Birth Defects and Antiretroviral Therapy

in the ANRS-EPF French Perinatal Cohort, among 13,000 live births from 1994 to 2010

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Context

- Mother To Child Transmission rates < 1% in industrialized countries in cART era

- **Current issues:**
  - Access to PMTCT program
  - Side-effects of ART in pregnancy

    → Birth defects ?

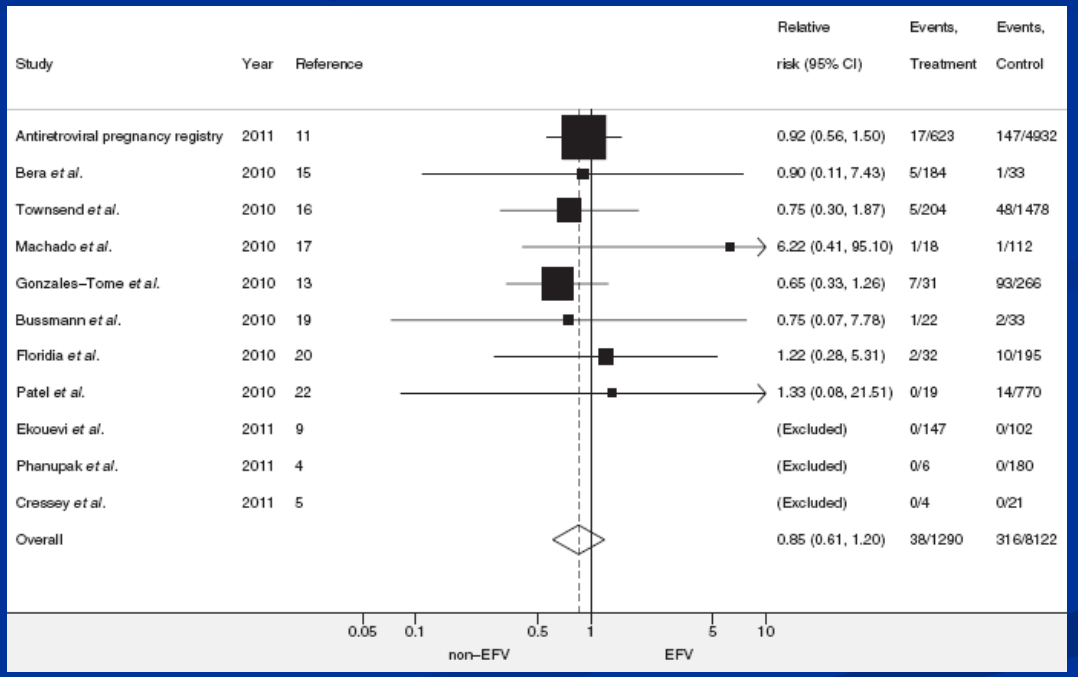
Efavirenz and neurological birth defects?

- **1998: high rates of neural tube defects in monkeys**

  (Cadman, J. GMHC Treat Issues, 1998)

- **2011: no association in meta-analysis**

  (Ford, N., et al. AIDS, 2011)



- **Overall birth defect associated to first trimester exposure**
  - **2010: AOR = 4.31** ; 95% CI [1.56 - 11.86] (Brogly SB, et al. Pediatr Infect Dis J, 2010)
  - **2012: AOR = 2.84** ; 95% CI [1.13 - 7.16] (Knapp KM, et al. Pediatr Infect Dis J, 2012)

Birth defects and other antiretroviral drugs ?

- **Higher prevalence of overall birth defects for didanosine and nelfinavir**
  - **From the Antiretroviral Pregnancy Registry**: N=14,700 infants (Antiretroviral Pregnancy Registry International Interim Report 2012)

- **Congenital heart defects associated with in utero ART**
  - **Zidovudine and CHD** (Brogly, S.B., et al. Pediatr Infect Dis J, 2010)
  - **Any ART and septal defects** (Watts, D.H., et al. J Perinat Med, 2011)

Objective

- No clear evidence of association between ART and birth defects

- Recent change of international recommandations: no interruption of EFV in pregnancy

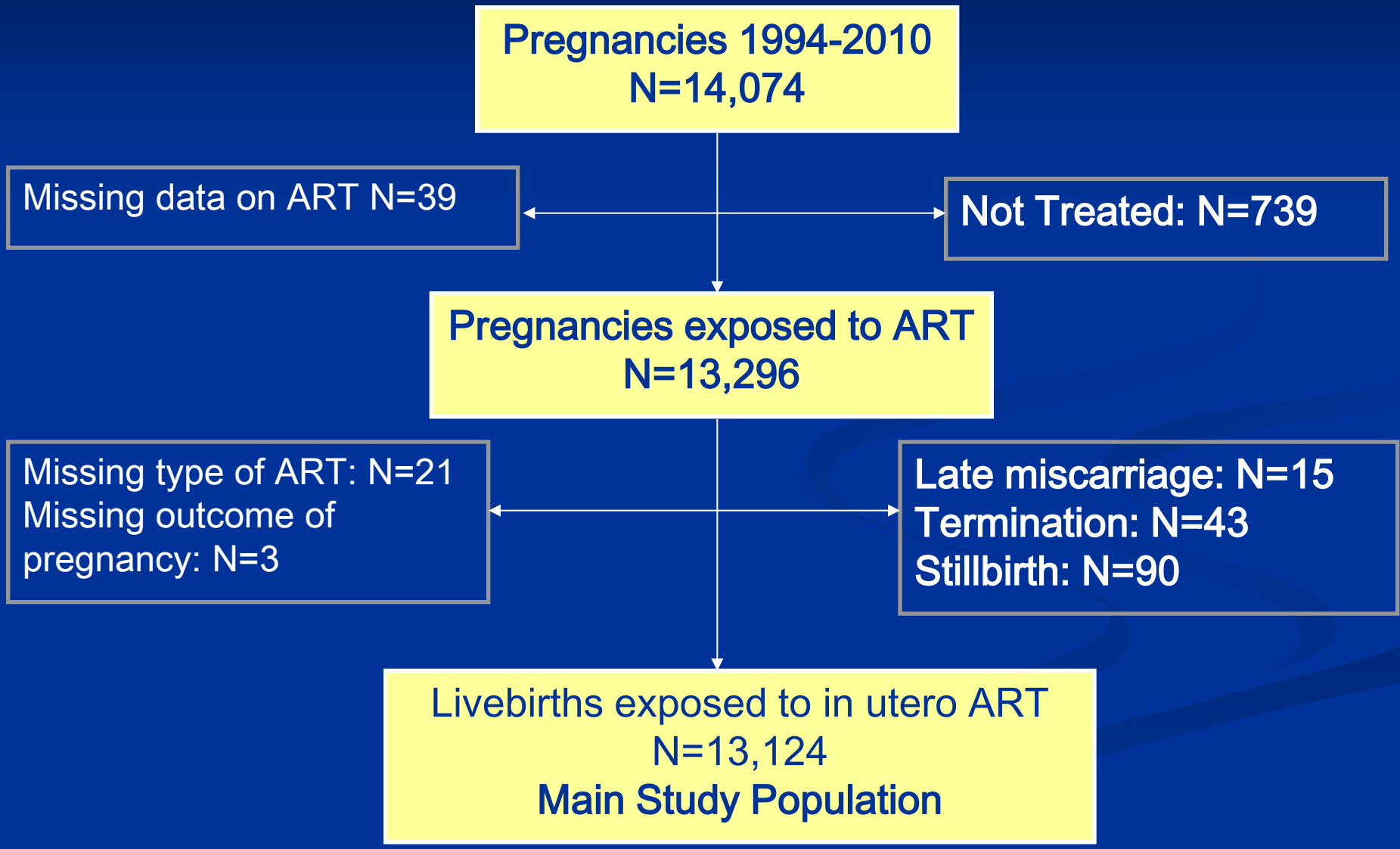
(AIDS Info, Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women, 2012)

→ Systematic analysis of each type of birth defect for each drug in the ANRS-EPF

The ANRS-EPF French Perinatal Cohort

- **National prospective multicentric cohort since 1985**
  - **Objective:** evaluation of PMTCT strategies
  - **Inclusion:** all **HIV-infected pregnant women** delivering in the 90 participating centers **(N=17,000)**
  - **Follow-up:**
    - **Non-infected children → 2 years of age**
    - **Infected children → 18 yrs**
- Coverage: about 70% of HIV-infected women in France

Study Population



Univariable and multivariable logistic regressions

- **Outcome: birth defects (BD)**
  - **Overall and by organ system**
  - Coded with International classification of diseases (ICD 10)
  - Using two types of BD classification
    - EUROCAT (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf)
    - MACDP(http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf)
- **Exposure: each ART drug during pregnancy**
  - **According to trimester of exposure**
- **Adjustment for potential confounders**

Efavirenz
(N=372 exposed in the first trimester)

	Overall Birth Defects		
Efavirenz	**AOR**	**95% CI**	**p**
Unexposed	1		
1st trimester	1.3	(0.9-1.9)	0.31
2nd-3rd trimester	1.2	(0.1-8.3)	

* Using MACDP classification

- Not associated with overall birth defects

Efavirenz
(N=372 exposed in the first trimester)

	Overall Birth Defects			Neurological Defects		
Efavirenz	**AOR**	**95% CI**	**p**	**AOR**	**95% CI**	**p**
Unexposed	1			1		
1st trimester	1.3	(0.9-1.9)	0.31	3.2	(1.1-9.1)	0.03
2nd-3rd trimester	1.2	(0.1-8.3)		NA		

* Using MACDP classification

- Not associated with overall birth defects
- But associated with neurological birth defects
  - N=4 (pachygyria, agenesis of CC, hydrocephaly, cerebral cyst)

Zidovudine

(N=3,267 exposed in the first trimester)

	Overall Birth Defects		
Zidovudine	**AOR**	**95% CI**	**p**
Unexposed	1		
1st trimester	1.4	(1.1-1.8)	0.002
2nd-3rd trimester	1.1	(0.9-1.4)	

- Association to overall birth defects

Zidovudine

(N=3,267 exposed in the first trimester)

	Overall Birth Defects			Congenital Heart Defects		
Zidovudine	**AOR**	**95% CI**	**p**	**AOR**	**95% CI**	**p**
Unexposed	1			1		
1st trimester	1.4	(1.1-1.8)	0.002	2.5	(1.6-4.2)	0.001
2nd-3rd trimester	1.1	(0.9-1.4)		1.6	(0.9-2.6)	

- Association to overall birth defects
- Association specific to heart defects
  - Both EUROCAT and MACDP, sensitivity analyses
  - Mostly Ventricular Septal Defects

Birth defects associated with other ART (1st trimester)

- **Didanosine (N=927 exposed):**
  - Head and neck defects: **AOR = 1.93 (1.11-3.34), p< 0.05**
- **Lamivudine (N=3,772 exposed):**
  - Musculoskeletal defects: **AOR=1.40 (1.05-1.87), p= 0.04**
  - Head and neck defects: **AOR=1.96 (1.20-3.21), p = 0.03**
- **Indinavir (N=350 exposed):**
  - Overall birth defects: **AOR = 1.52 (1.07-2.17), p=0.04**
  - But no specific defect
- **Nelfinavir (N=625 exposed): no association found**

Discussion (1)

- **Strengths**
  - **Largest prospective cohort** with homogeneous selection criteria, power > 80% for most molecules for OR=1.5
  - Thorough and **standardized follow-up** with active clinician participation
  - Sytematic analysis for all drugs
  - **Sensitivity analyses**, two classifications used, inclusion of TOP and SB, adjustment for several confounders

- **Limitations (also observed in most studies)**
  - Livebirths only
  - Intercurrent drugs used

Discussion (2)

- **Efavirenz associated with neurological birth defects (AOR= 3.2)**
  - Partly consistent with several studies (NTD reported in animal study and overall birth defects in 2 recent studies)
  - But no NTD observed in our study → unclear mechanism

- **Zidovudine associated with congenital heart defects (AOR= 2.5)**
  - **Robust association**, persisting in sensitivity analyses
  - Already described in one study (Brogly, S.B., et al. Pediatr Infect Dis J, 2010)
  - **Physiopathological mechanisms** yet to be elucidated

    → Mitochondrial toxicity ?

Conclusion

- **Recommandation to avoid efavirenz during pregnancy should be maintained in countries with access to other drug options**
  - → Need for epidemiological surveillance in countries where EFV is largely prescribed
- **Issue raised by the association between first trimester exposure to zidovudine and higher risk of congenital heart disease**
  - → Further detailed investigation to clarify mechanism
  - → Need for research on NRTI sparing ART for PMTCT

However, the potential risk of birth defects has to be balanced with the major success of current PMTCT strategies

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