JAIDS Journal of Acquired Immune Deficiency Syndromes Publish Ahead of Print
DOI: 10.1097/QAI.0000000000001922

Birth Defects Following Exposure to Efavirenz-Based Antiretroviral Therapy at Conception/First Trimester of Pregnancy: A Multi-Cohort Analysis

Begoña Martinez de Tejada, MD, PhD, European Pregnancy and Paediatric HIV Cohort Collaboration Study Group

See list of author contributions at the end of the manuscript

Submitted to: *J Acquir Immune Defic Syndr*

Word count (main text): 3500; 3 Tables; Supplementary Material (1 Table)

Short title: EFV birth defects in pregnancy

Corresponding author:

Begoña Martinez de Tejada, MD, PhD

Department of Obstetrics and Gynecology

Geneva University Hospitals and Faculty of Medicine

30 Boulevard de la Cluse

1211 Geneva 14 / Switzerland.

Tel.: ++41 22 382 68 16; fax: ++41 22 3824146.

E-mail: bamt@hcuge.ch

Conflicts of Interest and Source of Funding: The authors have no conflicts of interest to disclose. This work was partly funded by the EU Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement no. 260694.

Abstract

Background: To investigate the association between efavirenz (EFV) use during conception or first trimester (T1) of pregnancy and the occurrence of birth defects.

Setting: Seven observational studies of pregnant HIV-positive women across 13 European countries and Thailand.

Methods: Individual-level data were pooled on singleton pregnancies included in participating cohorts in 2002-2015. Birth defects were coded according to ICD-10 and the EUROCAT classification. We performed mixed-effects logistic regression models to assess the association between EFV-exposure in utero and likelihood of birth defects.

Results: We included 24,963 live births from 21,093 women. At conception, 30.2% (7537) women were on a non-EFV-based regimen, 4.8% (1200) on EFV and 65% (16,226) were unexposed to antiretroviral therapy (ART). There were 412 infants with ≥1 birth defect, a prevalence of 1.65% (95% CI: 1.50-1.82). Limb/musculoskeletal and congenital heart defects were the most common defects reported. Birth defects were present in 2.4%, 1.6% and 1.3% of infants exposed to respectively non-EFV, EFV and unexposed to ART during conception/T1 (p=0.135). The association between exposure to ART during conception/T1 and birth defects remained non-significant in adjusted analyses, as did exposure to EFV vs non-EFV (adjusted odds ratio 0.61; 95% CI: 0.36-1.03, p=0.067). Among the 21 birth defects in 19 infants on EFV, no neural tube defects were reported.

Conclusions: Prevalence of birth defects following exposure to EFV-based compared to non-EFV-based ART in conception/T1 was not statistically different in this multi-cohort study, and even lower. EFV is at least as safe as other ART drugs currently recommended for antenatal use.

Key Words: efavirenz, pregnancy, birth defects, first trimester, conception, HIV, ART

INTRODUCTION

Most of the 1.4 million pregnant women living with HIV who received antiretroviral therapy (ART) in 2016 received an efavirenz (EFV)-based regimen, in line with the World Health Organization (WHO) recommendations for the preferred first-line regimen.[1,2] EFV safety in pregnancy, particularly during the first trimester (T1), has been the focus of considerable investigation following findings of teratogenicity in animal studies and case reports of birth defects, in particular neural tube defects (NTDs).[3,4] These investigations included systematic reviews of EFV safety (updated three times), which found no increased risk of birth defects following T1 exposure.[5-7] In the most recent meta-analysis, including data from 23 studies and 2026 births, the rate of birth defects was not different for infants born to women receiving EFV-containing versus non-EFV-containing regimens during T1 (relative risk 0.78; 95% CI 0.56-1.08). The incidence of NTDs was low (0.05%) and similar in incidence to the general population.[5]

However, two small United States (US) cohorts reported an increased risk of birth defects associated with T1 EFV exposure.[8,9] The ANRS French Perinatal Cohort reported an increased risk of neurological defects (AOR=3.2; 1.1-9.1, p=0.03) among 372 infants with T1

EFV exposure versus those with other antiretroviral drugs exposure in a secondary analysis using a modified Metropolitan Atlanta Congenital Defects Program (MACDP) classification, but not in the primary analysis using the EUROCAT classification; they found no increased risk for overall birth defects.[10] In the Antiretroviral Pregnancy Registry (APR), the prevalence of birth defects in infants with T1 exposure to EFV is 2.2% (95% CI 1.4-3.4),[11] similar to that found in non-exposed infants.

The US perinatal guidelines include EFV as an alternative third agent for the treatment of pregnant women who are ARV-naive and do not recommend avoidance of EFV during T1, whilst United Kingdom (UK) guidelines recommend that women conceiving on an EFV regimen should remain on it and that EFV should be considered as an option for women starting ART in pregnancy.[12,13] However, historical concerns regarding the high teratogenic risk has meant that antenatal EFV use has been infrequent in resource-rich settings. For example, in the French Perinatal Cohort, less than 4% of pregnancies in 2000-2010 had T1 EFV exposure, and less than 1% had T2 or T3 exposure.[10]

Given the very large numbers of pregnant women and women of child-bearing potential on EFV-based regimens worldwide, there is a need for more safety data to improve the precision of the potential risk of birth defects associated with EFV use during pregnancy.

We conducted a pooled analysis of data on HIV pregnant women from observational studies across Europe and Thailand to assess the association between exposure to EFV in utero versus non-EFV-containing regimens by timing of exposure and the occurrence of birth defects. Our aim was to confirm that exposure to EFV during conception/T1 did not increase the likelihood of birth defects compared to non-EFV-based regimen or no ART.

METHODS

Study design

We conducted a pooled analysis of individual pregnancy data from seven observational studies of pregnant women living with HIV across 13 European countries and Thailand within the framework of the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC). Participating studies were: the European Collaborative Study (ECS) (including sites in Belgium, Denmark, Germany, Italy, Netherlands, Poland, Sweden and Ukraine), NENEXP (Catalonia), the Madrid Cohort of HIV-Infected Mother-Infant Pairs, the Swiss Mother and Child HIV Cohort Study (MoCHiV), the Program for HIV Prevention & Treatment (PHPT) cohort (Thailand), the United Kingdom and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC), and the "Victor Babes" Hospital Cohort, Bucharest (Romania). The ECS included only live births, the Madrid Cohort included live- and still-births, NENEXP included live- and stillbirths plus miscarriages, and the remaining studies collected data on all pregnancy outcomes.

Data were submitted to the coordinating center using a standardized format (modified HIV Collaboration Data Exchange Protocol, http://www.hicdep.org). Data collected included maternal demographics, ART use, maternal CD4 count and HIV RNA levels, intrapartum and neonatal antiretroviral prophylaxis, mode of delivery and infant outcomes (e.g. gestational age, birth weight, sex, birth defects). Each participating study was responsible for ensuring that ethics approval for the data merger and analysis was in place and for compliance with local and national data protection requirements.

Study population

We included 24,963 pregnancies ending in delivery of a singleton infant live-born at ≥22 gestational weeks between January 2002 and March 2015 and with antenatal ART (any duration) to evaluate the risk of birth defects among newborns exposed to EFV during T1 or at any time during pregnancy compared with those unexposed. A secondary analysis among 150 ART-exposed pregnancies with an estimated date of delivery between January 2002 and March 2015 (singleton pregnancies only) was conducted to describe birth defects in reported pregnancies ending in stillbirth or in termination of pregnancy due to ultrasound abnormalities.

Variables and definitions

Birth defects were coded according to the International Statistical Classification of Diseases and related health problems, 10th revision (ICD-10) codes (http://apps.who.int/classifications/icd10/browse/2010/en). The EUROCAT classification system was used to assess the overall birth defect rate and to classify birth defects into different organ systems (EUROCAT 2013). Data were requested on birth defects in live- and stillbirths, as well as for spontaneous abortions and terminations, from studies collecting such outcomes. The methodology of all included studies allowed data collection on birth defects apparent/diagnosed at birth or until hospital discharge. Data were also collected on any birth defect reported after postnatal discharge (i.e. during initial infant follow-up) in all studies, except the Ukraine ECS.

T1 was defined as 1 to 12 completed gestational weeks based on the last menstrual period. Fetal loss was defined as any pregnancy ending before 22 weeks and further classified as spontaneous abortion (ended spontaneously) or termination. Preterm deliveries were defined

as live birth between 22 and 36 completed weeks. Stillbirth was defined as the delivery of a dead fetus and neonatal death as death within the first 4 weeks of a live-newborn at ≥22 weeks. Low birth weight was defined as <2500g.[14] We used the lowest CD4 count and the highest HIV RNA load reported during pregnancy. Fetal exposure to ART was classified as EFV-based ART, non-EFV-based ART and none. Infants were further classified according to the timing of earliest in utero exposure to EFV, i.e. exposure during conception/T1 and T2/T3. Infant HIV status at 18 months was classified as positive, negative and unknown.

Statistical analysis

We expected a prevalence of 3% birth defects in infants exposed to EFV or non-EFV-based regimens during conception and/or T1.[15] We pre-specified that a more than 2% absolute difference in the proportions of birth defects (corresponding to a relative risk of 1.67) between infants exposed to EFV versus non-EFV-based regimen would be considered clinically relevant. The calculated number of pregnancies needed was 3040 (760 under EFV and 2280 under non-EFV at conception/T1) for a study power of 80% and a one-sided alpha error of 2.5%. We compared maternal and pregnancy characteristics in the three groups of fetal exposure to ART using Chi-2 tests for categorical variables or ANOVA for continuous variables; this did not take into account clustering of data at the mother level (as some contributed more than one pregnancy). Prevalence of birth defects was reported per 100 live births by ART exposure group. We estimated the 95% confidence intervals (95% CI) for proportions with the exact binomial method. We assessed the association between previous ART exposure group and birth defect using mixed-effects logistic regression model and reported p-values. We described the types of birth defects overall and by ART exposure group and the proportion of babies exposed to concomitant zidovudine during T1 among infants presenting a congenital heart defect.

There was clustering at the mother level (six cohorts consistently identified repeat pregnancies in the same woman, resulting in 3208 women known to be followed for two pregnancies, 518 for three pregnancies, 66 for four pregnancies, and four women for five pregnancies). To account for clustering of data at the mother level and at the cohort level, we performed mixed-effects logistic regression modelling to assess the likelihood of birth defects by several variables with the mother level nested into the cohort level as random effects. We first compared infant characteristics (sex, HIV status, preterm delivery and low birth weight) between those with at least one birth defect and those without, using the same statistical approach. Then, we assessed the association between the main predictor, ART exposure during conception/T1, and birth defect. Regarding the variables at the mother level, we evaluated the association between the following variables and occurrence of birth defects: maternal age (<25, 25-34, 35-39, ≥40 years), lowest CD4 count (≥350, 200-349 and <200 cells/mm^3), HIV RNA >50 copies/mL, ethnicity (white, black, Asian, other), and parity (primiparous, multiparous), reporting unadjusted odds ratios (OR) and OR adjusted for the pre-specified covariates (equivalent to prevalence risk ratios due to rare events). Finally, we reported descriptive statistics on stillbirths, spontaneous abortions and terminations due to ultrasound abnormalities.

All analyses were performed using Stata version intercooled 15 (StataCorp, College Station, TX, USA). Statistical significance was defined as $p<0.05$ (two-sided).

RESULTS

The dataset included 24,963 live births from singleton pregnancies. The characteristics of the pregnancies are presented in Table 1, stratified by ART exposure group, with pregnancy and infant characteristics significantly differing by group.

There were 412 infants with at least one birth defect, leading to a birth defect prevalence of 1.65% (95% CI 1.50-1.82) and a total of 453 birth defects. Among infants with multiple birth defects (n=34; 8.25%), 27 had two birth defects and seven had three birth defects. Of note, there were five mothers who each had two infants with a birth defect (in separate pregnancies).

The proportion of infants with birth defects was not significantly higher in those exposed to EFV-based regimens (2.4%) compared to those exposed to non-EFV-based regimens (1.6%) and to those not exposed to ART during conception/T1 when we took into consideration the clustering effect (1.3%; Table 1). Table 2 describes the 453 birth defects reported according to the EUROCAT organ system classification. Limb and musculoskeletal and congenital heart defects were the most common defects reported. In the group exposed to EFV during conception/T1, 21 birth defects were described among 19 infants: nine limb or musculoskeletal defects, four genetic syndromes/microdeletions, three congenital heart defects, two hypospadias, one microcephaly, one Hirschsprung's disease and one orofacial cleft defect. Among infants presenting a congenital heart defect and exposed to ART during conception/T1 (n=34), almost half (16/31) in the non-EVF based ART group and one-third (1/3) in the EFV-based ART group were concomitantly exposed to zidovudine.

Assessment of infant characteristics associated with birth defect showed that infants with at least one defect were more often boys compared with infants without any birth defect (230/412 [55.8%] versus 12,349/24,551 [50.5%],; p=0.038), with no differences regarding HIV vertical transmission status (p=0.655). We found a higher proportion of preterm birth in infants with birth defects compared to those without birth defects (24.5% [101/412] versus 10.8% [2640/24551], p<0.001), and no association with low birth weight (p=0.544). Maternal characteristics associated with birth defects are presented in Table 3. The results of birth defects by participating study are presented in the Supplemental

material,http://links.lww.com/QAI/B253. The highest prevalence of birth defects was reported from Madrid (5.7% of pregnancies; 95% CI 4.1-7.8%) and NENEXP (5.5% of pregnancies; 95% CI 3.9-7.6%); the lowest prevalence was reported from ECS (0.4% of pregnancies; 95% CI 0.3-0.6%).In the Spanish cohort, exposure to ART during conception/T1 was not significantly associated with birth defects in univariate analysis (p=0.135) or after adjustment for other important variables (p=0.179; Table 3). As repeat pregnancies in the same woman were not consistently identified in the Ukraine ECS, we performed the same analyses after exclusion of observations from this site (n=8190) and confirmed the same findings (data not shown). The risk of birth defects was not significantly increased in infants exposed to EFV during conception/T1 compared to non-EFV-based regimens (adjusted OR 0.61 (95% CI 0.36-1.03), p=0.067) (Table 3). Neither this OR nor its 95% CI met our pre-specified criterion for a clinically relevant difference. We did not find any other independent risk factors for birth defects. When we restricted the analysis to babies reported to be HIV-negative (n=20,116), 348 birth defects were observed (84.5% of 412 birth defects) and we confirmed the same findings (overall p-value=0.342; OR for EFV-based regimen compared to no ART 0.67; 95% CI 0.36-1.27; p=0.222; OR for EFV-based regimen compared to non-EFV-based regimen 0.63; 95% CI 0.34-1.17; p=0.145).

Descriptive analyses of birth defects among stillbirths and terminations

Among the seven studies, six (Madrid, NENEXP, NSHPC, MoCHIV, Victor and PHPT) reported data on stillbirths and spontaneous abortions. A total of 164 stillbirths, 54 spontaneous abortions and three terminations due to ultrasound abnormalities were reported. Information on birth defects was available for 148 stillbirths and were detected in 10 (6.8%). Information on ART exposure groups was available for 135 stillbirths. Of the 10 stillborn infants with birth defects, two had conception/T1 EFV exposure (15.4%, n=13), 3 had non-EFV ART exposure (5.6%, n=54) and five were non-exposed to ART (7.4%, n=68).

DISCUSSION

In this individual patient data analysis of almost 25,000 pregnancies, over one-third had T1 ART exposure, with only 14% exposed to EFV. This partly reflects guidelines on the use of ART during pregnancy over the course of the study period (2002 to 2015), with several European countries recommending that pregnant women and those planning a pregnancy should avoid EFV-containing regimens due to concerns around the increased risk of birth defects.[16-18]

By contrast, EFV is widely used globally as it is well tolerated, easy to monitor and efficient. WHO consolidated guidelines for resource-limited settings recommended EFV as a core first-line drug in 2013[19] and the implementation of Option B+, defined by initiation of ART for all women living with HIV during pregnancy or breastfeeding and continued for life, thus meaning that increasing numbers of women will be on EFV at conception. With the expanding use of EFV in childbearing women, especially in sub-Saharan Africa, it is crucial to assess whether there is an increased risk for birth defects with EFV use during pregnancy.

Our study of 1200 pregnancies with conception/T1 exposure (1.6%) to EFV show no higher risk of birth defects in pregnant women compared to no ART treatment (1.3%), or non-EFV-based regimen (2.4%). The comparative risk of birth defects among infants exposed to EFV-based regimens during conception/T1 tended to be lower compared to non-EFV ART, but did not meet our pre-specified criterion for a clinically relevant difference. This is consistent with the meta-analyses performed by Ford and colleagues showing no increased risk of birth defects with antenatal EFV use. The most recent reported a relative risk of birth defects of 0.78 (95% CI 0.56-1.08) for infants exposed to EFV-containing compared to non EFV-containing regimens.[5] This meta-analysis used prospective data from 23 studies and included

2026 births exposed to EFV and reported an incidence of NTDs of 0.05%. The authors stated the need for continued prospective surveillance of birth defects in EFV-exposed pregnancies.

This is underscored by the report from the ANRS French Perinatal Cohort of an increased risk of neurological defects (adjusted OR=3.2; 95% CI 1.1-9.1; p=0.03), but no increased risk of overall birth defects among infants exposed to EFV in T1.[10] Neurological defects reported in this study were ventricular dilatation with anomalies of the white substance, partial agenesis of the corpus callosum, subependymal cyst and pachygyria. The only case of neurological birth defect found in our study was a case of microcephaly, which has not been found to be associated with EFV used in any study.[20] A causal association between EFV and the different neurological anomalies reported above seems unlikely, especially as they do not correspond to a specific malformative pathway and the majority of them are also found in association with congenital infections, such as cytomegalovirus.[21,22] Of note, the increased risk of neurological defects in the ANRS cohort was only found with the MACDP classification and was due to the addition of cases of subependymal cyst. Using the EUROCAT classification, sub-ependymal cyst was excluded, and no increased risk was observed.

We observed that women exposed to non-EFV regimens had a trend towards a higher risk for birth defects than the group of non-treated women, but the difference was not statistically significant. In addition, the rate found in our study (2.4%) is in line with those reported in general pregnant populations.[23] Among newborns exposed to non-EFV regimens from T1, the most frequent birth defects were cardiac, urinary and genital malformations, which are also the most frequent in the non-exposed group and in the general population. There is ongoing discussion as to whether cardiac malformations are causally associated with

exposure to zidovudine during pregnancy. In our study, almost half of the infants presenting a congenital heart defect were exposed to zidovudine during T1. Several studies, including the ANRS French study, have found an association between congenital heart defects and exposure to zidovudine in T1.[8,10] In other studies, zidovudine was not found to significantly increase the risk of congenital heart defects and further data are necessary to confirm this risk.[24,25]

In the current study, infant abnormalities were associated with preterm birth and male gender, but not with HIV vertical transmission status, ART exposure, EFV exposure or low birth weight. The recent potential safety signal regarding the use of dolutegravir and NTDs in infants exposed at conception from the Tsepamo study in Botswana underscores the knowledge gap regarding safety in pregnancy of newer antiretroviral drugs and the need to strengthen the pharmacovigilance of the antenatal use of ART, particularly in low- and middle-income countries.[26,27] In Botswana, among 426 infants born to mothers on dolutegravir-based regimens at conception, four had an NTD, a prevalence almost 10-fold higher than that expected from normal rates or from infants exposed to other regimens.[28] In our study of infants born to women living with HIV in European settings between 2002 and 2015, there was a prevalence of NTDs of 0.02% overall. In EUROCAT registries, the prevalence of NTDs not associated with chromosomal abnormalities was reported to be around 0.09% during this period.[29]

A limitation found in most published studies was that data on stillbirth and abortion were not reported. Birth defects are associated with a higher rate of stillbirth, spontaneous abortion and termination of pregnancy. Therefore, including only live births could lead to underreporting of the birth defect risk. In our analysis, one of the two largest studies (ECS) did not collect

data on stillbirths. For the remaining studies, we obtained data on birth defects and ART exposure among 135 stillbirths. Twenty percent of birth defects were EFV-exposed among the stillbirths compared with 5% among the livebirths, whilst a greater proportion of women with stillbirths were on EFV (10%) and non-EFV ART (40%) than those having a live birth (4.8% and 30.2%, respectively).

The strengths of our study are the large sample size and the use of a standardized classification for birth defects. We used the EUROCAT classification system, which excludes most minor birth defects, as these anomalies are subject to considerable underreporting. In addition, our study population was followed in European countries where antenatal ultrasound follow-up is usually carried out, thus allowing diagnosis of birth defects that might not be clinically apparent at birth. Pediatric follow-up in all but one study (Ukraine ECS) meant that we were able to include any birth defect reported after postnatal discharge in at least the first six months of life. However, we cannot exclude the possibility of some underreporting due to late diagnosis of birth defects and not included in our data, but the proportion would probably be very small.

The main weakness of our study is the potential heterogeneity introduced by merging data from several cohorts/studies with different protocols. The Spanish studies reported the highest prevalence of birth defects, which might be related to the per-protocol ultrasound (abdominal and cardiac) follow-up performed in all children and not performed among children from other cohorts/studies. However, the participating cohorts all followed broadly similar prospective protocols with exposure to ART documented prior to the pregnancy outcomes. A further limitation was that not all the included studies reported data on pregnancy losses and stillbirth. Thus, there may have been underestimation of some birth defects and it is possible that they were differentially reported. Unfortunately, we did not have information about folic acid and co-medication use or maternal nutritional status.

CONCLUSIONS

Overall, our results demonstrate evidence of the safety of EFV when used from the start of pregnancy with no clinically relevant differences in the risk of birth defects compared with infants exposed to non-EFV-based regimen or non-exposed to ART. Considering the current study, the previous WHO meta-analysis[5] and recent data from the Tsepamo study,[30] there are now around 9000 EFV exposures periconception in large published studies with no increase in overall birth defects or NTDs reported. We suggest that licensed product information on EFV is updated and that the few remaining European guidelines that still recommend avoiding EFV should be reconsidered. Pharmacovigilance ART studies during pregnancy are essential to guarantee that the safest drugs are recommended for use before and during pregnancy.

Acknowledgments

*European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group author contributors:

Project team: Begoña Martinez de Tejada (Swiss Mother and Child Cohort Study); Angèle Gayet-Ageron (Division of Clinical Epidemiology, University Hospitals of Geneva; Swiss Mother and Child Cohort Study), Ursula Winterfeld (Swiss Teratogen Information Service and Service of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), Graziella Favarato (EPPICC data manager), Claire Thorne (EPPICC, UCL Great Ormond Street Institute of Child Health, UK).

Other writing group members (ordered alphabetically by cohort): Tessa Goetghebuer Henriette Scherpbier (European Collaborative Study West); Heather Bailey, Ruslan Malyuta Alla Volokha (European Collaborative Study Ukraine); Luis Prieto, Jose Tomas Ramos; Christian Kahlert, Christian Polli (MoCHiV, Swiss Mother and Child HIV Cohort Study); Natalia Mendoza-Palomar, Maria Teresa Coll, Antoni Noguera-Julan (NENEXP); Helen Peters (NSHPC); Cosmina Gingaras ("Victor Babes" Hospital Cohort, Romania); Sophie Le Coeur (Thai PHPT)

Author contributions: All members of the project team participated in discussions about the study design, choice of statistical analyses, and interpretation of the findings and were involved in the preparation and review of the final manuscript. Angèle Gayet-Ageron performed all statistical analyses. All members of the writing group were involved in the collection of data, interpretation of findings, and in the preparation and review of the final manuscript.

Other members of the EPPICC Study Group:

C. Giaquinto, O. Rampon, A. Mazza and A. De Rossi; I. Grosch Wörner; M. Kreyenbroek, M.H. Godfried, F.J.B. Nellen and L. van Leeuwen; L. Navér, A.B. Bohlin, S. Lindgren, A. Kaldma, E. Belfrage; J. Levy, P. Barlow, Y. Manigart, M. Hainaut; B. Vandercam, B. Brichard, D. Van der Linden, H. Waterloos; C. Viscoli; A. De Maria; G. Bentivoglio, S. Ferrero, C. Gotta; N.H. Valerius, V. Rosenfeldt; V. Savasi, S. Fiore, M Crivelli; A Viganò, V. Giacomet, C. Cerini, C. Raimondi and G. Zuccotti; S. Alberico, G Maso, M. Tropea, V. Barresi,. ssa W. Buffolano, R. Tiseo, P. Martinelli, M. Sansone, G. Maruotti, A. Agangi; C. Tibaldi, S. Marini, G. Masuelli, C. Benedetto; M. Marczynska, S. Dobosz, J. Popielska, A. Oldakowska (European Collaborative Study— Western sites); T. Pilipenko, A. Zayats, S.

Posokhova, T. Kaleeva, Y. Barishnikova, S. Servetsky, R. Teretsenko, A. Stelmah, G. Kiseleva, E. Dotsenko, O. A. Zalata, S. Solokha, M. P. Grazhdanov, E. Kulakovskaya, N. Bashkatova, V. Gigil, I. Raus, O. V. Yurchenko, I. Adeyanova, Z. Ruban, O. Govorun, O. Ostrovskaya, I. Kochergina, L. Kvasha, G. Kruglenko, N. Primak (European Collaborative Study –Ukraine); Maribel Gonzalez Tome, M.L. Navarro, M.J. Mellado, L. Escosa, C. Fernández-McPhee, M.A. Roa, J Beceiro, I. Olabarrieta, E. Munõz, Diana Mazariegos, M Carmen Viñuela (Madrid Cohort of HIV Infected Mother–Infant Pairs); C. Fortuny-Guasch, P. Soler-Palacín, V. Pineda, Ll Mayol, M. Mendez, N. Rovira, T. Vallmanya, A. Mur, L. Garcia, N. Rius, O. Calavia, N. Rovira, B. Guarch, M. Pedrini and N. López-Segura (NENEXP); K. Francis, A. Horn, P. Tookey, A. Judd (UK and Ireland National Study of HIV in Pregnancy and Childhood); L. Ene ("Victor Babes" Hospital Cohort, Romania); K. Aebi-Popp, I.Hoesli, P. Paioni, C. Rudin, A Scherrer (Swiss Mother and Child HIV Cohort Study).

REFERENCES

1. UNAIDS. On the fast-track to an AIDS-free generation. Geneva: UNAIDS; 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/GlobalPlan2016_en.pdf.
2. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd edition. Geneva: WHO; 2016.
3. Fundaro C, Genovese O, Rendeli C, et al. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002; 16:299-300.
4. De Santis M, Carducci B, De Santis L, et al. Periconceptional exposure to efavirenz and neural tube defects. *Arch Int Med* 2002;162:355.
5. Ford N, Mofenson L, Shubber Z, et al. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS* 2014;28 (Suppl 2):S123-131.

6. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. *AIDS* 2011; 25:2301-2304.

7. Ford N, Mofenson L, Kranzer K, 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.

8. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J* 2010;29:721-727.

9. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J* 2012; 31:164-170.

10. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French perinatal cohort study (ANRS CO1/CO11). *PLoS Med* 2014;11:e1001635.

11. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2017. 2018. Available at: www.APRegistry.com.

12. British HIV Association writing group, Gilleece Y, Tariq S, Bamford A, et al. British HIV Association guidelines for the management of HIV infection in pregnant women. Available at: http://www.bhiva.org/documents/Guidelines/Pregnancy/2018/BHIVA-Pregnancy-guidelines-consultation-draft-final.pdf.

13. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission: Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Department of Health and Human Services. 2017. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf.

14. United Nations Children's Fund and the World Health Organization. Low birthweight: country, regional and global estimates. UNICEF, New York. 2004.

15. World Health Organization. Congenital anomalies. Geneva: World Health Organization. 2017. Available at: http://www.who.int/topics/congenital_anomalies/en/.

16. Aebi-Popp K, Mulcahy F, Rudin C, et al National guidelines for the prevention of mother-to-child transmission of HIV across Europe - how do countries differ? *Eur J Public Health* 2013; 23:1053-1058.

17. Hainaut M, Goetghebuer T, Vanderfaeillie A, et al, Belgian current consensus for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV. *J Pédiatr Belge* 200911:70-73.

18. Grupo de expertos de la Secretaría del Plan Nacional sobre el Sida (SPNS), Grupo de Estudio de Sida (GeSIDA), /Sociedad Española de Ginecología y Obstetricia (SEGO) y Sociedad Española de Infectología Pediátrica (SEIP). Documento de consenso para el seguimiento de la infección por el VIH en relacion con la reproducción, embarazo, parto y profilaxis de la transmision vertical del nino expuesto. Madrid, Spain. 2018. Available at: http://gesida-seimc.org/wp-content/uploads/2018/01/gesida_borrador_9_ene_GUIA_PRACTICA_PARA_EL_SEGUIMIENTO_DE_LA_INFECCION_POR_VIH_EN_LA_REPRODUCCION.pdf.

19. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: WHO. 2013.

20. Albano JD, Beckerman K, Mofenson L, et al. Central nervous system and neural tube birth defects in The Antiretroviral Pregnancy Registry. Presented at: *IDSA ID Week, October 26-30, 2016.* New Orleans, USA. 2016.

21. Kawasaki H, Kosugi I, Meguro S, et al. Pathogenesis of developmental anomalies of the central nervous system induced by congenital cytomegalovirus infection. *Pathol Int* 2017; 67:72-82.

22. Frenkel LD, Gomez F, Sabahi F. The pathogenesis of microcephaly resulting from congenital infections: why is my baby's head so small? *Europ J Clin Microbiol Infect Dis* 2018; 37:209-226.

23. Morris JK, Springett AL, Greenlees R, et al. Trends in congenital anomalies in Europe from 1980 to 2012. *PloS one* 2018; 13:e0194986.

24. Vannappagari V, Albano JD, Koram N, et al. Prenatal exposure to zidovudine and risk for ventricular septal defects and congenital heart defects: data from the Antiretroviral Pregnancy Registry. *Eur J Obstet Gynecol Reprod Biol* 2016; 197:6-10.

25. Lipshultz SE, Williams PL, Zeldow B, et al. Cardiac effects of in-utero exposure to antiretroviral therapy in HIV-uninfected children born to HIV-infected mothers. *AIDS* 2015; 29:91-100.

26. Bailey H, Zash R, Rasi V, et al. HIV treatment in pregnancy. *Lancet HIV* 2018; 5:e457-e467.

27. Zash RM, Williams PL, Sibiude J, et al. Surveillance monitoring for safety of in utero antiretroviral therapy exposures: current strategies and challenges. *Expert Opin Drug Saf* 2016; 15:1501-1513.

28. World Health Organization. Potential safety issue affecting women living with HIV using dolutegravir at the time of conception. Geneva: WHO. 2018.

29. Khoshnood B, Loane M, de Walle H, et al. Long term trends in prevalence of neural tube defects in Europe: population based study. *BMJ* 2015; 351:h5949.

30. Zash R, Makhema J, Shapiro RL. Neural tube defects with dolutegravir treatment from the time of conception. *N Engl J Med.* 2018; 379:979-981.

Table 1. Pregnancy and infant characteristics by categories of exposure to antiretroviral therapy (ART) at conception and first trimester (T1)

Variables	**No ART at conception/T1** **N (%)**	**EFV-based ART at conception/T1** **N (%)**	**Non-EFV-based ART at conception/T1** **N (%)**	**P value**
	16,226 (65.0%)	1200 (4.8%)	7537 (30.2%)	
Maternal age (years) at delivery, (n=24,768)				<0.001
<25	4446 (27.6)	85 (7.1)	652 (8.8)	
25-34	9467 (58.6)	638 (53.4)	4127 (55.5)	
35-39	1879 (11.6)	372 (31.2)	2039 (27.4)	
≥40	351 (2.2)	99 (8.3)	613 (8.3)	
Maternal ethnicity (n=24,498)				<0.001
White	8984 (55.9)	192 (16.1)	2037 (28.1)	
Black	6601 (41.1)	940 (78.9)	4878 (67.3)	
Asian	346 (2.2)	48 (4.0)	227 (3.1)	
Other	130 (0.8)	11 (0.9)	104 (1.4)	
Cohorts or country				<0.001
MoCHIV (or Switzerland)	211 (1.3)	30 (2.5)	266 (3.5)	
Madrid	268 (1.7)	35 (2.9)	362 (4.8)	
NENEXP (Catalonia)	209 (1.3)	22 (1.8)	419 (5.6)	
NSHPC (UK/Ireland)	7177 (44.2)	1'035 (86.3)	5209 (69.1)	
Victor Babes (Romania)	37 (0.2)	6 (0.5)	62 (0.8)	
ECS (Other European Union countries and Ukraine)	8319 (51.3)	53 (4.4)	1184 (15.7)	
PHPT (Thailand)	5 (0.03)	19 (1.6)	35 (0.5)	
Primiparous (n=24,821)	8096 (50.1)	380 (31.8)	2331 (31.3)	<0.001
Injecting drug use during pregnancy (n=9981)	201 (2.5)	4 (3.4)	116 (6.3)	<0.001
Median time since HIV diagnosis by delivery, years (interquartile range) (n=23,801)	0.5 (0.4-2.7)	5.3 (3.2-8.0)	5.5 (3.0-8.5)	<0.001
Lowest CD4 count during pregnancy (n=20,178) cells/mm^3	7366 (58.5)	705 (62.7)	4035 (62.5)	<0.001

≥350 200-349 <200	3425 (27.2) 1805 (14.3)	305 (27.1) 115 (10.2)	1715 (26.6) 707 (11.0)	
HIV RNA >50 copies/ml during pregnancy (n=19,311)	9821 (86.2)	192 (16.5)	2112 (31.3)	<0.001
Delivery mode (n=24,842) Vaginal, spontaneous/ instrumental Cesarean section elective/emergency	 7350 (45.5) 8794 (54.5)	 516 (43.4) 674 (56.6)	 2667 (35.5) 4841 (64.5)	<0.001
Gestational age in weeks (n=24,963)				<0.001
≥37	14,638 (90.2)	1075 (89.6)	6509 (86.4)	
36-34	1082 (6.7)	75 (6.2)	670 (8.9)	
<34	506 (3.1)	50 (4.2)	358 (4.7)	
Low birth weight (n=24,222)	1923 (12.2)	151 (12.9)	1065 (14.6)	<0.001
Number of birth defects (n=24,963) Proportion with ≥ 1 birth defect, % (95% confidence interval)	210 1.3 (1.1-1.5)	19 1.6 (0.96-2.5)	183 2.4 (2.1-2.8)	0.135*

*p-value from mixed-effect logistic regression using the mother level nested into the cohort level as random effect. EFV: efavirenz

Table 2. Description of 453 birth defects among 412 live births, according to EUROCAT subgroups of birth defects

	Overall	No ART at conception/T1	EFV-based ART at conception/T1	Non-EFV-based ART at conception/T1
	N	**N**	**N**	**N**
Organ System Classification (EUROCAT)	453	226	22	205
Nervous system	***27***	***16***	***1***	***10***
Spina bifida	6	3	0	3
Hydrocephalus, dilatation of ventricular system	6	6	0	0
Microcephaly	8	3	1	4
Malformation of corpus callosum	1	0	0	1
Holoprosencephaly	1	1	0	0
Other malformations and unspecified	5	3	0	2
Eye, ear, face and neck	***11***	***2***	***0***	***9***
Malformation of eyelid	1	0	0	1
Microphtalmos	1	0	0	1
Cystic eyeball	1	0	0	1
Congenital glaucoma	1	1	0	0
Sinus, fistula or cyst of branchial cleft	6	1	0	5
Unspecified	1	0	0	1
Congenital heart defects (CHD)	***101***	***53***	***3***	***46***
Ventricular septal defect	20	12	0	8
Atrial septal defect	19	11	0	8

Tetralogy of Fallot	4	1	0	3
Atroventricular septal defect	3	2	1	0
Congenital malformation of cardiac septum, unspecified	10	4	0	6
Congenital pulmonary valve stenosis	3	2	1	0
Other malformation of pulmonary valve	2	0	0	2
Ebstein's anomaly	2	0	0	2
Hypoplastic right heart syndrome	1	0	0	1
Congenital stenosis of aortic valve	2	2	0	0
Hypoplastic left heart syndrome	1	0	0	1
Other specified congenital malformation of heart	1	1	0	1
Congenital malformation of heart, unspecified	28	15	1	12
Patent ductus arteriosus as only CHD in term infants (≥ 37 weeks)	2	1	0	1
Coarctation of aorta	1	1	0	0
Persistent left superior vena cava	1	0	0	1
Arteriovenous malformation of precerebral vessels	1	1	0	0
Respiratory	***6***	***3***	***0***	***3***
Other congenital lung malformations	5	3	0	2
Congenital lung malformation, unspecified	1	0	0	1
Orofacial clefts	***15***	***9***	***1***	***5***
Digestive	***28***	***11***	***1***	***16***
Other congenital mouth malformations	3	2	0	1
Atresia of oesophagus without fistula	3	1	0	2
Congenital absence, atresia and stenosis of duodenum	4	1	0	3

Congenital absence, atresia and stenosis of jejunum	3	1	0	2
Congenital absence, atresia and stenosis of small intestine, part unspecified	1	0	0	1
Congenital absence, atresia and stenosis of anus without fistula	4	2	0	2
Hirschsprung's disease	1	0	1	0
Congenital diaphragmatic hernia	4	1	0	3
Congenital malformations of intestinal fixation	1	0	0	1
Congenital malformation of intestine, unspecified	1	0	0	1
Other congenital malformations of liver	2	2	0	0
Other	1	1	0	0
Urinary	***60***	***27***	***0***	***33***
Renal agenesis	5	4	0	1
Cystic kidney disease	12	7	0	5
Renal dysplasia	1	1	0	0
Congenital hydronephrosis	22	8	0	14
Congenital occlusion of ureter	3	3	0	0
Other obstructive defects of renal pelvis and ureter	4	1	0	3
Accessory kidney	2	0	0	2
Ectopic kidney	1	1	0	0
Congenital malformation of kidney, unspecified	7	1	0	6
Exstrophy of urinary bladder	1	0	0	1
Congenital posterior urethral valves	1	1	0	0
Other and unspecified congenital malformations of bladder and urethra	1	0	0	1
Limb and musculoskeletal	***108***	***59***	***9***	***40***

Congenital dislocation of hip, unspecified	13	5	2	6
Other congenital deformities of hip	2	1	0	1
Congenital talipes calcaneovarus	1	0	1	0
Other congenital musculoskeletal deformities	2	1	0	1
Polydactyly, unspecified	70	41	5	24
Syndactyly	8	6	0	2
Reduction defects of upper limb	2	1	1	0
Unspecified reduction defect of lower limb	1	1	0	0
Phocomelia, unspecified limb(s)	1	0	0	1
Other congenital malformations of limb(s)	6	3	0	3
Other congenital malformations of skull and face bones	2	0	0	2
Abdominal wall defects	***2***	***1***	***0***	***1***
Gastroschisis	2	1	0	1
Genital	***31***	***14***	***2***	***15***
Developmental ovarian cyst	1	0	0	1
Other specified congenital malformations of female genitalia and unspecified	2	0	0	2
Hypospadias, unspecified	23	11	2	10
Absence and aplasia of testis	1	1	0	0
Other specified congenital malformations of male genital organs and unspecified	1	1	0	0
Indeterminate sex, unspecified	3	1	0	2
Genetic syndromes and microdeletions	***42***	***24***	***4***	***14***
Chromosomal	***2***	***2***	***0***	***0***

Other malformations	***20***	***5***	***2***	***13***

EFV: efavirenz; T1: 1st trimester

Table 3. Association between the presence of birth defects and first trimester exposure to efavirenz: unadjusted and adjusted analyses

	No birth defect (N=24,551) N (%)	Birth defect (N=412) N (%)	Unadjusted OR[†] (95% CI)	p-value	Adjusted OR[‡] (95% CI)	p-value
Exposure to ART during conception/T1				0.135		0.179
Non-EFV ART	7'354 (97.6)	183 (2.4)	1.00	-	1.00	-
EFV	1'181 (98.4)	19 (1.6)	0.75 (0.47-1.22)	0.250	0.61 (0.36-1.03)	0.067
Not on ART	16'016 (98.7)	210 (1.3)	1.16 (0.94-1.43)	0.175	0.92 (0.69-1.22)	0.566
Maternal age (in years)				0.061		0.163
<25	5'129 (99.0)	54 (1.0)	1.00	-	1.00	-
25-34	14'006 (98.4)	226 (1.6)	1.13 (0.83-1.54)	0.443	1.22 (0.85-1.76)	0.276
35-39	4'201 (97.9)	89 (2.1)	1.22 (0.85-1.74)	0.276	1.21 (0.80-1.76)	0.369
≥40	1'029 (96.8)	34 (3.2)	1.81 (1.15-2.83)	0.010	1.83 (1.07-3.11)	0.026
Lowest CD4 value during pregnancy				0.962		0.809
≥350	11,898 (98.3)	208 (1.7)	1.00	-	1.00	-
200-349	5353 (98.3)	92 (1.7)	1.01 (0.73-1.41)	0.938	1.00 (0.71-1.40)	0.998
<200	2,581 (98.3)	46 (1.8)	0.97 (0.75-1.25)	0.809	0.92 (0.71-1.19)	0.530
HIV RNA >50 copies/mL during pregnancy				0.705		0.970
≤50	7030 (97.8)	156 (2.2)	1.00	-	1.00	-
>50	11,903 (98.2)	222 (1.8)	1.04 (0.84-1.29)	0.705	0.99 (0.75-1.32)	0.970
Maternal ethnicity				0.694		0.852
White	11,088 (98.9)	125 (1.11)	1.00	-	1.00	-
Black	12,172 (98.0)	247 (2.0)	0.92 (0.70-1.21)	0.557	1.01 (0.74-	0.956

					1.37)	
Asian	611 (98.4)	10 (1.61)	0.83 (0.41-1.67)	0.603	0.83 (0.40-1.73)	0.613
Other	239 (97.6)	6 (2.4)	0.63 (0.26-1.49)	0.292	0.69 (0.24-1.98)	0.486
Parity				0.736		0.800
Multiparous	13,768 (98.2)	246 (1.8)	1.00	-	1.00	-
Primiparous	10,645 (98.5)	162 (1.5)	1.04 (0.84-1.27)	0.736	1.03 (0.81-1.31)	0.800

† Mixed-effects logistic regression models with the mother level nested in the cohort level as nested random effects. ǂ Multivariable mixed-effects logistic regression model with the mother level (variance 0.584) nested in the cohort level (variance 0.519) as nested random effects including 18,138 observations from 14,741 mothers, i.e. 3397 known to be repeated pregnancies.

EFV: efavirenz; ART: antiretroviral therapy; T1: 1st trimester; OR: odds ratio