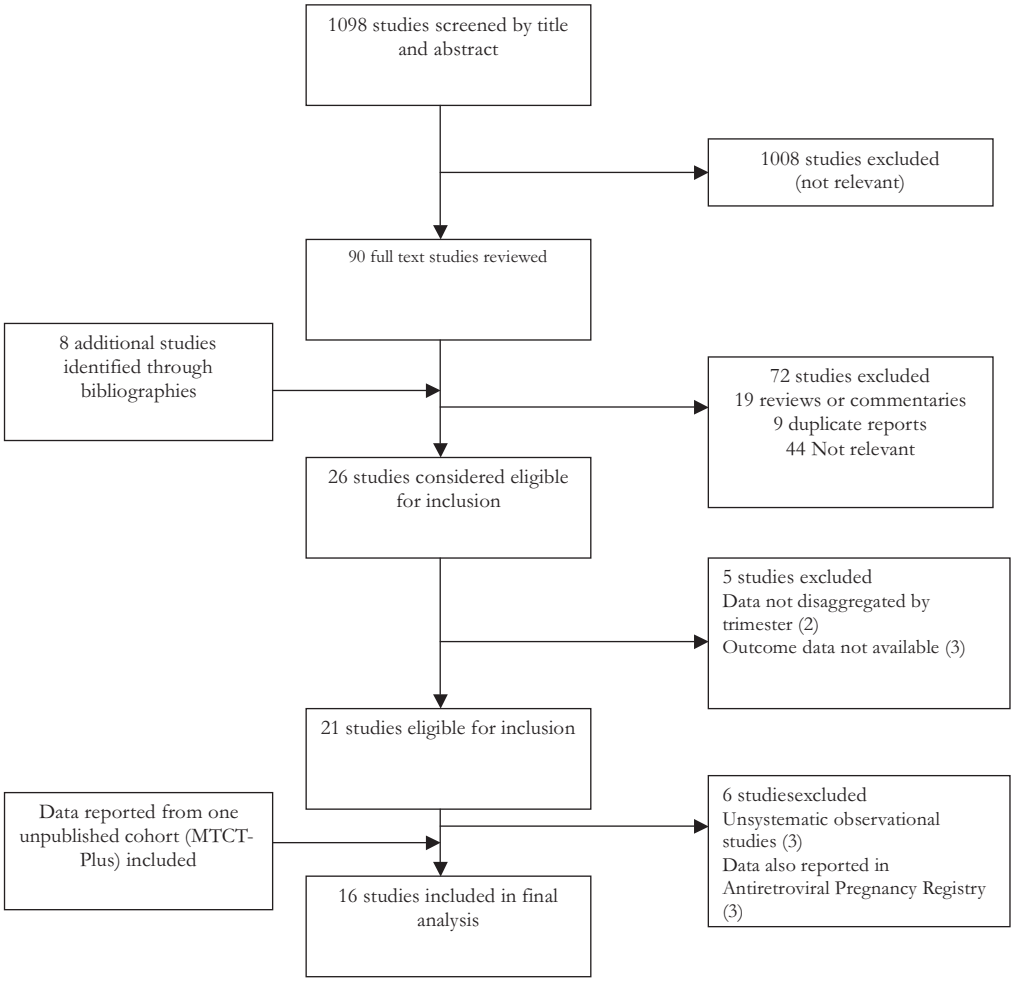

Fig. 1. Identification process for eligible studies.

women with live births) during first trimester, giving a pooled, nonsignificant relative risk of 0.87 (95% CI 0.61–1.24%, $P=0.45$) (Fig. 2); low heterogeneity was observed between studies ($I^2=0$, 95% CI 0–56.3%, $P=0.85$). Studies conducted in developed-country settings did not differ significantly compared with those in resource-limited settings ($P=0.46$); studies in which exposure was limited to first trimester did not differ from studies where mean exposure was longer ($P=0.78$); outcomes from journal publications and the public Antiretroviral Pregnancy Registry did not differ from outcomes reported as abstracts ($P=0.50$).

Incidence of overall birth defects among infants born to women who received efavirenz in the first trimester was 2.9% (95% CI 2.1–4.0%) and ranged from 0% [32] to 22.6% (95% CI 9.6–41.1%) [27]. Across all cohorts with birth defect data (1256 women with live births), one infant with a neural tube defect (myelomeningocele) was observed, giving an incidence proportion of 0.08% (95% CI 0.002–0.44%). (Table 2) An additional case of anophthalmia with severe oblique facial clefts and amniotic banding of the arm was reported with first trimester efavirenz exposure (4). Four prospective studies reported data for both first trimester (31 defects in 920 live births) and second/third trimester efavirenz exposure (19 defects in 695 live births) [4,5,11,27]; there was no difference in the pooled relative risk between these groups (RR = 0.91, 95% CI = 0.46–1.79%, $P=0.79$).

Secondary outcomes were reported variously across studies (Fig. 3). Seven studies reported spontaneous abortions in women with first trimester efavirenz exposure (39 abortuses in 628 pregnancies) [11,24,28–30,34,35] with prevalence rates ranging from 2.6% (95% CI 0.1–13.5%) to 16.7% (95% CI 2.1–48.4%). Six studies and one unpublished cohort (MTCT-Plus) reported on rates of stillbirths (24 stillbirths in 715 pregnancies) [5,11,23,24,28,30], with rates ranging from 0 (95% CI 0–9.3%) to 13% (95% CI 1.7–40.4%). Five studies reported on preterm deliveries (55 preterm deliveries in 399 live births) [5,23,24,26,28], with rates ranging from 9.1% (95% CI 1.1–29.1%) to 18.2% (95% CI 7.0–35.5%). Rates of termination of pregnancy, reported by five

Table 1. Study characteristics.

Study	Setting	Reporting period	Description	Median age (years)	Median CD4 cell count at pregnancy (cells/μl)	Median gestation at birth (weeks)	Median birthweight (g)	Total size of ART pregnancy cohort
MTCT-Plus Initiative*	Multisite**	1/2002–12/2007	Prospective multisite cohort	28	419	NS	NS	495
Westreich *et al.* [29]	South Africa	04/2004–03/2007	Prospective cohort	NS	NS	NS	NS	81
Antiretroviral Pregnancy Registry [4]	USA and international	01/1989–07/2009	Birth registry	28	NS	NS	NS	11369***
Bera *et al.* [11]	Hospital, South Africa	01/2006–12/2008	Prospective cohort	30	275	39	3000	851
Townsend *et al.* [5]	Birth registry, UK	1990–2007	Population based surveillance	30	400	38	2980	7135***
Coffie *et al.* [24]	Hospital, Cote d'Ivoire	2003–2009	Prospective cohort within clinical trial	NS	236	NS	2920	168
Laher *et al.* [30]*	Hospital, South Africa	08/2004–03/2008	Retrospective cohort	31	NS	37	NS	117
Machado *et al.* [26]	Hospital, Brazil	1996–2006	Prospective cohort	29	80% >200	37	NS	696
Gonzales-Tome *et al.* [27]	Hospitals, Spain	2000–2005	Prospective cohort	32	452	38	2815	619
Rossouw [31]	Hospital, South Africa	2002–2007	Retrospective cohort	32	245	NS	2260	37
Bussman *et al.* [23]	Hospital, Botswana	12/2002–01/2006	Prospective cohort	NS	348		2950	71
Floridia *et al.* [28]	Hospitals and university clinics, Italy	01/02–11/05	National surveillance study	34	500	NS	NS*	334
Joao *et al.* [32]	Hospital data, Brazil	01/2001–12/2004	Retrospective cohort	NS	NS	39	2895	90
Jeantils *et al.* [34]	Four hospitals, France	01/1989–12/2003	'DMI 2 system' Retrospective cohort	32.7	257	37	3140	12
Patel *et al.* [25]	European Collaborative Study	1986–12/2003	Prospective cohort	28	420	38	2940	1973
Batallan *et al.* [33]	Hospitals, France	01/1999–12/2002	Retrospective cohort	NS	NS	38	3224	7

NS, data not specified.
*Data on secondary pregnancy outcomes but not on birth defects.
**Uganda, Mozambique, Zambia, South Africa, Kenya, Rwanda, Cote d'Ivoire, Thailand, Cameroon (mtctplus.org).
***Number refers to total number of births, not pregnancies.

Table 2. Description of reported birth defects in infants born to women with first trimester efavirenz exposure.

Study	No. with EFV exposure in 1st trimester	Mean duration of EFV exposure during pregnancy	No. pregnancies with live births	No. birth defects (live births)	Description of birth defects
Westreich *et al.* [29]	60	NS	60	0	NR
Antiretroviral Pregnancy Registry [4]	501	NS	501	14[a]	Myelomeningocele (1), anophthalmia with severe oblique facial clefts and amniotic band on arm
Bera *et al.* [11]	195	39 weeks	184	5[d]	Arthrogryposis multiplex congenital[b], esophageal atresia with trachea esophageal fistula, polysyndactyly[c], postaxial polydactyly, central lower incisor
Townsend *et al.* [5]	205	NS	204	5	Undescended testes (2), hip dislocation (2), hypertrophic pyloric stenosis
Coffie *et al.* [24]	161	59 days	121	0	NR
Machado *et al.* [24]	19	Not reported	18	1	Undescended testes
Gonzales–Tome [27]	31	2 months	31	7	Renal dilatation (4), angiomatosis, dermoid cyst, acetabular dysplasia, inguinal hernia
Rossouw *et al.* [31]	37	NS	31	0	NR
Bussman *et al.* [23]	38	43 days	22	1	Bone dysplasia
Floridia *et al.* [28]	39	NS	32	2	Bilateral clubfoot, undescended testes
Joao *et al.* [32]	23	15 weeks (median)	21	0	NR
Jeantils *et al.* [34]	12	8 weeks	7	1[e]	Right arm angioma
Patel *et al.* [25]	19	40 days	19	0	NR
Batallan *et al.* [33]	5	23.7 weeks	5	0	NR
TOTAL	1345	–	1256	36	—

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]Arthrogryposis multiplex congenita: birth defects included joint contractures, webbed limbs, pulmonary hypoplasia, absent sacrum, and unilateral cleft lip and palate.
[c]Polysyndactyly, polysyndactaly with syndactyly: extra digits fully formed with phanges and nail, fingers were postaxial and toes were preaxial fused with big toe.
[d]One additional birth defect was noted in stillbirth (trisomy 18).
[e]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.

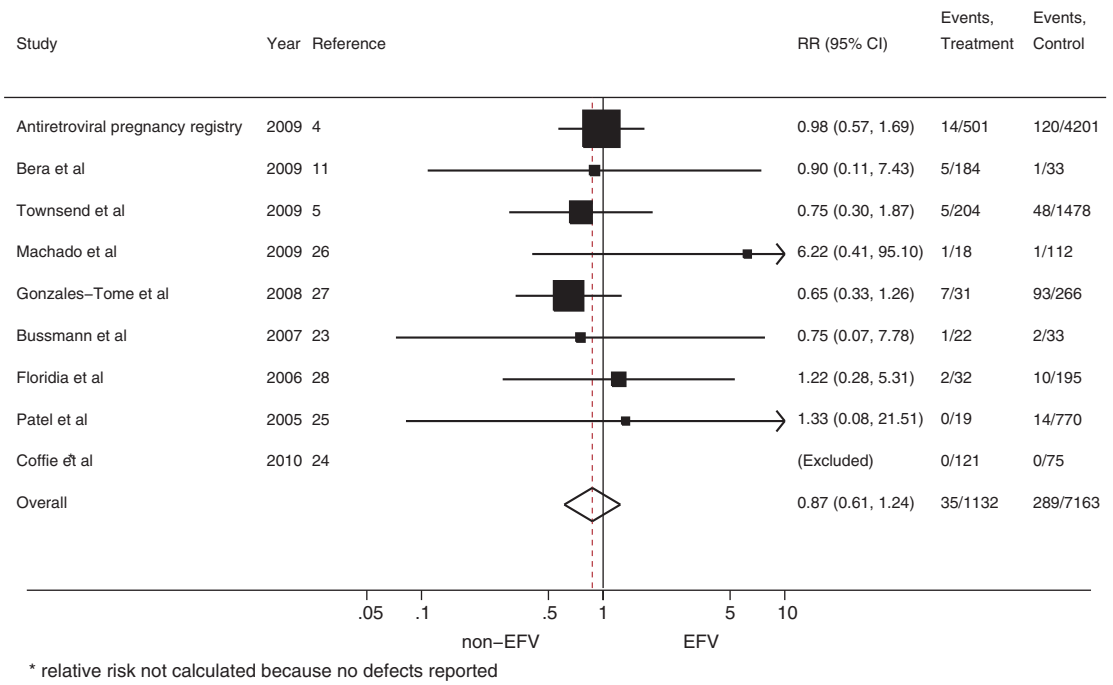

Fig. 2. Relative risk of birth defects among women exposed to efavirenz vs. non-efavirenz containing regimens during the first trimester.

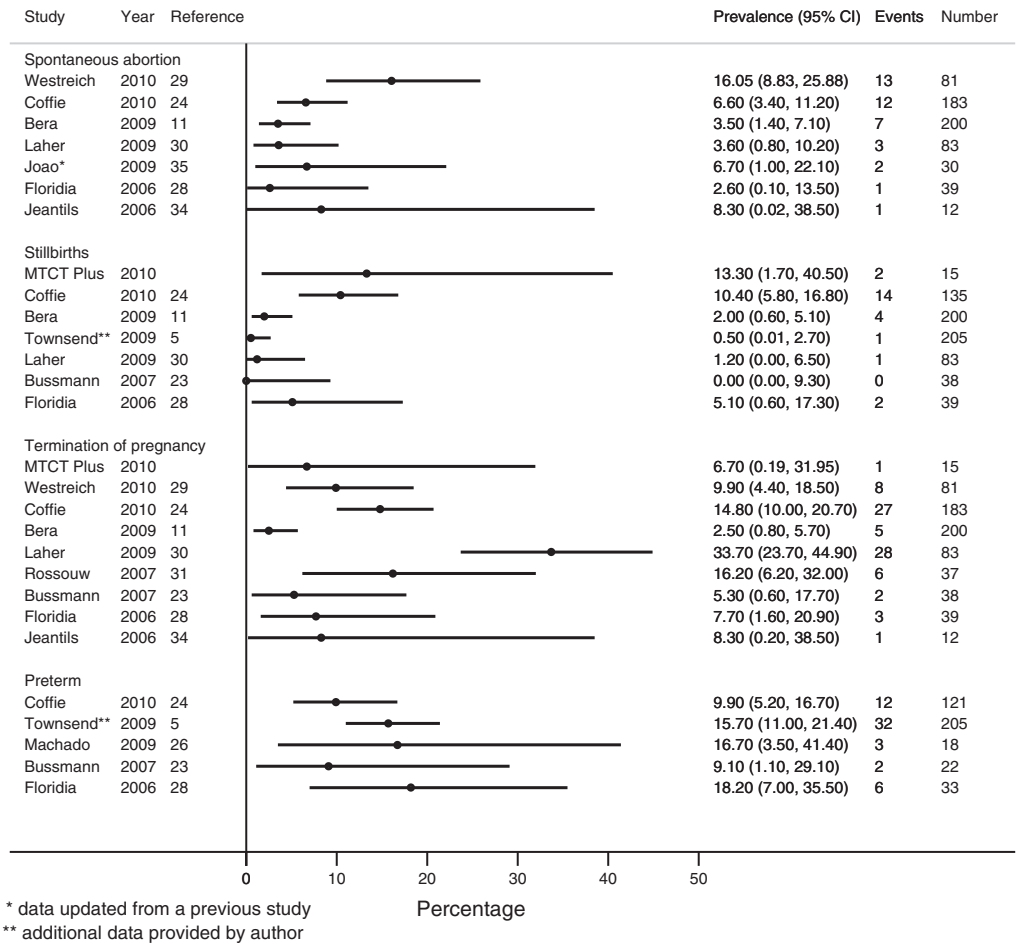

Fig. 3. Secondary outcomes among women exposed to efavirenz in the first trimester.

prospective studies [11,21,22,26,28], three retrospective reviews [30,31,34] and one unpublished cohort (MTCT-Plus) (81 terminations in 688 pregnancies), ranged from 2.5% (95% CI 0.8–5.7%) to 33.7% (95% CI 23.7–44.9%). One of these studies reported a relative risk of termination 5.73 times higher (95% CI 1.45- 22.75%; $P = 0.0017$) among women exposed to efavirenz compared with other antiretroviral drugs; termination requests were based on verbal information alone (i.e., decisions were not based on ultrasound scans) [30].

Our GRADE assessment rated the quality of studies as being low. The main limitations were that the majority of studies failed to consider potential threats to validity; five studies considered sources of bias and only three studies adjusted for potential confounders. Most studies were also limited by a small sample size and low event rate that resulted in low statistical confidence around the point estimate.

Discussion

The recommendation against using efavirenz in pregnancy is largely based on neural tube defects noted in animal studies and retrospective human case reports. However, the relevance of animal data to human pregnancies is unclear as only around 30 of the approximately 1200 animal teratogens are teratogenic in humans [36], and unsystematic, retrospective reports are not adequate to provide a meaningful measure of risk.

Our systematic review of the available evidence to date found no increased risk of overall birth defects among women exposed to efavirenz during the first trimester of pregnancy compared with exposure to other antiretroviral drugs. The incidence of overall birth defects with first trimester efavirenz use (2.9%) was similar to the ranges reported in the general population; 2.7% in the United States [37], 2–5% in France [38], and 2.5–8% in South Africa [39]. Only one case of a neural tube defect was reported across all cohorts reporting congenital birth defects among first-trimester exposed women (1256 women with live births), giving a point prevalence (0.08%) that is within the range reported among the general population in the United Kingdom (0.14%) [40] and South Africa (0.36%) [41]. Although these data should provide reassurance to health providers confronted with women who become pregnant while on efavirenz, the low incidence of neural tube defects in the general population means that a larger sample size is still needed to be able to definitively rule out an increased risk of this specific defect. The range in prevalence of secondary outcomes is an effect of both variability in the sample size of individual studies and the diversity of settings included in the review, resulting in differing background rates of these outcomes in the general population. Pooled estimates are not provided for secondary outcomes for this reason.

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. In addition, our primary analysis was limited to data that were derived from prospective studies, which are less subject to reporting bias than retrospective reports. Nevertheless, there may be a publication bias towards reporting birth defects when a women is on efavirenz and but not reporting birth outcomes if no birth defects occur. Such a publication bias would be expected to lead to an overestimation of the risk of efavirenz compared with other antiretroviral drugs.

An important limitation is that few studies reported on risk of bias or attempted to control for potential confounders, and we were therefore not able to assess the potential effect of these in this review. In particular, women on efavirenz may differ from those not on efavirenz; the latter group may comprise 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 diet). 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 importantly, and moreover would be expected to result in an overestimation of the relative risk of birth defects in the efavirenz group.

The main limitation to this review is the limited sample size. Despite calls for more systematic recording of birth outcomes from women receiving antiretroviral drugs during pregnancy [42], such data remains persistently under-reported, and while there has been a rapid increase in women of childbearing age receiving efavirenz in Africa in recent years, we were only able to identify one registry report from Africa. The few prospective cohorts that do provide reports are inconsistent in reporting of birth outcomes beyond overall birth defects.

Our review provides several directions for research and practice. First, the establishment of prospective birth registries should be supported, particularly in African countries where the majority of first-trimester exposures occur. A number of treatment cohorts contacted during the conduct of this review stated that first-trimester efavirenz exposures were not uncommon, but that such data were not routinely captured. This represents an important missed opportunity. Second, there is a need to support the standardized collection of birth outcome data such that meaningful comparisons can be made with respect not only to rates of birth defects but also other important outcomes such as termination of pregnancy and spontaneous abortions, stillbirths, and preterm

deliveries. Third, women in childbearing age represent a substantial proportion of the total number of people infected with HIV in developing countries [43], and healthcare providers will continue to be faced with women presenting with unintended pregnancies while taking efavirenz. The high rate of termination of pregnancy reported in some cohorts points to a need for improved counseling for women inadvertently exposed during pregnancy. Fourth, periconceptional provision of high-dose folates have proven efficacy in preventing neural tube defects among women with prior risk and could be considered for women of childbearing age who are receiving efavirenz and are likely to become pregnant in settings where folate supplementation is not provided [44]. Finally, efforts must continue to support HIV-positive women to seek care early in their pregnancy.

The potential risks of efavirenz in the first trimester need to be better quantified for healthcare providers, particularly in Africa, where women will continue to be exposed to efavirenz. Given an underlying incidence of neural tube defects in the general population of 0.1–0.4%, even a five-fold increase in risk would give an overall incidence of less than 1%. Valproic acid, an established human teratogen, is associated with a 10-fold increase in the risk of neural tube defects, with an incidence of neural tube defects in 1–2% of infants with first trimester exposures to the drug [45]. Such a level of risk can be ruled out on the basis of available cohort data for first trimester efavirenz exposure presented in this study. Finally, it is important to note that the neural tube closes by around day 28 of gestation, therefore use of efavirenz after this period should not be associated with a risk for neural tube defect.

As with use of any drug in pregnancy, the benefits of the drug need to be weighed against the potential risk. The balance of risks and benefits of efavirenz in pregnancy merits some recalibration, particularly in resource-limited settings where drug formularies are limited, women of childbearing age represent the majority of those infected with HIV, coinfection with tuberculosis is frequent, and the risk of mortality in those who are eligible for ART (CD4 cell count <350 cells/μl or advanced clinical disease) is high. It is also critical that as efavirenz use increases among women in these countries that support is given to establish adequate pharmacovigilance systems to better define the risk.

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The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of their respective organizations.

N.F. and A.C. conceived the study. N.F., L.M. and K.K., undertook searches, extracted data, and conducted authors for additional data. N.F. performed the statistical analyses and wrote the first draft. All authors supported the interpretation of results, provided comments on subsequent drafts and approved the final version.

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