Original Article

Developmental delay and behavioral disorders in 59 HIV-exposed uninfected infants

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Background: Antiretroviral therapy (ART) in HIV pregnant women has led to a dramatic decrease in the rate of HIV mother-to-child transmission but this benefit is counterbalanced with adverse effects related to in utero and neonatal exposure to ART. In 2013, some parents described neurodevelopmental disorders in their children.

Methods: A standardized letter was sent to the 133 women who delivered in Nantes hospital from 01/01/2003 to 31/12/2012 (167 births).

Results: Response rate was 33%. Over a 10-year period, 7 children had behavioral disorders and/or cognitive/developmental delay, 1 child had developmental delay + growth retardation and 2 experienced cancer.

Conclusions: We found a significant association between neurodevelopmental disorders, preterm birth and exposure to 3 nucleoside reverse transcriptase inhibitors (NRTIs). Further studies are needed and long-term follow-up into adulthood should continue.

Keywords: Behavioral disorders; developmental delay; HIV-exposed uninfected infants (HEU)

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Introduction

Antiretroviral therapy (ART) in HIV pregnant women has led to a dramatic decrease in the rate of HIV mother-to-child transmission, with almost no transmission when viral load is suppressed at delivery and mothers do not breastfeed (1). However, this benefit is counterbalanced with possible adverse drug effects related to in utero and neonatal exposure to antiretroviral (ARV) drugs: premature delivery, birth defects, short-term reversible biological abnormalities (anemia, neutropenia, hyperlactatemia) or persistent clinical and biological abnormalities (mitochondrial toxicity) (2-4). In high-income countries, guidelines recommend treating pregnant women with triple-combination ART and to increase the number of HIV infected women receiving therapy before conception; so fetuses are more and more exposed to ARV during gestation. Data about ART exposure are discordant: studies in Pediatric HIV/AIDS Cohort Study (PHACS) found an association with in utero atazanavir (ATV) exposure (a preferred ARV for HIV pregnant women) and late language emergence (5-7); other studies found no evidence of developmental delay in HIV-exposed uninfected infants (HEU) (8).

Methods

In the outpatient department of Infectious Diseases, we have a dedicated team (infectiologist and pediatrician) who follows all the pregnant HIV infected women and their HEU infants, until the age of 24 months. According to

Table 1 In utero and per partum antiretroviral exposure in 59 HIV-exposed-uninfected children

In utero and per partum antiretroviral exposure	N (%)
In utero exposure	
2 NRTIs + PI/r	37 (63.0)
ZDV/3TC	23 (62.2)
ABC/3TC	12 (32.4)
TDF/FTC	2 (5.4)
2 NRTIs + NNRTI	
NVP	15 (25.4)
ZDV/3TC	5 (33.0)
ABC/3TC	9 (60.0)
TDF/FTC	1 (7.0)
EFV	
TDF/FTC	1 (1.7)
3 NRTIs	
ZDV/3TC/ABC	1 (1.7)
3 NRTIs + PI/r	3 (5.0)
ZDV/3TC/ABC	1 (33.3)
ZDV/3TC + ddI	2 (66.7)
NVP + PI/r	1 (1.7)
ZDV	1 (1.7)
Per partum ZDV exposure	48 (81.0)

NRTIs, nucleoside reverse transcriptase inhibitors; PI/r, boosted protease inhibitor; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir; TDF, tenofovir; FTC, emtricitabine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; EFV, efavirenz; ddI, didanosine.

French national guidelines, there is no more follow-up after this period.

Some parents spontaneously notified behavioral problems with their children and in October 2013, we decided to send a standardized letter to all the mothers who delivered over a 10-year period (from 01/01/2003 to 31/12/2012) in our hospital.

This letter included four questions: does your child present with growth retardation? Does your child present cognitive/delayed development (academic difficulties)? Does your child have behavioral problems (difficulties in relationships with other children or adults)? Does your child present cancer or other symptoms?

Data concerning mothers and children were extracted from electronic medical records: ARV exposure, gestational age, mode of delivery, demographic factors.

Lactate (LA) measurements were performed at regular intervals (1, 3, 6, 12 and 24 months) in routine follow-up and hyperlactatemia was defined by two determinations >2.5 mmol/L. Mothers/children characteristics were compared using chi-square tests.

Results

During this 10-year period, the number of pregnancies has gradually increased from 10 in 2003 to 30 in 2012 and 133 women delivered 167 infants (four sets of twins). No child was breastfed; all were followed until the age of 2 years.

We received 54 letters concerning 55 children, a 33% response rate. For four additional children, abnormalities were orally reported from parents to the pediatrician or the infectiologist and added to the database.

ART during pregnancy (*Table 1*) was generally consistent with French guidelines: 2 nucleoside reverse transcriptase inhibitors (NRTIs) + boosted protease inhibitor (PI/r) in 63% of patients and 2 NRTIs + nevirapine (NVP) for 25%. Among this cohort of 59 children [median age (IQR): 5 years (22 months–11 years 7 months)], 56% had had in utero zidovudine (ZDV) exposure and 39% abacavir (ABC) exposure; rate of tenofovir (TDF) exposure was low (only 7% of the cohort). In utero exposure to 3 or more NRTIs was reported in four children (6.8%), associated with boosted PI in three [because of high viral load (5.5 $\log_{10}$ c/mL) in two patients and high rate of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) resistance mutations in the third patient]. Most of children (81%) had had per partum ZDV exposure. The rate of premature birth was 6.8%. Seventeen (29%) lived in a monoparental family and 59% had one or two parents from sub-Saharan Africa. Significant hyperlactatemia was measured in 26 patients.

Abnormalities (defined as positive parental response to one or more item of the questionnaire) were notified in ten children (*Table 2*): three children had behavioral disorders; four had cognitive/developmental delay together with behavioral disorders; one had cognitive/developmental delay associated with height and weight growth retardation. Two children had had neoplasia (medullar pilocytic astrocytoma at the age of 3 years and myofibroblastic proliferation at the age of 3 months).

Table 2 Behavioral disorders, cognitive/developmental delay, weight and growth retardation and cancers in 10 HIV-exposed-uninfected children

Clinical abnormalities	Total behavioral disorders	Behavioral disorders	Behavioral disorders + developmental delay	Total cognitive/ developmental delay	Cognitive/ developmental delay	Cognitive/developmental delay + delay in weight gain and growth	Cancer
N	7	3	4	5	4	1	2
In utero ZDV exposure	7/7	3/3	4/4	5/5	4/4	1/1	0/2
Per-partum ZDV	7/7	3/3	4/4	4/5, MD =1	4/4	MD	2/2
Post-partum ZDV	2/7	3/3	4/4	5/5	4/4	1/1	2/2
Premature birth, (gestational age <37 weeks gestation)	2/4 [29, 35]	0/3	2/4 [29, 35]	3/5 [29, 31, 35]	2/4 [29, 35]	1/1 [31]	0/2

ZDV, zidovudine; MD, missing data.

Table 3 Comparison between children with no abnormalities reported by parents to those with (behavioral disorders, cognitive/developmental delay, weight and growth retardation or cancers)

Clinical abnormalities	Behavioral disorders, cognitive/developmental delay, delay in weight gain and growth or cancers		
	Yes	No	P
N	10	49	–
In utero ZDV exposure	8	25	0.16
In utero 3 NRTIs exposure	3	1	0.01
Per-partum ZDV	9/9	40/49	0.99
Hyperlactatemia	3	23	0.49
One parent family	4	13	0.45
Parents from sub-Saharan Africa	4	31	0.29
Premature birth, (gestational age <37 weeks gestation)	3	1	0.01

ZDV, zidovudine; NRTIs, nucleoside reverse transcriptase inhibitors.

Among these ten children, eight had had in utero ZDV exposure and nine per partum ZDV exposure. Three children had been exposed to 3 NRTIs [ZDV + lamivudine (3TC) + didanosine (ddI), n=2; ZDV + 3TC + ABC, n=1]. Four children lived in a one-parent family and four had one or two parents from sub-Saharan Africa.

We compared the children with no abnormalities reported by parents to those with (*Table 3*): in this cohort of 59 children, with 5.8 years average follow-up (range, 1.8–11.7 years), we didn't find a significant association between cancer, cognitive/developmental delay and/or behavioral disorders (n=10) and in utero (P=0.16) or per partum ZDV exposure (P=0.99); however, exposure to 3 NRTIs was significantly more frequent in infants with clinical abnormality (P=0.01). Median LA levels or significant episode of hyperlactatemia (P=0.49) were not different between the two groups.

To live in a one-parent family or to have parents from sub-Saharan Africa was not associated with symptoms. Clinical abnormality(ies) in infants was significantly associated with preterm birth (P=0.01).

Discussion

The significant findings of our study were (I) the lack of association between clinical abnormalities and prenatal or postnatal exposure to ZDV; (II) the higher frequency of prenatal exposure to 3 NRTIs in the group with

clinical abnormalities; (III) the lack of correlation with hyperlactatemia in the group with abnormalities.

Some studies report a higher rate of preterm delivery in HIV + women (9) but the rate of premature birth in our study was 6.8%, in a similar range as that reported for European countries (10). Not surprisingly we found an association between preterm birth and clinical abnormalities: severe prematurity increases the risk of cerebral events, such as hypoxic brain injury and cerebral hemorrhage, which will affect future neuro-developmental potential.

All NRTIs have affinity with human DNA, a genotoxic potential. The inhibitory effect of ZDV on both HIV reverse transcriptase and DNA polymerase γ, an essential protein for mitochondrial DNA replication, is well known (2,3); the impact of the other NRTIs and other classes of ARV is less clear. Mitochondrial dysfunction due to ARV exposure before, during, or after birth is a broader toxicity that could have a continuing influence on childhood development; so, it is not surprising to find in our study a significant association between antenatal exposure to multiple NRTIs and developmental delay and/or behavioral disorders; however PACTG 219/219C found no overall association between ARV exposure in utero and neurologic development at 2 years of age in 1,037 HEU (9). Data from follow-up of PACTG 076 infants through age 6 years did not indicate any differences in growth parameters between infants who were exposed to the ZDV regimen and those who received placebo, and no malignancies were noted (11). The French Perinatal Cohort found a significant association of first-trimester ZDV exposure with congenital heart defects (12); this association has not been reported in the Antiretroviral Pregnancy Registry (13); in our study, no congenital abnormality was identified while 56% of children were exposed to AZT but it is likely that ARV therapy was introduced rather in the second trimester of pregnancy according to the French guidelines at this period [2003–2012]. The French Perinatal Cohort and PACTG 219/219C found no increase in early childhood cancer associated with ART exposure in HIV-exposed uninfected children (9,12). Malee found higher rates of mental health problems among HEU than HIV infected infants, not linked to in utero exposure to ART but in the caregiver-child relationship and the caregiving environment (14). Alimenti found that altered development and behavior in 39 HEU aged from 18 to 36 months was not linked to ART but with maternal substance use (15). In our study, we didn't find any association between factors like living in a one parent family or to have a parent from Sub-Saharan Africa and no child was exposed to maternal substance use.

There are many limitations to our data: the small sample size of the cohort, the lack of matched control group and objectives measures to assess abnormalities and the declarative character of disorders but our results are consistent with results of other studies.

Conclusions

Increasing numbers of uninfected children will have prolonged in utero exposure to multiple ARV agents used for treatment of their mother's HIV infection. Further studies are needed to detect and evaluate the type and rate of abnormalities, using longer follow-up period, more patients, matched group and more objective measures, Long-term follow-up into adulthood should continue because of the theoretical concerns regarding the potential for carcinogenicity of NRTIs.

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Footnote

Conflicts of Interest: V Reliquet has received travel grants from Merck-Sharp and Dohme and honoraria from Gilead Sciences and Janssen-Cilag. F Raffi received research funding or honoraria from or consulted for Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Ferrer, Gilead Sciences, GlaxoSmith Kline, Janssen-Cilag, Merck-Sharp and Dohme, Pfizer, Splicos, ViiV Healthcare. C Brunet-Cartier received honoraria from Janssen-Cilag. E Launay has no conflicts of interest to declare.

Informed Consent: Every parent gave informed consent.

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