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.

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].

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

| Year | 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 |
|------|--------------|-----------------------------------------------|------------------------------------------------------|--------------------------------------------|----------------------------------|------------------------------------------|------------------------|------------------------|
| 1996 | Start AZT on the 14th week of pregnancy | Start AZT or AZT+3TC on the 14th week of pregnancy | If maternal VL<10,000 c/ml, AZT + Efavirenz if maternal VL>10,000 c/ml : HAART | Start HAART at the beginning of 3rd trimester of pregnancy | Start HAART at 28 WA, or before 20 WA if risk of prematurity | Start HAART before 28 WA, or before 20 WA if risk of prematurity | = 2008 |
| 2002 | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who | Treatment regimen during pregnancy for women who |
| 2004 | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy | Women who weren’t treated before pregnancy |
| 2006 | No recommendation | No recommendation | No recommendation | No recommendation | No recommendation | No recommendation | No recommendation | No recommendation |
| 2008 | Route of delivery | Route of delivery | Route of delivery | Route of delivery | Route of delivery | Route of delivery | Route of delivery | Route of delivery |
| 2010 | Treatment during delivery | Treatment during delivery | Treatment during delivery | Treatment during delivery | Treatment during delivery | Treatment during delivery | Treatment during delivery | Treatment during delivery |
| 1996 | Intravenous AZT | Intravenous AZT | Intravenous AZT | Intravenous AZT | Intravenous AZT | Intravenous AZT | Intravenous AZT | Intravenous AZT |
| = 1996 | = 1996 | = 1996 | = 1996 | = 1996 | = 1996 | = 1996 | = 1996 | = 1996 |

1: Exclude Dideoxycytidine 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 amenorrhoea, ECS: Elective caesarean section, WA: weeks of amenorrhoea, NVP: nevirapine, NFV: nelfinavir, LPV: lopinavir/low dose ritonavir

Figure 1: Evolution of maternal treatments during the follow-up period.
by drug abuse decreased steadily all along the observation period so mothers as reported elsewhere [10]. The proportion of women infected was sexual. Three women were themselves born from HIV-1 seropositive mono-dual therapy group. The main route of maternal contamination the HAART group were approximately 2 years older than those in the 222 mothers.

Four twin pregnancies were observed, these 311 infants corresponded to the study period [9] (twice for 36 of them and 3 times for 3 others) and 175 in the HAART group. As 39 women gave birth several times during i.e. 311 infants, were included, 136 in the mono-dual therapy group, (pregnancy conducted under multi-therapy with a fusion inhibitor), 1 seropositive mothers at Nice University Hospital. All but one performed with Statview software version 5.0 for Windows.

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, 

| Treatment groups | Viral load Copies per ml | Newborn prophylactic group |
|-----------------|--------------------------|----------------------------|
| Mono-Dual therapy (136) | VL<400 (20/166) AZT+3TC or AZT+NVP | 31/136 (23%) |
| VL<1000 | AZT alone | 7/35 (20%) |
| (35/88) AZT+3TC or AZT+NVP | 28/35 (80%) |
| VL>400 | AZT alone | 105/136 (77%) |
| HAART (166) | AZT+3TC or AZT+NVP | 8/20 (40%) |
| VL>1000 | 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 |
|------|------------------|-------|---|
| 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 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%) |
| | Mono-Dual therapy | 92/167 (55%) |
| | HAART | 35/167 (21%) |
| | 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.

| 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 postnatal exposure (days) | 35.7±8.3 38.6±7.8 33.3±7.8 | <0.0001 |
| AZT (%) | 217/307 (71%) 88/136 (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.

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), nephrothiatis (n: 2), pulmonary pneumocystosis infection (n: 1) and retro-placental haemato ma (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 retardation (n: 1) and retro-placental haematoma (n: 1).

Table 2: Mothers’ demographic data Maternal characteristics.

| MaternalCD4 T-cell count (i/ml) | Mono-Dual therapy | HAART | p |
|--------------------------------|------------------|-------|---|
| Median of the periods | 509 ± 266 538 ± 281 484 ± 252 | NS |
| Maternal viral load (log10) | 2.36 ± 1 2.65 ± 1.05 2.1±0.83 | <0.0001 |
| Undetectable viral load (400 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 5: Viral load, newborn prophylaxis and treatment groups.
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 90s 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 role 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
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 twice more times 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 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 pharmacodynamics 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 theoretically 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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