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NEURODEVELOPPEMENT DES ENFANTS EXPOSES IN UTERO A UN TRAITEMENT ANTIRETROVIRAL : UNE ETUDE DESCRIPTIVE

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
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Table of contents

1. Abbreviations

ART: AntiRetroviral Therapy
ARV: anti-rétroviraux
CAMSP: early medical-social action centre
CDC: Center for Disease Control
HBV: Hepatitis B Virus
HEU: HIV Exposed-Uninfected
HIV: Human-Immunodeficiency Virus
HUU: HIV-Unexposed Uninfected
NNRTI: Non-Nucleoside Reverse-Transcriptase Inhibitor
NRTI: Nucleoside Reverse-Transcriptase Inhibitor
VIH : Virus de l'Immunodéficience Humaine

2. Abstract in French

Introduction :
Il y a environ 15 millions d'enfants entre 0 et 14 ans exposés et non infectés par le VIH dans le monde. Ces enfants sont exposés à un traitement antirétroviral in utero et les effets de cette exposition ne sont pas clairs. Nous avons étudié l'effet de la trithérapie antirétrovirale sur le neurodéveloppement de ces enfants. L'objectif primaire était d'évaluer le neurodéveloppement de ces enfants avant l'âge de 6 ans. Ensuite, nous avons cherché une association entre le traitement antirétroviral et un retard de développement. Nous nous sommes également intéressés à l'impact de la socialisation, de l'existence d'une fratrie et de l'exposition à un multilinguisme à domicile sur le développement du langage.

Matériels et méthodes :
Nous avons mené une étude rétrospective, monocentrique au CHRU de Tours. Les enfants nés de mères porteuses du VIH entre 2015 et 2019 ont été inclus. Les enfants prématurés étaient exclus. Le développement des enfants a été évalué par un examen clinique par 2 médecins expérimentés dans l'évaluation du développement entre 12 et 72 mois de vie. Nous avons sélectionné des critères des échelles de Brunet-Lézine, DF-mot et Denver II pour évaluer le développement des enfants.

Résultats :
73 enfants étaient éligibles. 5 ont été exclus du fait de leur prématurité. 25 ont été perdus de vue. Les enfants ont été évalués à un âge médian de 20 mois. Parmi les 43 enfants évalués, 15 (34,9%) avaient un retard du neurodéveloppement. Parmi eux, 14 avaient un décalage de langage (33,3%), 4 (9,3%) un décalage dans l'acquisition de la motricité fine, 2 (4,8%) dans l'acquisition de la motricité globale et 2 (4,7%) un décalage dans les interactions. Nous n'avons pas trouvé d'association statistique entre une classe de traitement antirétroviral et un retard de développement ($p = 0,271$). Il n'y avait pas d'association entre la socialisation de l'enfant et le neurodéveloppement ($p = 0,647$), l'existence d'un multilinguisme et le neurodéveloppement ($p = 0,749$) ou la présence d'une fratrie et le neurodéveloppement ($p = 0,789$).

Discussion :
Les enfants exposés et non infectés par le VIH semblent plus fréquemment avoir un décalage de développement par rapport à la population générale, surtout dans le domaine du langage. Des études prospectives comparatives et une plus large cohorte sont nécessaires avec un suivi à long terme pour évaluer si le décalage du développement persiste après la petite enfance et si ces enfants conservent un trouble du neurodéveloppement à plus long terme.

Mots-clés :
VIH, ARV, grossesse, neurodéveloppement, enfants exposés-non infectés, petite enfance

3. Abstract

Introduction:
HIV exposed-uninfected children are estimated at 15 million between 0 and 14 years old worldwide. These children are exposed to antiretroviral therapy in utero and the effects of this exposure are unclear. We studied ART effect on HEU children neurodevelopment. The primary objective was to assess the neurodevelopment of these children before 6 years old. Secondly, we assessed if an ART is associated with a worse neurodevelopmental outcome. Finally, the socialization, brotherhood and multilingualism impact on language development was also studied.

Methods:
We conducted a retrospective monocentric study at Tours university hospital centre, France. Children born from mothers living with HIV from 2015 to 2019 were enrolled. Preterm children were excluded. The children's development was assessed by clinical evaluation by 2 physicians specialised in the evaluation of the development of children aged 12 to 72 months. We chose some criteria from Brunet-Lezine, DF-mot, Denver II scales to evaluate development of children. BiostatTGV was used for statistical association analysis.

Results:
73 children were eligible. 5 were excluded due to their prematurity. 25 were lost in follow-up. Children were assessed at a 20-month median age (IQR 18-30,5). Among the 43 children assessed, 15 children (34,9%) had a neurodevelopment delay. Among them, we found 14 language delays (33,3%), 4 delays of fine motor acquisition (9,3%), 2 gross motor delays (4,8%) and 2 social delays (4,7%). There was not a statistical association between a treatment class and neurodevelopment (p = 0,271). There were neither statistical difference for the association between socialization and neurodevelopment (p = 0,647) nor multilingualism and neurodevelopment (p = 0,749) nor the presence of brothers and sisters and neurodevelopment (p = 0,789).

Discussion:
HEU children seem to have a poorer neurodevelopment outcome in early childhood compared to general population especially in the language domain. Prospective studies with a comparative group from general population and large cohorts are needed with long-term focus. This will provide a better understanding about the persistence of neurodevelopment delay after early childhood and the appearance of a neurodevelopmental disorder in the long run.

Keywords:
HIV, ART, pregnancy, neurodevelopment, HIV-exposed uninfected, early childhood

4. Introduction

Around 1.4 million HIV-infected mothers give birth each year in the world and 82% of these mothers take an antiretroviral therapy (ART)[1]. It decreases the human immunodeficiency virus (HIV) perinatal transmission. Besides, the number of HIV exposed-uninfected (HEU) children increases over and over. This population is estimated at 15 million children[2] aged 0-14 years in 2019, up from 11.6 million in 2009. In France, around 1500 children are born from HIV-infected mothers[3] each year.

ARTs are classified according to their effect: nucleoside reverse transcriptase inhibitor (NRTI), integrase inhibitor, non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor, fusion inhibitor[4].

ART have a transplacental passage[5]. Large studies have shown that HEU children have higher mortality than HIV-unexposed uninfected (HUU) children[6-10] with an increased risk and severity of common childhood infections[6-8,11-12]. Some recent meta-analysis showed a twofold higher child mortality for HEU children compared to HUU children in the first 1–2 years of life, and a similar risk between 2- and 5-years old children[9-10]. Even if there are benefits from ART in reducing HIV transmission, there is a risk for ART to have negative effects on the developing fetus.

A recent meta-analysis[13] studied congenital malformations after a fetal exposure to ART. In the same study, in subgroup analysis, zidovudine and protease inhibitor users had a 10% increased risk of congenital anomalies, and integrase inhibitor users had a 60% increased risk. A study[14] suggests an increased risk of defects of the small intestine.

Observational studies also noticed a higher rate of pre-term birth and growth restriction[15], increased morbidity and mortality[16] and a higher risk of infection[17].

Concerning neurodevelopment, ART can go through the hematoencephalic barrier[18]. A meta-analysis studying[19] HEU children neurodevelopment found that these children have poorer motor and cognitive development than HIV unexposed uninfected children. Nevertheless, another study[20] didn't find any development difference between these population.

In France and in the world, there is a growing focus on a healthy growth and development[21-22]. The period of brain maturation spans the first 1000 days (including in utero period and the first 2 years)[23]. Recent French guidelines about neurodevelopmental disorders[24] suggest that an exposure to some medications or toxics in this period may have long-term consequences alongside premature birth, microcephaly, some congenital infections. In these medications, antiepileptic drugs have well documented effects on neurodevelopment with some drugs associated with autism[25]. Some pollutants such as bisphenol A are also associated with worse neurological outcomes[26]. As HEU children population is growing, it has become urgent to identify the effects of ART exposure.

However, only a few teams studied ART impact on neurodevelopment of children[27-28]. HEU children are different in terms of ART exposure duration. They are exposed to different antiretroviral drug classes and combinations. Some ART have a fetal toxicity

and are not prescribed during pregnancy. However, the effect of allowed ART during pregnancy is yet to be known.

In addition, 200 million children are developmentally delayed in countries with low and middle-income households[29]. Having more resources does not result on less children with developmental delay. In the United States of America, 17% of children were reported to have developmental delay or disability between 2009 and 2017[30]. According to the Dictionary of Developmental Disabilities Terminology, developmental delay is a condition in which the child is not developing and/or does not reach skills in accordance with the sequence of predetermined stages[31]. Development disabilities is defined by the United States Center for Disease Control (CDC) as a group of conditions due to a physical, learning, language, or behaviour deficiency. These conditions start during the developmental period and may impact the day-to-day functioning. It usually lasts throughout a person's lifetime[32]. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5[33] defines Neurodevelopmental disorders as "a group of conditions with onset in the developmental period. The disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning".

The delay can be specific, or it can affect multiple domains. If we consider the Bayley Scales of Infant and Toddler Development[34], there are five development domains: cognitive, language, motor, socio-emotional and adaptive behaviour. If there is a significant delay in most developmental areas, it is called a global developmental delay[35].

A study exploring the effect of in utero exposure to protease inhibitor in mices shown that mices exposed to these treatments have delays in the milestone development, especially concerning reflexes. This area impacts the ability for dynamic postural adjustments, muscular strength. The same study hypothesizes that there would be a disrupted underlying neurocircuitry[36].

We studied ART effect on HEU children neurodevelopment. The primary objective was to assess the neurodevelopment of these children before 6 years old. Secondly, we assessed if an ART is associated with a worse neurodevelopmental outcome. Finally, the socialization, brotherhood and multilingualism impact on language development was also studied.

5. Methods

We conducted a retrospective monocentric study in Tours, France. Mothers could be treated with a 3-drug ART before starting their pregnancy. In this case, when the treatment was compatible with pregnancy and well taken by the patients, the treatment was not modified due to pregnancy. If one of these conditions wasn't fulfilled, the treatment was modified by the infectiologist. If the mother didn't have a treatment before pregnancy, whatever the reason, an antiretroviral therapy compatible with pregnancy was introduced, as soon as possible. The choice of antiretroviral therapy, if introduced or modified during pregnancy, was left to the mother's infectiologist, respecting safety condition and information available about these treatments at this time.

Children born from January 2015 to December 2019, from mothers treated with antiretroviral therapy for HIV during their pregnancy, were eligible. Only children born from mothers followed up in Tours university hospital for HIV were included. Children born preterm before 37 weeks of gestational age were excluded, because it is a known independent factor of developmental delay and neurodevelopment disorder[37-38]. Every child was given a preventive HIV treatment according to their mother viral load at delivery. If viral load was detectable, they were given an ART for 4 weeks. If not, they were given an oral treatment of zidovudin for 4 weeks.

In the paediatric unit of Tours hospital, HEU children born from mothers followed up in our hospital have five follow-up check-ups appointments with a paediatric infectiologist at first, third, sixth, twelveth and twenty-fourth month after birth. They have the benefit of an additional check-up at the early medical-social action centre (CAMSP) of our hospital between 18 and 24 months of age. They are reconvened afterwards in case they miss an appointment. Children development was evaluated by 2 medical directors of CAMSP during this period, who have the experience of evaluating neurodevelopment. The evaluation examination duration was one hour and half to two hours. They used a personal evaluation grid based on validated scales[39-41] and development milestones. Before examining children, they discussed with parents to get some information about all the development of their child and vision integrative. They also collected some information about the family situation and the foreign language spoken at home. The neurodevelopmental examination evaluated motor, cognitive, speech and social development. We chose some criteria from French neurodevelopment evaluation grids used by our clinicians (Brunet-Lezine[39], DF-mot[40], Denver II[41]) to assess if development was normal.

Concerning the language, we considered that children who could tell 5 words at 18 months had a normal development. They should be able to associate words and formulate them in a comprehensive way at 24 months old and use pronouns (I, you, he, she) at 30 months old. They should have a language allowing interaction with other people at 3 years old.

For global motor skills, we considered that a child should have an independent walk at 14 months old, an easy run at 24 months old and should climb the stairs with alternating feet at 30 months old.
For fine motor skills, we used 4 criteria to determine the normal children development stage. First, they should embed the round at 12 months old. Then, they should make a tower of 3 cubes at 18 months old and make a tower of 5 cubes at 20 months old. They should finally draw a circle at 32 months old.
For social skills, we considered the reaction when we call the child by his name at 6 months old. He should point with his finger at 14 months old and play imitation games at 20 months old.
Since all children were not assessed at the same stage and age, we considered that a skill was not acquired at the time we conducted the assessment.
Then, we performed a data analysis on data extracted from the hospital's information system. The hospital information system is fed with consultation reports redacted by doctors.
We extracted different type of information like children's sex, term of birth, if children were born from assisted reproduction, birth weight, if children were treated with zidovudine at birth or another HIV neonatal treatment. We collected information about mothers' pregnancy: their antiretroviral therapy and modifications made, viral load before delivery and delivery route. We also obtained information about family status (siblings, how the child is cared of, multilingualism).
Then, we received neurodevelopment evaluations from CAMSP, the age at evaluation, and the examination results. In case of an effective neurodevelopment delay pointed out, these children had a follow-up at CAMSP with a possible rehabilitation according to the type of delay.
Finally, data were processed with biostaTGV website[42] to look for an association between a neurodevelopmental delay and a given treatment class (NRTI, NNRTI, protease inhibitor, integrase inhibitor, fusion inhibitor) A Fischer test was used because of the limited population. We also analysed the effect of multilingualism at home, the presence of older brothers and sisters and socialization of the children to assess a potential effect on language. Statistical significance was obtained for a p-value inferior to 0,5.

6. Results

On the 73 eligible children during the study period, 5 were born preterm before 37 weeks of gestation and they were consequently excluded. Three pregnancies were not followed because of inobservant women, and we didn't know the exact term but children didn't have any classical complication of preterm birth as enteral feeding, respiratory distress, or digestive complication so we included them as term born children. Twenty-five children didn't come to the evaluation at CAMSP despite many reminder calls and given appointments. Consequently, we didn't include them in this analysis. Among them, 4 children didn't come because they moved out from the Tours area. Overall, 43 children were assessed for development. The flow-chart is developed in Figure 1.

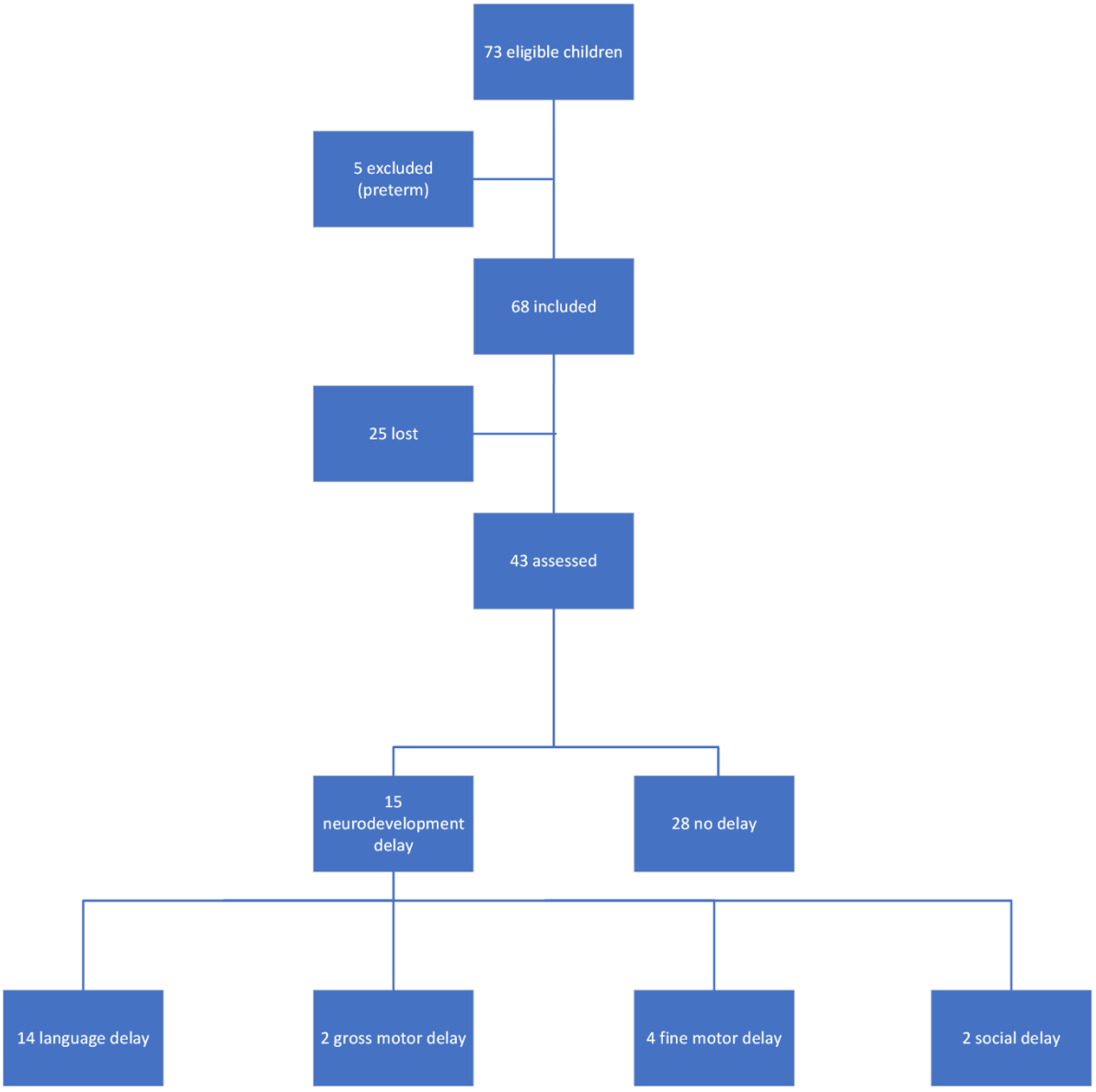

Figure 1. Flow-chart

The mothers median age was 33 years old. The main ethnic origin was sub-Saharian Africa (74,4%), 82% were from French-speaking countries. Mothers' characteristics are summarized in Table 1.

Table 1. Mothers' characteristics

	Total included	Total assessed
	N (%) (n = 68)	N (%) (n = 43)
Ethnic origin		
Sub-Saharian Africa	31 (45,6)	32 (74,4)
Western Europe	5 (7,4)	5 (11,6)
Eastern Europe	3 (4,4)	3 (7)
Caribbean (Saint Martin)	1 (1,5)	0 (0)
Missing	28 (41,2)	3 (7)
During pregnancy		
Assisted reproduction	4 (5,9)	3 (7)
ART		
Treated	66 (97)	41 (95,3)
Not treated	2 (2,9)	2 (4,7)
Maternal treatment at start		
NRTI	65 (95,6)	41 (95,3)
NNRTI	18 (26,5)	10 (23,3)
Protease inhibitor	32 (47,1)	23 (53,5)
Integrase inhibitor	18 (26,5)	9 (20,9)
Treatment change	20 (30,3)	12 (29,3)
Positive viral load	13 (19,4)	7 (16,7)
At birth		
Age		
< 25	6 (8,8)	2 (4,7)
25-29	9 (13,2)	7 (16,3)
30-34	26 (38,2)	16 (37,2)
≥ 35	25 (36,8)	17 (39,5)
Median (IQR)	33 (30-36)	33 (30-37)
Missing	2 (2,9)	1 (2,3)
Positive viral load	4 (6)	3 (7,1)
CD4 cell count		
Median (IQR)	508,5 (382,75-688,5)	517 (395,25-693,75)
Missing	14 (20,6)	9 (20,9)
Delivery route		
Vaginal	48 (70,6)	32 (74,4)
Caesarean	20 (29,4)	11 (25,6)

ART : antiretroviral therapy, NRTI : nucleoside reverse transcriptase inhibitor, NNRTI : non-nucleoside reverse transcriptase inhibitor, IQR : inter quartile range

All assessed mothers had an ART introduced before starting their pregnancy except 5 (11,6%). Over these 5 mothers, 2 didn't have a treatment until delivery, the others started a treatment at a variable time in their pregnancy. Twelve women (29,3%) underwent a change in their ART because of pregnancy incompatibility or treatment efficacy. Two women underwent 2 switches of treatment during pregnancy. Mothers underwent different HIV treatments: 95,3% were treated with NRTI, 20,9% with NNRTI, 53,5% with protease inhibitor and 20,9% with integrase inhibitor. Viral load was detectable in pregnancy for 7 women and at delivery for 3 women. The ART of the mothers are described in Table 2.

Table 2. Antiretroviral therapies of mothers

Class	Treatment	Number of exposed children (%) (n=43)
Nucleoside reverse transcriptase inhibitor	ABACAVIR	3 (7)
	EMTRICITABINE	34 (79,1)
	LAMIVUDINE	6 (14)
	TENOFOVIR	35 (81,4)
	ZIDOVUDINE	3 (7)
	Total	**41 (95,3)**
Integrase inhibitor	DOLUTEGRAVIR	1 (2,3)
	ELVITEGRAVIR	2 (4,7)
	RALTEGRAVIR	6 (14)
	Total	**9 (20,9)**
Non-nucleoside reverse transcriptase inhibitor	EFAVIRENZ	1 (2,3)
	NEVIRAPINE	3 (7)
	RILPIVIRINE	6 (14)
	Total	**10 (23,3)**
Protease inhibitor	ATAZANAVIR	8 (18,6)
	DARUNAVIR	11 (25,6)
	LOPINAVIR	4 (9,3)
	RITONAVIR	22 (51,2)
	Total	**23 (53,5)**

Over the 43 children assessed, there were 23 girls (53,5%) and 20 boys (46,5%). At birth, 16,3% of children were hypotrophic and 9,3% were macrosomic. Three children were born from assisted reproduction. Forty children took oral zidovudin treatment for 4 weeks to prevent HIV transmission with a negative maternal viral load and 2 got ART because of a maternal positive viral load at delivery. One child got only oral zidovudine treatment whereas his mother had a positive viral load.
Median age at evaluation at CAMSP was 20 months old. All children were evaluated after 18 months of age except 1 who had a consultation at 12 months old because of

a leukodystrophy of unknown origin. At assessment, 83,7% were socialized at school, nursery or at childminder with other children. At home, there was a multilingual environment for 14 (32,6%) children: 3 with Arabic (21,4%), 1 with English (7,1%), 1 with Russian (7,1%), 1 with Portuguese (7,1%), 5 with African dialect (35,7%), 1 with English and Russian (7,1%), 1 with Russian and Chechen (7,1%). Eight children (18,6%) were firstborn.

Fifteen children had at least one delay (34,9%). Among these children, 4 had delays in more than one domain of development (9,3%). There were 2 children with gross motor delay (4,8%), 4 with fine motor delay (9,3%), 14 with language delay (33,3%) and 2 with social delay (4,7%). One child with a language delay had a serous otitis, another one with language delay had a perceptive deafness and one child with fine motor and social delay had leukodystrophy. This last child was assessed at 12 months old so our criteria couldn't neither find a gross motor delay because the first gross motor criteria was assessed at 14 months old nor a language delay because the first criteria was assessed at 17 months of age. Among children having a language delay, 3 children (25%) had multilingualism at home, 3 (25%) had a delay in another domain and 3 were firstborn (25%).

For gross motor assessment, 41 children (97,6%) had an autonomous walk at 14 months old, 14 (100%) got easy running at 24 months old and 11 (91,7%) could climb stairs alternating feet at 30 months old.

For fine motor assessment, 42 children (97,7%) could embed the circle at 12 months old, 41 (97,6%) could make a tower of 3 cubes at 18 months old, 22 (95,7%) could make a tower of 5 cubes at 20 months old and 8 (80%) could copy a circle at 32 months old.

Concerning language assessment, 34 children (81%) had a 5 words vocabulary at 17 months old, 8 (57,1%) could associate words at 24 months old, 8 (66,7%) used pronouns at 30 months old and 4 (57,1%) had a language allowing interaction with other people at 36 months old.

For social delay, 42 (97,7%) of children had a reaction when they were called by their name at 6 months old, 42 (100%) got pointing at 14 months old and 22 (95,7%) could play imitation games at 20 months old. The children characteristics are summarized in Table 3, 4 and 5.

Table 3. Children characteristics at birth

	Total assessed N (%) (n = 43)
Gender	
Male	20 (46,5)
Female	23 (53,5)
Birthweight	
Low (< 2500)	1 (2,3)
Normal (2500-4000)	40 (93)
High (> 4000)	1 (2,3)
Missing	1 (2,3)
Median (IQR)	3372,5 (3073,75-3602,5)
Size for gestational age (percentile)	
Small (<10th)	7 (16,3)
Appropriate (10-90th)	30 (69,8)
Large (>90th)	4 (9,3)
Missing	2 (4,7)
Gestation at delivery (weeks)	
Median (IQR)	39 (38-40)
Missing	2 (4,7)
Neonatal treatment	
Oral Zidovudin	41 (95,3)
ART	3 (7)
IQR: inter quartile range, ART: antiretroviral therapy	

Table 4. Children characteristics at assessment

	Total assessed N (%) (n = 43)
Siblings	
Median (IQR)	2 (1-3)
Missing	1 (2,3)
Socialization	
Yes	36 (83,7)
No	6 (14)
Missing	1 (2,3)
Multilingualism at home	
Yes	14 (32,6)
No	23 (53,5)
Missing	6 (14)
IQR: inter quartile range	

Table 5. Details of clinical assessment

	Total N (%) (n = 43)
Age (months)	
Median (IQR)	20 (18-30,5)
Neurodevelopment delay	15 (34,9)
Gross motor delay (n = 42)	2 (4,8)
Autonomous walk at 14 months old (n=42)	41 (97,6)
Easy running at 24 months old (n=14)	14 (100)
Climb stairs alternating feets at 30 months old (n=12)	11 (91,7)
Fine motor delay (n = 43)	4 (9,3)
Embed the circle at 12 months old (n=43)	42 (97,7)
Tower of 3 cubes at 18 months old (n=42)	41 (97,6)
Tower of 5 cubes at 20 months old (n=23)	22 (95,7)
Copy a circle at 32 months old (n=10)	8 (80)
Language delay (n = 42)	14 (33,3)
5 words at 17 months old (n=42)	34 (81)
Word association at 24 months old (n=14)	8 (57,1)
Pronouns at 30 months old (n=12)	8 (66,7)
Language allowing interaction with other people at 36 months old (n=7)	4 (57,1)
Social delay (n = 43)	2 (4,7)
Reaction when called by his name at 6 months old (n=43)	42 (97,7)
Pointing at 14 months old (n=42)	42 (100)
Play imitation games at 20 months old (n=23)	22 (95,7)

IQR: inter quartile range

For the association between treatment classes and neurodevelopmental delay, we couldn't analyse NRTI as all mothers who had received a treatment during pregnancy had an NRTI in their ART.

When we compare treatment classes, there is not a statistical difference between the third treatment class in the ART and children neurodevelopment (p = 0,271). One child was exposed to integrase and protease inhibitor besides a NRTI and didn't have a

delay. Therefore, the total of children is 44 and not 43. If we compare each class exposure to no treatment, there is not a statistical difference either (Table 6).

Table 6. In utero treatment exposure and neurodevelopmental delay

Treatment class	Standard neurodevelopment		Neurodevelopment delay		Total	p
None	1	50%	1	50%	2	
Integrase inhibitor	5	55,56%	4	44,44%	9	1
NNRTI	9	90%	1	10%	10	0,328
Protease inhibitor	14	60,87%	9	39,13%	23	1
Total	**29**	**65,12%**	**15**	**34,9%**	**44**	**0,271**

NNRTI : non-nucleoside reverse transcriptase inhibitor

There is neither statistical difference for the association between socialization and neurodevelopment (p = 0,647) nor multilingualism and neurodevelopment (p = 0,749) nor the presence of brothers and sisters and neurodevelopment (p = 0,789).

7. Discussion

According to these results, HEU children seem to have a poorer neurodevelopment outcome in early childhood compared to general population. In this cohort, 34,9% of children had a neurodevelopmental delay. It is higher than the estimated prevalence in the United States of America in 2016 (4,67%)[30], in Nigeria in 2016 (0,9%)[43] or in the United Kingdom (12% with mild to severe delays)[44]. In Australia, a broader definition of neurodevelopment delays is used, and it is estimated at 7% of children aged from 0 to 14 years old[45]. In low- and middle-income countries (LMIC), a study estimated that around 36,8% of children have a poor cognitive and socioemotional development between 2005 and 2015[46]. It can be explained by the fact that these countries have a cumulative effect of many causes of neurodevelopmental delay such as malnutrition, more frequent post-natal infections, or poverty.

Fine motor, gross motor and social delay estimates are consistent with other studies in general population[47].

Language delay seems to be the most important delay. In a systematic review, prevalence of isolated speech and language delays in general population was estimated at 6%[48]. Results from our study show a much higher risk of language delay. Many hypotheses can be made to explain these results.

First, multilingual environment could be a potential factor as children ear many languages at home and must process all the languages at once. Our study shows that there is only 25% of children with a language delay who were exposed to multilingualism at home. Among children exposed to multilingualism (14 children), we found only 4 children (28,6%) with language delay. Studies shaw that children raised in a bilingual environment acquired less words in each language they ear. Nevertheless, all languages combined, they acquired the same number or more words than the average[49-50].

Another hypothesis is that children with older brother or sister develop language sooner and they are less likely to develop a language delay. In our study, among children with language delay, only 25% were firstborn and among children in families with older children, 37,5% had a language delay. There was not a statistical difference either. This result is consistent with a study which showed that firstborns and secondborns did not differ in the language development either at 21 or 24 months of age[51].

Socialization was also studied because we assumed that a child who was cared of with other children could have a better language development. Among socialized children, 32,4% had a neurodevelopmental delay. 46,67% of children with a neurodevelopmental delay were not socialized. Consequently, socialization doesn't seem to be a protective or an aggravative factor of neurodevelopmental delay.

For ART, only the third class associated to NRTI was analysed. In our analysis, we didn't find a difference between these therapies. It is probably due to the size of the cohort or due to the important number of neurodevelopmental delays within each class. However, NNRTI seems to be a protective factor for neurodevelopmental delay as only

10% of children have one in this group. This difference is worth thinking about and should be explored more accurately with a clinical and physiological scope.
NRTI were not analysed because every treated mother had at least 1 NRTI in their ART. As it seems to be a lot of neurodevelopment delay with every third associated treatment class, NRTI should be also explored as a potential neurodevelopmental delay inductor. For this, children born from mothers with a hepatitis B virus (HBV) infection could be studied to isolate NRTI effect. If indicated, women are treated with tenofovir, which is a NRTI, as a first-line agent during pregnancy to prevent vertical transmission[52]. Children exposed to this treatment in utero should be followed and assessed for their neurodevelopment.
Another French study[27] evaluated HEU children for neurodevelopment with a letter sent to parents. This study found a significant association between neurodevelopmental disorders and 3 non-nucleoside reverse transcriptase inhibitor exposure. Our study results concur with this. It is also consistent with a South-African study which found a delayed receptive and expressive language development[28].
A strength of our study is that it is based on children clinical assessment by trained doctors used to neurodevelopment disorders and delays. We chose to rely on criteria extracted from frequently used scales, but we didn't used complete scale to assess development of children. These items were the ones that we found in the children assessment reports and that we found relevant for this study.
There are many limitations to our data. First, it is a monocentric study because only few centres have a neurodevelopment follow-up by a specialized team of this population. The sample size was small and there were many losses of follow-up. In fact, mothers living with HIV are less care compliant and are more likely to miss appointments[53]. To limit this, families were called days before the appointment, but it wasn't sufficient, and many didn't come to their child clinical assessment.
Another limitation of our study is that children were not evaluated at a same age due to our study design.
Even if we didn't find a statistical difference, there is certainly an association between at least HEU children neurodevelopmental delay and in utero ART exposure as more than one third of children had a delay in our cohort. It would be interesting to build a prospective study with more children, at a regional or national scope to have a larger cohort. To ascertain a delay, children should be assessed at fixed ages such as 24 months old, to have more comparable children. The evaluation should also be based on standardized and validated neurodevelopment evaluation scales. As in our study children were seen early in their developmental course, there should be a focus on long-term follow-up as a neurodevelopmental delay or disability could appear after these ages.

8. Conclusion

Children exposed in utero to ART seem to have more developmental delay, especially language delay. It is urgent to confirm these results as it represents an increasing number of children. Prospective studies with a comparative group from general population and large cohorts are needed with long-term focus. This will provide a better understanding about the persistence of neurodevelopment delay after early childhood and the appearance of a neurodevelopmental disorder in the long run.

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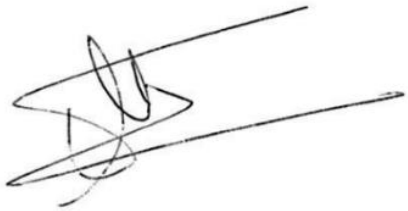

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33 pages – 6 tableaux – 1 figure

Résumé :

Introduction. Il y a environ 15 millions d'enfants entre 0 et 14 ans exposés et non infectés par le VIH dans le monde. Ces enfants sont exposés à un traitement antirétroviral in utero et les effets de cette exposition ne sont pas clairs. Nous avons étudié l'effet de la trithérapie antirétrovirale sur le neurodéveloppement de ces enfants. L'objectif primaire était d'évaluer le neurodéveloppement de ces enfants avant l'âge de 6 ans. Ensuite, nous avons cherché une association entre le traitement antirétroviral et un retard de développement. Nous nous sommes également intéressés à l'impact de la socialisation, de l'existence d'une fratrie et de l'exposition à un multilinguisme à domicile sur le développement du langage.

Matériels et méthodes. Nous avons mené une étude rétrospective, monocentrique au CHRU de Tours. Les enfants nés de mères porteuses du VIH entre 2015 et 2019 ont été inclus. Les enfants prématurés étaient exclus. Le développement des enfants a été évalué par un examen clinique par 2 médecins expérimentés dans l'évaluation du développement entre 12 et 72 mois de vie. Nous avons sélectionné des critères des échelles de Brunet-Lézine, DF-mot et Denver II pour évaluer le développement des enfants.

Résultats. 73 enfants étaient éligibles. 5 ont été exclus du fait de leur prématurité. 25 ont été perdus de vue. Les enfants ont été évalués à un âge médian de 20 mois. Parmi les 43 enfants évalués, 15 (34,9%) avaient un retard du neurodéveloppement. Parmi eux, 14 avaient un décalage de langage (33,3%), 4 (9,3%) un décalage dans l'acquisition de la motricité fine, 2 (4,8%) dans l'acquisition de la motricité globale et 2 (4,7%) un décalage dans les interactions. Nous n'avons pas trouvé d'association statistique entre une classe de traitement antirétroviral et un retard de développement (p = 0,271). Il n'y avait pas d'association entre la socialisation de l'enfant et le neurodéveloppement (p = 0,647), l'existence d'un multilinguisme et le neurodéveloppement (p = 0,749) ou la présence d'une fratrie et le neurodéveloppement (p = 0,789).

Conclusion. Les enfants exposés et non infectés par le VIH semblent plus fréquemment avoir un décalage de développement par rapport à la population générale, surtout dans le domaine du langage. Des études prospectives comparatives et une plus large cohorte sont nécessaires avec un suivi à long terme pour évaluer si le décalage du développement persiste après la petite enfance et si ces enfants conservent un trouble du neurodéveloppement à plus long terme.

Mots clés : VIH, ARV, grossesse, neurodéveloppement, enfants exposés-non infectés, petite enfance

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