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# Risk of cancer in children exposed to didanosine *in utero*

# *The ANRS French Perinatal Cohort*


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## ABSTRACT


**Background:** Antiretroviral treatment during pregnancy has been effective in reducing perinatal HIV transmission. Some nucleos(t)ide reverse transcriptase inhibitors (NRTIs) display genotoxicity *in vitro* so we evaluated the incidence of cancer among children exposed to NRTIs *in utero* between 1990 and 2014 in the ANRS French Perinatal Cohort (EPF).

**Methods:** We updated the evaluation of cancer incidence among children exposed to NRTIs in the cohort by cross checking with the French national cancer registry. Associations between cancer risk and exposure to the various NRTIs were evaluated by univariate survival analysis and Cox proportional hazard models. Standardized incidence ratios (SIR) were used to compare risks with those for the general population.

**Results:** Twenty-one cancers were identified in 15163 children (median age: 9.9 years [interquartile range (IQR): 5.8-14.2]) exposed to at least one NRTI in utero between 1990 and 2014. Five children were exposed to zidovudine monotherapy, and 16 to various combinations, seven including didanosine. Didanosine was included in only 10% of the prescriptions but was associated with one third of the cancers. Compared with the 2281 children exposed to zidovudine monotherapy, the risk of cancer was higher in the 1461 children exposed to combinations including didanosine (adjusted HR = 3.0 [0.9-9.8]), but similar for all other NRTI combinations. The risk was specifically higher in children exposed during the first trimester, than never exposed, to didanosine (HR=5.5 [2.1-14.4]); it was not significantly associated with second or third trimester exposure to didanosine (HR=1.6 [0.2-12.2]). Overall, the total number of cases was not significantly different from that expected for the general population (SIR = 0.8 [0.47-1.24]), but among those exposed to didanosine it was twice that expected (SIR = 2.5 [1.01-5.19]). Three cases of pineoblastoma, a very rare cancer, were observed, whereas 0.03 were expected; two of these cases were associated with didanosine exposure.

**Conclusions:** There are strong arguments to suggest that didanosine displays transplacental oncogenicity. Although these findings cannot be extrapolated to other NRTIs, they stress the need for comprehensive evaluation of the transplacental genotoxicity of this class of antiretrovirals.


## OBJECTIVE

Some nucleos(t)ide reverse transcriptase inhibitors (NRTIs) display genotoxicity *in vitro*. A previous work showed an association between *in utero* exposure to ddI-3TC and pediatric cancer (Benhammou et al. AIDS 2008).

**We aimed to reevaluate the incidence of cancer among children exposed *in utero* to NRTIs between 1990 and 2014 in the ANRS French Perinatal Cohort (EPF).**

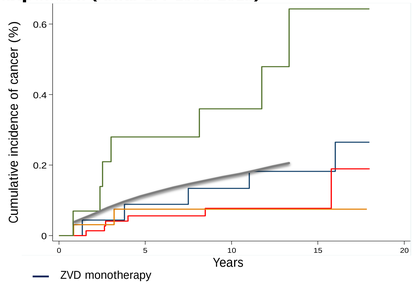
## PATIENTS AND METHODS

- **Two sources of data**
  - ***The EPF cohort (ANRS- CO1/CO11 French Perinatal Cohort):*** has been included HIV infected pregnant women and their children since 1986 in 90 maternities in France
  - ***The French national childhood cancer registries:*** exhaustive notification of hematopoietic malignancies and solid tumors in children <15 years in mainland France
- **Eligible children *(N=15163)***
  - **born alive to HIV-infected women** included in **mainland sites of EPF** (i.e. not including overseas regions), **between 1990 and 2014**
  - **not diagnosed as HIV-infected**
  - **exposed** to at least one **NRTI *in utero***
- **Cancer detection**
  - → **Standardized EPF questionnaires** until the age of 24 months
  - → **Spontaneous notifications** to the coordinating center after 2 years of age
  - → **Probabilistic cross-checking of EPF and childhood cancer registries** based on date of birth, sex, and place of birth, then concordant entries checked on clinical sites
- **Statistical analysis**
  - → Identification of cancer incidence among children exposed to the general population: **standardized incidence ratio (SIR)**
  - → Risk factors of cancer identified among EPF data: univariate and multivariate **survival analyses** (Cox model)

### Table 1 – Description of cancers (ANRS-EPF 1990-2015)

| | N |
|---|---|
| **Hematologic tumors** | |
| Acute lymphoblastic leukemia | 6 |
| Lymphoma | 4 |
| **Central nervous system tumors** | |
| Glioma | 4 |
| Pineoblastoma | 3 |
| **Retinoblastoma** | 3 |
| **Rhabdomyosarcoma** | 1 |
| **Total** | **21** |

### Figure 1 – Cumulative probability of cancer incidence according to the type of NRTI exposure (ANRS-EPF 1990-2015)




O/E: Observed/expected number of cases; NRTIs: nucleos(t)ide reverse transcriptase inhibitors; AHR: adjusted hazard ratio, adjusted on term at delivery, per partum zidovudine infusion and postnatal NRTI in the child; GW: gestational week; ZVD: zidovudine; 3TC: lamivudine; ddI: didanosine; d4T: stavudine; ddC: zalcitabine; ABC: abacavir; TDF: tenofovir; FTC: emtricitabine

### Table 2 – Comparison with general 0-14 years population (ANRS-EPF 1990-2015)

| | O/E | N | PY | SIR |
|---|---|---|---|---|
| **All NRTIs** | 19/24.2 | 15163 | 147502 | **0.8 (0.5-1.2)** |
| **Didanosine** | 7/2.8 | 1461 | 17526 | **2.5 (1.0-5.2)** |

### Table 3 – Factors associated with risk of cancer in children exposed *in utero* to NRTIs (ANRS-EPF 1990-2015)

| | | | Multivariate analysis | |
|---|---|---|---|---|
| | N | n | AHR | P |
| **Term at delivery (GW)** | | | | |
| <33 | 488 | 3 | 5.3 (1.5-18.8) | |
| 33-36 | 1616 | 4 | 2.2 (0.7-6.6) | |
| >36 | 12994 | 14 | 1 | 0.02 |
| **NRTI administered during pregnancy** | | | | |
| **ddI ± other NRTI** | 1461 | 7 | **3.0 (0.9-9.8)** | |
| d4T or ddC ± other NRTI except ddI | 649 | 1 | 0.8 (0.1-7.0) | |
| ABC or TDF / FTC or 3TC | 3239 | 2 | 0.7 (0.1-4.0) | |
| ZVD + any other NRTI except ddI, d4T, and ddC | 7533 | 6 | 0.6 (0.2-2.2) | |
| ZVD monotherapy | 2281 | 5 | 1 | 0.06 |

### Table 4 – Association between exposure to didanosine in the first trimester and cancer (ANRS-EPF 1990-2015)

| Didanosine | N | n | Crude HR | P |
|---|---|---|---|---|
| **1st trimester** | 948 | 6 | **5.5 (2.1-14.4)** | |
| **2nd–3rd trimester** | 511 | 1 | 1.6 (0.2-12.2) | |
| **No** | 13702 | 14 | 1 | 0.0005 |

## RESULTS

- **Description of cancers identified in children exposed *in utero* to NRTI**

  In total, **21 cases of cancer** identified by 31 May 2015 among 15163 HIV-uninfected children born alive in the EPF cohort between 1990 and 2014 (Table 1).

- **Comparison with general pediatric population**

  Compared to the general 0-14 years population, the incidence rate of cancer was (Table 2):
  - not significantly different in children exposed *in utero* to NRTIs overall: **SIR = 0.8 (0.5-1.2)**
  - significantly higher in children exposed *in utero* to ddI: **SIR = 2.5 (1.0-5.2)**
  - **3 cases of pineoblastoma (0.03 expected)**

- **Factors associated with the risk of cancer in children exposed *in utero* to NRTIs in EPF**
  - Strong and specific association with exposure to combinations including **didanosine**, compared to zidovudine monotherapy : **AHR=3.0 (0.9-9.8)** (Figure 1, Table 3), especially for exposure to ddI **during the first trimester** of pregnancy (Table 4).

## CONCLUSION

- **There are strong arguments to suggest that didanosine displays transplacental oncogenicity.**
- **Although these findings cannot be extrapolated to other NRTIs, they stress the need for comprehensive evaluation of the transplacental genotoxicity of this class of antiretrovirals.**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