**A systematic review of the teratogenicity of efavirenz**  
(WHO ART Guidelines Meeting Review, October 2009)

**Introduction**

The WHO advocates for non-nucleoside reverse transcriptase inhibitor (NNRTI) based antiretroviral treatment (ART) as first line treatment for HIV-1 infection. Historically, efavirenz (EFV) and nevirapine (NVP) are the main antiretrovirals in this therapeutic class.

Due to wide availability in fixed-dose combinations, cost, and proven efficacy in low and middle income countries (LMIC) 67% of patients in LMIC are on NVP based ART. However, due to toxicity concerns at higher CD4 thresholds, potential high risk of virological failure with tenofovir (TDF) and NVP, drug interactions between NVP and rifampicin, and dosing inconvenience many countries are switching from NVP to EFV. LMIC often procure large amounts of one NNRTI in hopes of scaling up treatment to the maximum number of HIV-infected persons. Women of reproductive age must be considered in this process.

Women diagnosed in the second or third trimester of pregnancy needing ART can likely receive EFV without a malformation concern. However, broader use of EFV in women of reproductive age is concerning. These women may conceive while on EFV-based ART and continue EFV well into the high risk first trimester, before their pregnancy is diagnosed.

The United States Food and Drug Administration (FDA) classified EFV as a Pregnancy Category D medication, based on studies in animals and retrospective case reports which showed that the drug may be associated with neural tube and/or central nervous system abnormalities. Generally, a category D drug should only be used if the potential benefit outweighs potential risk. If women of childbearing potential are to receive EFV as part of ART, they must also receive counselling regarding the potential risk of malformation with EFV in early pregnancy and be provided with effective contraception.

The benefits of ART in pregnant women are clear. It reduces transmission of HIV to the foetus and prevents opportunistic infections in the mother. In high income countries protease inhibitors are often used in the pregnant population. In LMIC, protease inhibitors are seldom available thereby requiring reliance on NVP, EFV, or TDF as a third (in addition to AZT and 3TC) antiretroviral agent in women of reproductive age. This systematic review will compare birth defects in pregnant women exposed to EFV, NVP, lopinavir/ritonavir (LPV/r), or TDF using the Antiretroviral Pregnancy Registry (APR), and review the literature on pregnancy outcomes with EFV.

**Methods**

The PubMed and EMBASE databases were searched for evidence of birth defects of EFV using the following strategies:

'drug toxicity'/exp OR 'adverse drug reaction'/exp OR 'drug safety'/exp OR 'drug tolerability'/exp AND efavirenz:ti

213 results, search conducted on 3/July/2009 (Embase).

efavirenz AND pregnant OR efavirenz AND pregnancy

57 results, search conducted on 24/9/09 (PubMed).

Nine studies from these two databases included pregnancy outcome data for EFV, and were included.
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(UNICEF SP Philippines Technical Paper, October 2009)

Results

EFV Animal Studies

Malformations were observed in three of 20 fetus/infants from EFV treated cynomolgus
monkeys (vs. 0 of 20 unexposed monkeys) in a developmental toxicity study. Anencephaly
and unilateral anophthalmia were observed in one fetus, microphthalmia was observed in
another fetus, and cleft palate was observed in a third fetus. The monkeys were dosed to
achieve concentrations similar to those in humans on EFV 600 mg daily. EFV crosses the
placenta in monkeys, and fetus plasma concentrations are similar to those in the mother.

An increase in fetal resorptions was seen in EFV exposed pregnant rats, when peak plasma
concentrations and AUC values were similar to those achieved in humans on EFV 600 mg
daily. No reproductive toxicities were seen in pregnant rabbits at doses that produced peak
plasma concentrations similar to, and AUC values approximately half of, those achieved in
humans given 600 mg daily. It is worth noting that of the 1200 known animal teratogens only
30 are teratogenic to humans

EFV Retrospective studies

A study in Botswana evaluated the impact of EFV on pregnancy outcomes in 451 female
participants. First trimester EFV exposure occurred in 38 of the 71 pregnancies; 22 of these
38 pregnancies resulted in live births (57.9%) while 16 resulted in abortions (42.1%). The
median time of EFV exposure was 43 days (IQR: 31-60 days), all women were switched to
non-EFV containing ART the same day that pregnancy was diagnosed. Among the 17
liveborn infants who were not exposed to EFV based ART, two minor congenital
abnormalities were detected (one infant with polydactyly and one infant with an umbilical
hernia) while there were two stillbirths. Of the 22 EFV exposed live births one infant had a
major congenital abnormality (bone dysplasia) while there were two premature births. There
was no difference in median birth weight, gender, occurrence of early pregnancy loss, and
stillbirths between mothers who were or were not on EFV containing ART.

In a study from Thailand, 38 of 606 females were switched from NVP to EFV containing
regimen due to NVP toxicity after the first trimester. The mean time of exposure was 7 ±
4.9 weeks. Four infants (10.5%) were born pre-term (<37 weeks gestation) and six (15.8%)
had low birth weight (<2.5 kg). All infants exposed to EFV were reported healthy at birth and
no congenital anomaly was observed. These rates were not higher than the rates observed in
the NVP based regimen group (18.5% pre-term birth, p=0.295 and 16.0% low birth weight
p=0.639).

A retrospective analysis in France evaluated the impact of EFV exposure (average eight
weeks, range 2-20 weeks) in 12 pregnant women. Two women had miscarriages and three
women had abortions, prior to knowledge of pregnancy outcome. Seven infants were born,
and there were three abnormalities. One born infant had two benign angiomas in the right
arm, the second developed severe hyptrophy due to placental infarction and was medically
aborted, while the third infant developed multiple deformities in the pulmonary bicuspid
valve, had accelerated maturation of the skeleton, and anomalies in the pulmonary circulation
and was also medically aborted. There were no reports of neural tube defects.

In a retrospective study, data from seven women who received EFV during pregnancy with
term delivery were examined. Of seven infants who were born alive, five were exposed to
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EFV from conception and two were exposed from 12 and 14 weeks after amenorrhea. Therapy with EFV was continued in five cases and discontinued in two cases at two and four weeks gestation. The mean birth-weight for all seven newborns was 3.224 kg (2.7-4.17 kg) and Apgar score of 9-10. Clinical examination of all infants (7/7 cases) at birth and after a mean follow-up of 20.6 months (6/6 cases) was normal.

A retrospective analysis in South Africa evaluated the impact of EFV exposure in 37 women. 15% of the women chose to have an early termination of pregnancy. There were no reports of morphological abnormalities, neural tube defects, or overt developmental delay. Another retrospective analysis in South Africa evaluated the impact of EFV exposure in 83 women. The mean exposure was 97.05 days (range 12-343). There were three miscarriages, one stillbirth, and 28 elective terminations.

The European Collaborative Study reported no congenital abnormalities (0%, 95% CI 0-17.6%) in 19 mothers who were on EFV based ART for a median of 40 days into their pregnancy (range 24-106 days). The antiretroviral registry has received retrospective reports of three meningomyelocele (neural tube) defects and two Dandy Walker defects. All cases occurred in mothers who were on EFV-based ART during their first trimester.

Antiretroviral Pregnancy Registry (June 2009 Interim Report, containing reports submitted until 31 January 2009)
The APR is designed to detect an early signal of teratogenicity in pregnant women exposed to antiretrovirals. Birth defects are defined as “any major structural or chromosomal defect diagnosed by six years of age, or any cluster of two or more conditional abnormalities.” Prospective reports mean that the healthcare provider submitted information about the pregnant patient and the antiretroviral exposure(s) prior to the pregnancy outcome and submitted follow up information after the pregnancy outcome. Overall, the prevalence of birth defects in women exposed to any antiretroviral during the first trimester of pregnancy is 2.9/100 live births (95% CI 2.4-3.4), while women exposed during the second or third trimester had a birth defect prevalence of 2.5/100 live births (95% CI 2.1-2.9). Sufficient data exists to determine a two-fold increased risk of overall birth defects for 14 antiretrovirals in the APR including abacavir, tenofovir, lopinavir, efavirenz, and nevirapine. For zidovudine and lamivudine sufficient data exists to detect a 1.5-fold increased risk of overall birth defects and a two-fold increase in birth defects in the cardiovascular or genitourinary systems.

The most recent antiretroviral pregnancy registry received prospective reports on 518 pregnancies exposed to EFV-containing regimens, a majority of which were first-trimester exposures. Birth defects occurred in 14 of 477 live births who were exposed during the first trimester (2.94%) and two of 41 live births exposed during the second or third trimester (4.89%). Defects reported in fourteen infants with first trimester exposure to EFV were: 1) polydactyly, 2) hydronephrosis, 3) bilateral hip dislocation and umbilical hernia, 4) bilateral hip dislocation, 5) urinary obstruction, duplicated right collecting system with obstructed upper pole moiety, possibly associated with vesicoureteral reflux, 6) polydactyly, and 7) long bones malformation, 8) postaxial polydactyly both hands, 9) shortening of right leg, 10) cutis aplasia (scalp), 11) hip dysplasia and pulmonary stenosis, 12) unspecified heart anomaly, 13) sacral myelomeningocele and hydrocephalus with fetal alcohol syndrome, and 14) bilateral facial cleft, anophthalmia, and amniotic band.
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<table>
<thead>
<tr>
<th>Exposure</th>
<th>1st trimester malformation rate (95% CI)</th>
<th># of malformations/# exposed</th>
<th>2nd/3rd trimester malformation rate (95% CI)</th>
<th># of malformations/# exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>2.94% (1.6-4.9%)</td>
<td>14/477</td>
<td>4.88% (0.6-16.5%)</td>
<td>2/41</td>
</tr>
<tr>
<td>NVP</td>
<td>2.20% (1.3-3.5%)</td>
<td>18/817</td>
<td>2.33% (1.5-3.4%)</td>
<td>27/1157</td>
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<tr>
<td>LPVr</td>
<td>1.70% (0.7-3.3%)</td>
<td>8/470</td>
<td>2.22% (1.4-3.3%)</td>
<td>25/1126</td>
</tr>
<tr>
<td>ABC</td>
<td>2.96% (1.8-4.6%)</td>
<td>18/608</td>
<td>2.83% (1.8-4.2%)</td>
<td>25/882</td>
</tr>
<tr>
<td>TDF</td>
<td>2.36% (1.4-3.8%)</td>
<td>16/678</td>
<td>1.56% (0.6-3.4%)</td>
<td>6/385</td>
</tr>
<tr>
<td>AZT</td>
<td>3.06% (2.5-3.7%)</td>
<td>95/3108</td>
<td>2.56% (2.2-3.0%)</td>
<td>162/6336</td>
</tr>
<tr>
<td>3TC</td>
<td>2.88% (2.3-3.5%)</td>
<td>93/3226</td>
<td>2.52% (2.1-3.0%)</td>
<td>122/4846</td>
</tr>
<tr>
<td>CDC MACDP</td>
<td>2.87%</td>
<td>130/4530</td>
<td>2.50%</td>
<td>147/5874</td>
</tr>
</tbody>
</table>

The table above compares overall rates of birth defects after exposure to antiretrovirals to the CDC’s Metropolitan Atlanta Congenital Defects Program, which actively searches for birth defects in all births in five metropolitan counties in the state of Georgia, United States. Annually 50,000 infants are born in this population of approximately 2.9 million. The published data included births from 1968-2003. The data included on antiretrovirals are from prospective reports from the APR. This includes reports submitted until 31 January 2009.

Discussion
The overall rate of birth defects with EFV exposure doesn’t appear to be significantly greater than that with exposure to NVP, LPV/r, TDF, or to that of the population in Atlanta, USA. It has been emphasized that more reports are needed to quantify the risk of rare birth defects. In 2006 the incidence of anecephaly was 11.6 / 100,000 births and meningomyelocele/spina bifida was 17.8 / 100,000 births in the USA. Given the baseline prevalence of these neural tube defects is low, in order to quantify an increased risk many more EFV exposures are needed. One of the best ways to achieve this is by increased reporting to the APR.

The only prospective neural tube defect case in the APR was reported after first trimester exposure with EFV. This defect was meningomyelocele. However, assuming there is an increased risk of neural tube defects with first trimester exposure, because it is a rare event, the overall birth defect rate would remain similar to CDC MACDP data and the risk of the rare neural tube defects would remain low. For example, if there was a five-fold increase in the spina bifida rate due to EFV exposure, that would increase incidence of this rare defect to neural tube defects to 89/100,000 births.

An issue with reporting first trimester cases together is that it may skew the rates for defects with a shorter window of risk. For example, closure of the neural tube is complete by 25 days after conception, or about six menstrual weeks of gestation. Thus, women with exposure in the late first trimester only would not provide informative data as to risk of neural tube defect
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since exposure did not occur in the key period. However, they would be included in cases with first trimester exposure, artificially inflating the denominator.

Several studies suggested that EFV is more durable than NVP, that EFV is less likely than NVP to lead to virological failure with rifampicin, that there are concerning toxicities with NVP and that there may be a high risk of virological failure with NVP and TDF. For these reasons EFV is becoming a more attractive first line NNRTI than NVP in LMIC. Protease inhibitors, triple nucleoside therapy, or continued use of NVP appear to be the main alternatives. Given these data, and the importance of ART in mothers and the foetus, continued surveillance of the risks of first trimester EFV and other ARV exposure are crucial. In the meantime, the benefits of EFV use must be weighed against the potential risks.