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Management of Newborns from HIV-1 Seropositive Mothers: Results of a Single Center Implementation of the French National Guidelines

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Abstract

Background: Management of newborns from HIV-1 seropositive mothers is a well standardized practice that changed over the last fifteen years. It would be of great interest to analyse this evolution.

Methods: This retrospective study included infants born from HIV-1 seropositive mothers followed at the Nice University Hospital between 1995 and 2009. All the mother-child pairs were included in the French survey and received care according to the French successive guidelines. Two groups were defined: the first one with children born from mothers treated by mono or dual therapy and the second with those born from mothers receiving Highly Active Anti Retroviral Treatment (HAART).

Results: Three hundred and eleven children were included. The mothers' mean viral load was lower in the HAART group (2.1 ± 0.83 versus 2.85 ± 1.5 log10, p<0.0001). No significant difference was observed between the 2 groups regarding frequency of prematurity. Newborns from HAART group had moderate neutropenia. Four children were found to be infected during the study period (transmission rate: 1.3%) among which only 1 in the HAART group.

Conclusions: In industrialized countries, the risk of MTCT is very low. This results from optimized healthcare and efficiency of antiretroviral therapy in HIV-infected mothers. Our data showed that implementation of the French national guideline is effective at the level of a single university hospital.

Keywords: HAART; HIV-1; Mother-to-child transmission; Newborn; Pregnancy

Introduction

Mother-to-child transmission (MTCT) of Human Immunodeficiency virus Type-1 (HIV-1) is by far the most dreadful complication of a seropositive woman's pregnancy. In France during the last 20 years, the rate of MTCT has decreased from 20% to less than 1%, due to progress in the mothers' care and advances in antiretroviral therapy that successive national recommendations have taken into account [1-4]. During this period, more than 300 children were born from HIV-1 seropositive mothers in the Nice University Hospital. We analysed the effects of these evolutions on our patient cohort.

Subjects and Methods

All children born from HIV-1 seropositive mothers in the Nice University Hospital, France, between January 1st, 1995 to December 31st, 2009 were included. Data were extracted from a database set up in the department of paediatric haematology in 1994. Analysis was conducted in July 2010, so that the youngest infant was 6 months old at closure of the study. The evolution of the French recommendations for the prevention of HIV-1 mother to child transmission from 1996 to 2010 is represented in Table 1.

Mother-child pairs were split up in two groups according to the mother's prenatal antiretroviral therapy (Figure 1). The first group consisted of children born from mothers treated by mono or dual therapy i.e. one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs). The second group included those who were born from women receiving Highly Active Anti Retroviral Treatment (HAART) i.e. an association of two NRTIs and a Protease Inhibitor (PI) or a Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI). No pregnancy conducted under integrase inhibitor or CCR5 antagonist was observed during the study period. One pregnancy was conducted under multi-therapy including a fusion inhibitor (T20- Fuzeon®); the infant was excluded from the study.

Ninety six percent of the mothers received azidothymidine infusion during labour (2 mg/kg bolus then 1 mg/kg/hour) as recommended. All the newborns received zidovudine (AZT) initiated during the first hours of life (2 mg/kg four times a day). Children considered of being at high transmission risk according to the French recommendation received post exposure drug combinations of AZT and/or lamivudine (3TC) and/or nevirapine (NVP) [3]. Between 1997 and 1998, 28 mother-infant pairs were included in the ANRS075 study and randomized to received AZT+3TC or AZT only. This study conducted by the French Agence Nationale pour la Recherche sur le SIDA (ANRS) was designed to analyse the effect of the adjunction of lamivudine in the prevention of MTCT [5]. Among the 35 newborns who received nevirapine as a part of their prophylactic treatment, 10 were included in the ACTG316 – ANRS083 study. This randomized double-blind study was designed to evaluate the benefit of nevirapine adjunction to the mother and child

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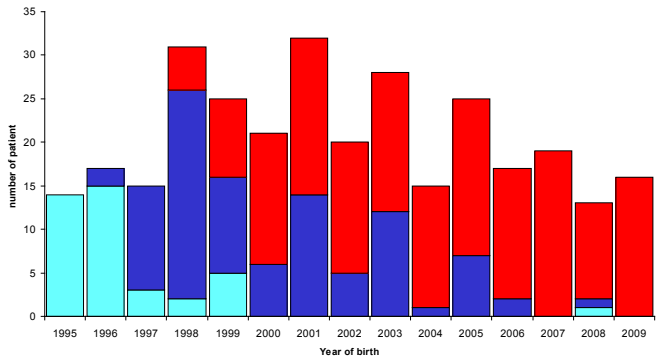
in the prevention of HIV-1 MTCT [6]. Total blood count was obtained at birth to eliminate severe intra-uterine haematological toxicity [7]. Infant breastfeeding was avoided even if the mother's viral load was undetectable [3,8].

Maternal characteristics considered were:

- Demographic data, age at childbirth, mode of infection, serological status against rubella, toxoplasmosis and B and C hepatitis.
- HIV-1 viral load (PCR-RNA HIV-1) and absolute count of CD4 T-cell lymphocytes ($CD3^+$-$CD4^+$) obtained during the last month of pregnancy.
- Anti-retroviral drug combination administered during pregnancy.



(Blue: mono dual therapy; light blue: monotherapy, dark blue: dual therapy, Red: HAART)

Figure 1: Evolution of maternal treatments during the follow-up period.

Perinatal characteristics considered were:

- Complications of pregnancy and mode of delivery (elective caesarean section compared to emergency caesarean section or vaginal delivery).

Each infant was examined by the same paediatrician (MF) a few hours after birth (prior to the introduction of prophylactic treatment), and at 2 weeks, 1, 3 and 6 months of age, according to national guidelines.

Collected data on children were:

- growth parameters (weight, height, cranial perimeter)
- main clinical abnormalities
- anti-retroviral drug combination and length of exposure
- complete blood cell count at birth

The mothers' viral loads (HIV-1 PCR-RNA) measured at the end of pregnancy, the children's virological evaluations (viral co-culture, HIV-1 PCR-RNA and proviral DNA) and the T-cell subpopulation analyses were all respectively performed in the Departments of Virology and Immunology of the Nice University Hospital.

In infants, HIV-1 infection was assessed if two consecutive direct virological samples were positive: viral co-culture and/or HIV-1 PCR-RNA greater than 400 copies per ml and / or positive proviral HIV-1-DNA. Children with 4 negative direct virological samples obtained during the first semester of life (week 1, months 1, 3 and 6) were considered not infected [3].

	1996	1999	2002	2004	2006	2008	2010
Main concept	Implementation of protocol ACTG076-ANRS024 (33)	Long term follow-up of infant exposed to NRTI in utero	Start HAART after 12 WA. Infant follow-up	HAART only No mono or dual therapy	Concern about toxicity of HAART on mother and infant	Same concept Few changes	Same concept Few changes
Treatment regimen during pregnancy for women who weren't treated before pregnancy	Start AZT on the 14th week of pregnancy	Start AZT or AZT+3TC on the 14th week of pregnancy	If maternal VL<10,000c/ml: AZT + ECS If maternal VL>10,000 c/ml : HAART	Start HAART at the beginning of 3rd trimester of pregnancy	Start HAART before 28 WA, or before 20 WA if risk of prematurity	Start HAART, before 26 WA, or before 20 WA if risk of prematurity	= 2008
Treatment regimen during pregnancy for women who were treated before pregnancy	In case of bi-therapy: stop one NRTI until the end the 3rd trimester of pregnancy. Stop any PI (ritonavir or indinavir)	Same treatment if good efficacy and tolerance. If CD4<350/ml or VL>5.000 c/ml: treatment change[1]	Same treatment if good efficacy and tolerance. If CD4<350/ml or VL>400 c/ml, treatment change[2]	Same treatment if good efficacy and tolerance. If VL>400 c/ml, treatment change[2]	Same treatment if good efficacy and tolerance. If VL>50 c/ml, treatment change[2]	No Change	= 2008
Route of delivery	No recommendation	No recommendation but ECS seems to reduce the risk of MCT	ECS if VL>400c/ml under HAART or if AZT alone during pregnancy	ECS only if VL>400c/ml under HAART just before delivery	ECS only if VL>50c/ml under HAART just before delivery	ECS if VL>400c/ml	= 2008
Treatment during delivery	Intravenous AZT	= 1996	= 1996	= 1996	= 1996	= 1996	= 1996
Treatment for the newborn	AZT: 2 mg/kg four time a days- 6 weeks	AZT: same dose + 3TC in MCT high risk situations	= 1996 AZT: same dose + 3TC or NVP if maternal VL> 1,000c/ml at delivery	AZT*: same dose + 3TC and NFV or NVP if maternal VL> 1,000c/ml at delivery or no maternal treatment	= 2004	AZT*: same dose + 3TC and LPV or NVP if maternal VL>1,000c/ml at delivery or no maternal treatment	Same concept. Reduction of AZT post-natal exposure to 4 weeks

1: Exclude Dideoxycytosine and Efavirenz; 2: Exclude Didanosine+Stavudine
*: with specific recommendations for premature newborn and/or in case of intravenous administration
VL: viral load, MCT: mother to child transmission, WA: weeks of amenorrhea, ECS: Elective caesarean section, WA : weeks of amenorrhea, NVP: nevirapine, NFV: nelfinavir, LPV: lopinavir/low dose ritonavir

Table 1: Evolution of the French recommendations for the prevention of HIV-1 mother to child transmission.

	ALL	*MONO-DUAL THERAPY*	*HAART*	*p*
Median of the periods	2002	1998 (1995-2008)	2004 (1998-2009)	
Mother-infant pairs	311	136	175	
Mean maternal age at delivery (years)	32.6±6.7	31.5±4.7	33.6±7.8	0.0003
Route of transmission (sexual / IVDU)	181/50	70/28	111/22*	0.03

*: + 3 mothers infected by MTCT, IVDU: intra venous drug user Table 2: Mothers' demographic data

Table 2: Mothers' demographic data Maternal characteristics.

	ALL	*MONO-DUAL THERAPY*	*HAART*	*p*
MaternalCD4 T-cell count (/ml)	509 ± 266	538 ± 281	484 ± 252	NS
Maternal viral load (log10)	2.36 ± 1	2.85 ± 1.05	2.1±0.83	<0.0001
Undetectable viral load (40 c/ml)*	119/253	19/88	100/165	0.0001
Undetectable viral load (400 c/ml)**	184/253	48/88	136/165	<0.03

*: 1.6 log10, **: 2.6 log10, NS: p non significant

Table 3: Maternal immunological and virological status.

Viral Load	*Delivery*	*Treatment group*	*N* (%)*
PCR-RNA HIV-1 below 400 c/ml (167/254*)	E.C.S	Mono Dual therapy	30/167 (18%)
		HAART	92/167 (55%)
	Others	Mono Dual therapy	10/167 (6%)
		HAART	35/167 (21%)
PCR-RNA HIV-1 above 1000 c/ml (55/254)	E.C.S	Mono Dual therapy	19/35 (54%)
		HAART	16/35 (46%)
	Others	Mono Dual therapy	16/55 (29%)
		HAART	4/55 (7%)

*: number of positive values/ total number of values, E.C.S: elective caesarean section

Table 4: Viral load, route of delivery and treatment groups.

Statistical Analyses

Results are expressed as means and standard deviations. Comparison of qualitative variables was performed by Fisher's exact test. Given the non-normal distribution of most quantitative variables, nonparametric tests of Mann-Whitney or Kruskal-Wallis were used. The significance was established for $p < 0.05$. Analytical statistics were performed with Statview software version 5.0 for Windows.

Results

During the study period, 312 infants were born alive from HIV-1 seropositive mothers at Nice University Hospital. All but one (pregnancy conducted under multi-therapy with a fusion inhibitor), i.e. 311 infants, were included, 136 in the mono-dual therapy group and 175 in the HAART group. As 39 women gave birth several times during the study period [9] (twice for 36 of them and 3 times for 3 others) and 4 twin pregnancies were observed, these 311 infants corresponded to 222 mothers.

Maternal characteristics are represented in Table 2. Mothers from the HAART group were approximately 2 years older than those in the mono-dual therapy group. The main route of maternal contamination was sexual. Three women were themselves born from HIV-1 seropositive mothers as reported elsewhere [10]. The proportion of women infected by drug abuse decreased steadily all along the observation period so that it reached statistical significance between the 2 groups (28% in the mono-dual therapy group versus 16.5% in the HAART group, $p = 0.03$). The proportion of co-infected HIV-HCV patients also decreased, but not significantly so (34% in the mono-dual group versus 22% in HAART group). These similar evolutions are probably related. Rates of immunization against toxoplasmosis, rubella and B hepatitis were similar in both groups. The mean maternal viral load was significantly lower in the HAART group, while the proportion of patients with undetectable viral load was significantly higher in the same group compared to the mono-dual therapy group (Table 3).

Complications were observed in 56 pregnancies (18%) with no significant difference between both groups: intra uterine growth retardation (n: 10), premature rupture of membranes (n: 9), gestational diabetes mellitus (n: 9), threatened preterm labour (n: 8), maternal thrombocytopenia (n: 7), toxaemia gravidis (n: 4), maternal anaemia (n: 4), cholestasis (n: 3), nephrolithiasis (n: 2), pulmonary pneumocystosis infection (n: 1) and retro-placental haematoma (n: 1).

The rate of elective caesarean section deliveries was significantly higher in the HAART group: 74% versus 44% in the mono-dual therapy group ($p = 0.01$). In the last month of pregnancy, the viral load was below 400 copies per ml for 167 women (66% of the study population) and above 1,000 copies per ml for 55 (21% of the study population) (Table 4). Among the latter, 21 (8.3% of the total study population) had a viral load above 10,000 copies per ml. Relationships between maternal viral load, group of treatment and mode of delivery are given in Table 5.

Child characteristics are represented in Table 6. Infant term was significantly shorter in the HAART group but prevalence of preterm

Treatment groups	*Viral load Copies per ml*	*Newborn prophylactic group*	*N* (%)*
Mono-Dual therapy (136)	VL<400	AZT alone	36/48 (75%)
	(48/88)*	AZT+3TC or AZT+NVP	12/48 (25%)
	VL>1.000	AZT alone	7/35 (20%)
	(35/88)	AZT+3TC or AZT+NVP	28/35 (80%)
HAART (166)	VL<400	AZT alone	105/136 (77%)
	(136/166)	AZT+3TC or AZT+NVP	31/136 (23%)
	VL>1.000	AZT alone	12/20 (60%)
	(20/166)	AZT+3TC or AZT+NVP	8/20 (40%)

*: number of positive values/ total number of values, VL: viral load

Table 5: Viral load, newborn prophylaxis and treatment groups.

	ALL	*MONO-DUAL THERAPY*	*HAART*	*p*
Term (weeks)	38.1±2	38.5±2.4	37.8±1.7	<0.0001
Number of preterm infants (%)	42/292 (14.4%)	19/129 (14.7%)	23/163 (14.1%)	NS
Birth weight (g)	2925±569	2982±622	2872±525	<0.04
AZT dose per Kg per days (mg)	7.7±0.7	7.8±0.7	7.7±0.7	NS
Length of post natal exposure (days)	35.7±8.3	38.6±7.8	33.3±7.8	<0.0001
AZT (%)	217/307 (71%)	86/136 (63%)	131/171 (77%)	NS
AZT+3TC*, ** (%)	54/307 (18%)	37/136 (27%)	17/171 (10%)	0.001
AZT + NVP*** (%)	36/307 (12%)	13/136 (10%)	23/171 (13%)	NS

*: 28 patients included in the ANRS075 study (see text);
**: 1 child received AZT+3TC+LPV;
***: 10 mother-child pairs included in the pACTG316-ANRS083 study (nevirapine arm; see text)

Table 6: Newborns' characteristics.

Patients	*1*	*2*	*3*	*4*
Group	Mono Dual therapy	Mono Dual therapy	HAART	Mono Dual therapy
Sex	M	F	F	F
Year of birth	1996	1997	1998	2005
Maternal age (years)	31.8	34.9	39	33.4
Maternal CD4 T-cells count (/ml)	98	64	3%*	540
Maternal viral load (c/ml) [log10]	Unknown	340.000	880.000	400
		[5.53]	[5.94]	[2.6]
Maternal treatment	AZT	AZT+3TC	AZT+3TC+NFV	AZT+3TC
Maternal mode of contamination	IVDU	Sexual	Sexual	Sexual
Mode of delivery	Vaginal	Vaginal	Elective caesarean	Elective caesarean
Co-infection	HCV	No	No	No
Children prophylaxis	AZT	AZT+3TC	AZT+3TC	AZT
Birth term (weeks)	42.9	40.1	39	38
Birth weight (g)	3,300	3,700	1,900	3,270

*: no absolute count available
IVDU : intravenous drug user, AZT : azidothymidine, 3TC : lamivudine, NFV : nelfinavir

Table 7: Four infected children's characteristics.

birth was similar (around 15%). The birth weight was significantly lower in the HAART group with an average difference of approximately 100 grams. There was no significant difference in the frequency of neonatal complications among the two groups (18/136 events in the mono-dual therapy group and 25/175 in the HAART group). Neonatal respiratory distress syndrome was observed in 20 patients, 14 were small for gestational age and 5 suffered from ventricular septal defect. One newborn needed surgical correction for diaphragmatic hernia, another for gastroschisis. Three newborns were hospitalized for a severe withdrawal syndrome.

Seventy percent of the newborns received AZT monotherapy as prophylactic post exposure treatment with no difference between groups (Table 6). AZT + lamivudine combination was significantly less administrated in the HAART group. Thirty six newborns received AZT + nevirapine. This dual therapy was prescribed at the same frequency in the two groups. In July 2004, AZT treatment was shortened from 6 to 4 weeks. Neonatal prophylaxis is summarized in Tables 5 and 6. During the mono dual therapy era, most of the children with undetectable maternal viral load received AZT alone while most of the newborns with maternal viral loads higher than 1,000 copies/ml received a reinforced combination of antiretroviral drugs. In the HAART group, among the children from mothers with high level of viral replication, less than 50% received post exposure combination therapy.

At birth, the haemoglobin level did not differ between the 2 groups (mono dual therapy group: 9.2 mmol/L ± 1.22; HAART group: 9.2 mmol/L ± 1.3). However, the mean corpuscular volume was significantly lower in the HAART group than in the mono dual group (115 µ3 ± 13.7 versus 120.5 µ3 ± 8.9; p = 0.0001). The total leukocytes count was also significantly lower in children exposed to combination therapy in utero (11,610 ± 4,233 versus 13,470 ± 5,026 per ml in the mono dual therapy group, p <0.003).

Four of the 311 children born from HIV-1 seropositive mother were infected (transmission rate: 1.3%); one in the HAART therapy group and 3 in the mono dual group (Table 7). Two mothers had very high viral load levels during the last month of pregnancy. Three mothers had a profound CD4-T cell depletion. One child, born in 2005, was infected though the immuno-virological status of his mother was not alarming. Although no statistical analysis is feasible and that no conclusion can reasonably be drawn, the rate of MTCT were 2.2% (3/136) in the mono dual therapy group and four times lower (1/175 = 0.6 %) in the HAART group.

Discussion

Each year in France, less than 20 children are infected by HIV-1 through MTCT [1,3]. As in most industrialized countries, the MTCT rate is actually less than 1% while in the early 90^{ies} it reached the level of 20% [4,11]. Our single institutional study aimed to analyze our practice based on the French national guidelines in the management of the HIV-1 mother-child pairs during the past 15 years.

We observed significant changes in the mothers' profiles. Mothers in the HAART group were older at the time of their pregnancy. This trend was also found in the French Perinatal Survey [11]. The hypothesis of a "late planned pregnancy" to minimize the risk of transmission may partly explain this difference. Furthermore this trend is not specific to HIV seropositive women [12]. The main route of maternal contamination in our cohort was sexual. We found a significant reduction of contamination by intra venous drug abuse, as observed in the UK - Irish cohort published in 2008 [13].

The therapeutic strategy to limit MTCT has dramatically changed over time [14-18]. The prescription of HAART to pregnant mothers has demonstrated its effectiveness in the reduction of viral load [15,16], its safety [15] and therefore, a significantly reduced transmission rate of HIV [1,3,15,18]. We observed a significant decrease of maternal viral loads measured at the end of the pregnancy over the study period (figure 2). At the same time, the rate of mothers with undetectable PCR-RNA at delivery increased from 20% during the period of mono dual therapy to more than 60% during the HAART era. More surprisingly, the mean maternal CD4 T-cell count measured in the last trimester of pregnancy remained stable over the two periods (figure 3). This underlines and confirms that the main rule in the MTCT challenge today remains to obtain and to maintain an undetectable viral load in late pregnancy [3].

We did not find a higher frequency of adverse events in pregnant women receiving HAART combination compared to those under mono-dual therapy. The overall prevalence of gestational diabetes

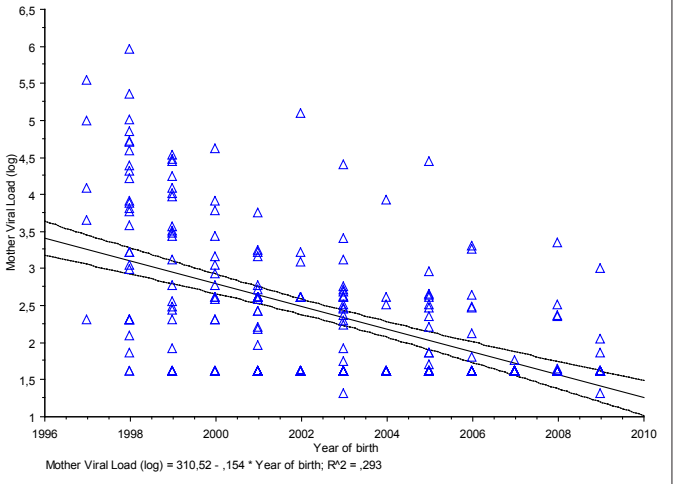


Figure 2: Evolution of the mother mean viral load measured in the last month of pregnancy during the follow-up period.

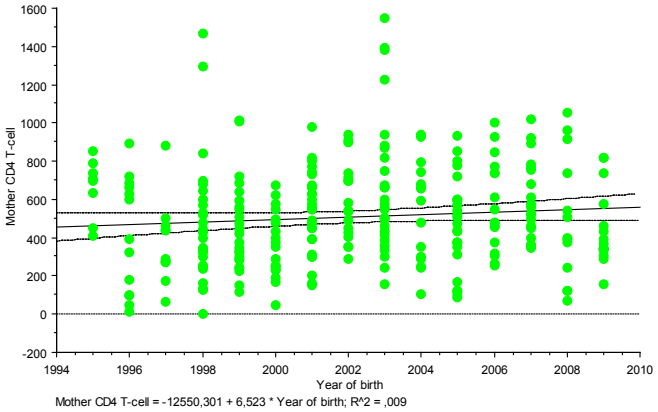


Figure 3: Evolution of the mother mean CD4 T-cell count measured in the last month of pregnancy during the follow-up period.

mellitus that we observed (2.9%) was not significantly different in both groups and far lower than those reported by a Spanish team who found prevalence approximately 7% in a similar cohort [19]. There was no significant difference regarding frequency of neonatal complications identified in each group. Our findings were similar to those found in cohorts from other studies [11,17,18,20]. Birth weight was lower in the HAART group. It is likely that this difference is related to a significantly lower gestational age in this group. However, we cannot rule out the fact that this difference, already reported in the literature, may be the consequence of maternal treatment with combination therapy [21]. The prematurity rate is similar in both treatment groups (approximately 15%). This is almost two times more than the overall rate for the French population, which is approximately 9% [22]. This prevalence is similar to that reported in the London study [23], and lower than the observations of a US study [24]. The US study reported a prematurity rate of 22% in newborns from HIV seropositive mothers receiving PI.

The frequency of elective caesarean section is nearly two times more in the HAART group compared to the mono-dual therapy group. The protective effect of this route of birth was initially demonstrated in 1999 [14]. However, it is now considered that it brings no significant advantage in HAART-treated women when viral replication is controlled [3,25]. Nevertheless in our cohort, 20% of the seropositive pregnant patients from mono dual therapy group and 50% of the HAART-patients underwent elective caesarean section despite undetectable viral loads.

Zidovudine (AZT) is the most widely worldwide prescribed drug in infants for the prevention of HIV-1 MTCT worldwide [1,3]. All children in our study received AZT. A single dose of nevirapine was added for 36 newborns (due to the inclusion in the ACTG316 - ANRS083 study for 10 of them) [6]. The ACTG316 - ANRS083 study was a phase III international randomized trial designed to test the effectiveness of the addition of nevirapine in the reduction of MTCT. It failed to demonstrate superiority of this strategy in industrialized countries, but seems to be beneficial in developing countries [1,26].

According to the most recent French national guidelines, child post exposure prophylaxis should be intensified if the mother's viral load is higher than 1,000 copies/ml [3]. In our population, 55 children were born from mothers with high viral load. Among these children, 19 (54.2%) received AZT alone instead of multi drug combination. Only 1 newborn out of 311 received reinforced post exposure prophylaxis including a PI. Our main reason was the difficulty of using PI in newborns, namely due to pharmakodynamics particularities [3]. Although these molecules prevent mature HIV protein formation within cells in which the HIV is already integrated, the biological rationale for use of a PI as post exposure prophylaxis in MTCT is questionable [27]. We therefore considered that the risk-benefit ratio did not plead in favour of using this therapeutic strategy.

In newborns treated with AZT during the neonatal period, we observed hematologic toxicity mainly on the granulocyte lineage. Toxicity was more severe in the group of children exposed *in utero* to HAART. Nucleoside analogues (mainly AZT) are most often incriminated [2,7]. This toxicity on non-erythroblast lineage extends several months after birth [28]. Therefore, we decided shortly after the publication of these data to reduce the duration of postnatal exposure to treatment from 6 to 4 weeks. Furthermore this drugs class has been also involved in the occurrence of mitochondrial cytopathy [29]. Protease inhibitors have a low placental transfer and are theorically not involved in hematological toxicity [2].

Four children were infected during the past 15 years in Nice (1.3% of children born from HIV-1 seropositive mother). Three presented with one or more risk factors recently identified by the French national survey. These factors are lack of compliance, obstetric complications (particularly preterm birth) and/or delayed treatment [3,30]. The last infant did not exhibit any particular risk factor according to the French national survey. This situation corresponds to the "residual" risks of contamination on which our efforts and vigilance should now focus [31].

Conclusions

The management of newborns from HIV-1 seropositive mothers has changed significantly over the last fifteen years. This study reports the results of HIV MTCT prevention in a wide population of children born over the last 15 years and followed in a single institution. It provides additional evidence to confirm the efficacy and safety of the national recommended strategies during pregnancy (including the use of HAART) and neonatal period. The use of AZT monotherapy during pregnancy initiated in the mid-90s, and whose effectiveness on the HIV MTCT is proven, has now been widely replaced by HAART. Elective caesarean delivery remains essential only when control of viral replication is not optimal and / or compliance to antiretroviral treatment is poor. Nowadays, these strategies have reduced the risk of transmission under 1%. Future studies should focus on infected newborns in order to identify the residual risk factors that could explain failures. Recent published data have shown that the length of undetectable viral load and the duration of optimal antiretroviral strategy play a crucial role. Also, other variables such as the possibility to reduce the foetus/children's exposure to antiretroviral drugs in order to limit their potential toxicity while maintaining the effectiveness of prophylaxis should be considered.

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To all mother-infant pairs

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