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ORIGINAL PAPER

Vertical transmission of HIV in Belgium: a 1986–2002 retrospective analysis

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Abstract Prophylactic interventions have lead to the reduction of the mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 (HIV-1) to less than 2% in industrialized countries. The aim of this study was to evaluate the changes over time in vertical transmission according to the standard care of prophylaxis in the practice of a single large reference center and to identify the risk factors for failure. The rate of MTCT decreased progressively from 10% in 1986–1993 to 4.7% in 1999–2002, reflecting the progressive implementation of newly available means of prevention. During the last period evaluated (1999–2002), where highly active antiretroviral therapy (HAART) prophylaxis was the standard of care, 17% of women had a viral load between 400 and 20,000 copies/ml around delivery and 5% had a viral load above 20,000 copies/ml. High viral load and low CD4 lymphocyte count were strongly associated with vertical transmission. The rate of MTCT in women who received HAART for more than one month during pregnancy was 1.7%, compared to 13.3% in women treated with HAART for less than one month. The risk of vertical transmission in the absence of therapy was four times higher than before the era of antiretroviral therapy (ART; p=0.05). In conclusion, since the prevention of MTCT of HIV with HAART is the standard of care, a short duration or absence of ART during pregnancy linked to late or absent prenatal care is associated with a high risk of transmission. The early detection of HIV-1 infection in pregnant women, and close follow up and support during pregnancy are crucial to the success of the prevention of transmission.

Keywords Vertical transmission · HIV infection · Pregnancy · Mother-to-child transmission

Abbreviations

MTCT	Mother-to-child transmission
HIV	Human immunodeficiency virus
ZDV	Zidovudine
HAART	Highly active antiretroviral therapy
ART	Antiretroviral therapy
CDC	Centers for Disease Control and Prevention
PCR	Polymerase chain reaction
OR	Odds ratio
CI	Confidence interval

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Introduction

Without any prophylaxis, the mother-to-child transmission (MTCT) rate of the human immunodeficiency virus type 1 (HIV-1) varies from 12 to 20% in industrialized countries, but reaches 35 to 40% in Africa, where breast-feeding is the norm [10, 17].

Formula feeding was the first measure proposed to reduce the exposure of the newborn to the virus. In 1994,

the efficacy of zidovudine (ZDV) given to the mother during pregnancy and delivery and to the newborn has been demonstrated to reduce MTCT [2]. In 1998, elective cesarean section has been recommended as an additional effective measure [6, 10, 11, 13]. Since 1996, the administration of highly active antiretroviral therapy (HAART) to HIV-infected pregnant women has been progressively generalized in industrialized countries. The combination of these preventive measures have lead to the reduction of MTCT to less than 2% [1, 12].

Between 1986 and 2002, 361 singletons babies born to HIV-infected mothers were followed up from birth in our center. During this period of time, the measures to prevent vertical transmission were made a part of standard care at the time they were implemented in most industrialized countries. This retrospective cohort study was conducted to evaluate the changes over time in the vertical transmission rates.

Methods

This is a retrospective cohort study on vertical transmission in infants born to HIV-1-infected mothers over the period 1986–2002.

Study population

All 361 singleton babies born alive between 1986 and 2002 from an HIV-1-infected mother and followed up since birth in our center were included in this study; eight twin pairs were excluded.

As the prophylactic measures used changed over time, we divided the whole group into three birth cohorts:

- Births between 1986 and 1993 (cohort 86–93): preventive measures included obstetrical interventions to shorten the duration of membrane rupture and the exposure of the newborn to the mother's blood and vaginal secretions, together with the avoidance of breast-feeding.
- Births between 1994 and 1998 (cohort 94–98): in addition to the above, ZDV was given to the mother during the last trimester of pregnancy, intravenously during delivery and orally to the infant over the first 6 weeks of life. During a short period of time (October 1997 to 1998), the combination of ZDV and lamivudine was used in newborns.
- Births between 1999 and 2002 (cohort 99–02): the recommendation to perform an elective cesarean section at 38 weeks of gestation was introduced for all pregnancies and HAART was given during (at least) the last trimester of pregnancy.

Data collection

The following data were abstracted from the mothers' medical records: ethnicity, parity, maternal age at delivery, time of maternal HIV diagnosis (before pregnancy, during pregnancy, or at delivery), type, and duration of maternal antiretroviral therapy (ART) regimen, viral load, CD4 lymphocyte count and maternal CDC stage at delivery. The obstetrical data included: date, mode of delivery, gestational age, episiotomy, and time between rupture of the amniotic membranes and delivery. The data from the newborns included: birth weight and diagnosis of HIV infection. Before 1994, viral culture and the persistence of HIV-1-specific antibodies after the age of 18 months were used to establish HIV infection in children, but since 1994, the diagnosis of HIV infection is based on the detection of proviral HIV DNA and/or by the determination of plasma HIV RNA viral load in two separate blood samples (Amplicor method).

Outcome

The main outcome was the MTCT of HIV. Secondary outcomes were preterm birth (<37 weeks of gestation) and low birth weight (<2,500 g).

Statistical analysis

We computed the risk of vertical transmission of HIV and the risk of preterm birth according to maternal characteristics, preventive measures used, and period. We used logistic regression modeling to estimate the adjusted odds ratios (ORs) for the associations of different interventions implemented during pregnancy with the outcomes. Among 361 pregnancies, 34 were second and four were third consecutive pregnancies to the same mother in the cohort; they were considered as independent events. As data are often missing for the first period (1986–1993), some analyses only included the last two periods.

Statistical significance was assigned by a two-sided alpha level of 0.05. All p-values are two-tailed. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL).

Results

The distribution of the maternal characteristics of the 361 infants included in the study, divided into the time cohorts, is shown in Table 1. Most of the mothers were of sub-Saharan African origin and had acquired HIV heterosexually. Maternal age and the proportion of non-European mothers increased over time.

Table 1 Maternal characteristics according to birth cohort

	Cohort 86–93 *n*=100	Cohort 94–98 *n*=111	Cohort 99–02 *n*=150	
	n (%), mean (standard deviation)			*p*-value
Maternal age (years)	27.6 (4.7)	29.5 (4.4)	30.7 (5.5)	<0.001
Parity				
One	16 (21.3%)	30 (28.0%)	50 (33.3%)	
Two to three	41 (54.7%)	50 (46.7%)	82 (54.7%)	
Four or more	18 (24.0%)	27 (25.2%)	18 (12.0%)	0.03
Non-European mother	61 (69.3%)	86 (79.6%)	124 (84.9%)	0.02
Time of maternal HIV diagnosis				
Before pregnancy		52 (50.5%)	88 (58.7%)	
During pregnancy		48 (46.6%)	57 (38.0%)	
During delivery	NA	3 (2.9%)	5 (3.3%)	0.38*
Maternal CDC stage at delivery				
A		90 (88.2%)	98 (66.7%)	
B		6 (5.9%)	39 (26.5%)	
C	NA	6 (5.9%)	10 (6.8%)	<0.001
Viral load at delivery (copies/ml)				
≤400			114 (78.1%)	
401–20,000			25 (17.1%)	
>20,000	NA	NA	7 (4.8%)	–
CD4 at delivery <100 cells/ml	NA	5 (5.6%)	1 (0.7%)	0.03*
CD4 at delivery (cells/ml)[£]	NA	450 (6–1,515)	412 (90–1,656)	0.31

*Exact test
[£] Median (min–max) and Mann-Whitney test
NA=not available

Risk of vertical transmission

Table 2 describes the outcomes for each birth cohort according to the preventive measures other than avoiding breast-feeding. None of the mothers had ART given during pregnancy between 86–93, whereas, respectively, 86% and 95% of the 94–98 and 99–02 cohorts received antiretroviral prophylaxis. Over the whole period, vertical transmission occurred in 26 of the 361 infants. There was a progressive decline, although not significant, in the risk of vertical transmission between cohort 86–93 and cohort 99–02. A subgroup analysis of the women who did not receive ART during pregnancy showed a strong linear increase over time in the risk of vertical transmission: the risk was 10/100 (10.0%; 95%CI: 4.9%–17.6%) in the 86–93 cohort, 3/16 (18.8%; 95%CI: 4.0%–45.7%) in the 94–98 cohort, and

Table 2 Preventive measures and outcomes distribution according to birth cohort

	Cohort 86–93 *n*=100	Cohort 94–98 *n*=111	Cohort 99–02 *n*=150	*p*-value
Type of ART regimen during pregnancy				
No ART	100 (100%)	16 (14.4%)	8 (5.3%)	
Mono or dual therapy	0 (0%)	94 (84.7%)	11 (7.3%)	
Triple or quadruple therapy	0 (0%)	1 (0.9%)	131 (87.3%)	<0.001[§]
More than one month of ART during pregnancy	0 (0%)	58 (59.8%)	122 (81.3%)	<0.001[§]
Elective cesarian section	8 (8.7%)	37 (33.9%)	89 (59.7%)	<0.001
Less than 4 h between rupture of the amniotic membranes and childbirth	19 (57.6%)	75 (75.8%)	130 (87.8%)	<0.001
Episiotomy	19 (27.9%)	11 (10.1%)	8 (5.4%)	<0.001
Vertical transmission	*10 (10.0%)*	*9 (8.1%)*	*7 (4.7%)*	*0.10**
Gestational age at birth <37 weeks	12 (12.0%)	13 (11.7%)	20 (13.3%)	0.91[£]
Birth weight <2,500 g	13 (13.5%)	14 (12.6%)	20 (13.3%)	0.98[£]

*Test for linear trend
[£] Pearson chi-square
[§] *p*-value for the comparison between cohort 94–98 and cohort 99–02

reached 3/8 (37.5%; 95%CI: 8.5%–75.5%) in the 99–02 cohort. Between 1999 and 2002, seven of the 150 infants were infected (4.7%; 95%CI: 1.9%–9.4%): three were born to mothers who did not receive ART prophylaxis because HIV diagnosis was made at delivery, two were born to mothers who received HAART for less than one month, and two to mothers who received HAART for more than one month during pregnancy.

High viral load and low CD4 lymphocyte count were strongly associated with vertical transmission. In the last cohort, among the seven mothers with a viral load >20,000 copies/ml around the time of delivery, two infants were infected, compared with four infants (3%) born to 139 mothers who had a viral load <20,000 copies/ml (risk ratio [RR]: 9.9; 95%CI: 2.2–45.3; p=0.027). In the period 94–02, among six mothers who had CD4 lymphocyte count <100 cells/ml, three transmissions occurred, compared with 11/229 (5%) among the mothers with a higher level of CD4 (RR: 10.4; 95%CI: 3.9–27.9; p=0.003).

Table 3 shows the associations between the type and duration of prophylaxis during pregnancy, obstetrical characteristics, and the risk of MTCT. The lowest risk of vertical transmission (1.7%; 95%CI: 0.2%–6.1%) was observed for mothers who received HAART for >1 month during pregnancy. Among the women who received prophylaxis, the risk of vertical transmission was greater when HAART was administered for <1 month as compared to >1 month (adjusted OR=6.7). Women who received a mono or a dual therapy for >1 month during pregnancy had a higher risk of transmission compared with those who received HAART for >1 month (adjusted OR=2.5), but this difference was not statistically significant. Performing an episiotomy was not a risk factor of vertical transmission after adjustment for treatment.

Table 4 shows the characteristics of mothers and pregnancies where vertical transmission occurred despite ART prophylaxis administered for >1 month during pregnancy. In the last three infants, the transmission occurred most probably during delivery, since the first polymerase chain reaction (PCR) obtained at birth was negative. The first mother was severely immunodepressed and reported a poor adherence to treatment and the second received ZDV only during the third trimester. The last two mothers had detectable viral load on delivery.

Risk of preterm delivery

Table 5 shows the association between the type and duration of ART prophylaxis during pregnancy and preterm delivery. Since the introduction of ART, mothers remaining untreated during pregnancy were more likely to be diagnosed late or to deliver prematurely. Therefore, the reference group we used was the group of women treated with mono or dual therapy.

The risk of preterm delivery (<37 weeks) was higher for women who received HAART and for untreated women compared to women who received mono or dual therapy. Interestingly, this risk was higher in women treated with HAART for <1 month compared to women treated with HAART for a longer duration. Among the women treated for >1 month, HAART was associated with low birth weight (<2,500 g) (adjusted OR: 1.4; 95%CI: 0.4–4.6 for

Table 3 Crude and adjusted odds ratio (OR) for the risk of vertical transmission according to the type and duration of antiretroviral therapy (ART) during pregnancy and according to obstetrical characteristics (1994–2002)

	Infected infants, *n* (%)	Crude OR (95%CI)	*p*-value*	Adjusted[£] OR (95%CI)	*p*-value*
Type of ART					
None	6/24 (25.0%)	19.0 (3.6–101.5)		25.9 (3.5–190.8)	
Mono or dual therapy ≤1 month	3/28 (10.7%)	6.8 (1.1–43.1)		6.7 (0.8–58.4)	
Mono or dual therapy >1 month	2/64 (3.1%)	1.8 (0.3–13.4)		2.5 (0.3–20.0)	
Tri or quadri-therapy ≤1 month	2/15 (13.3%)	8.8 (1.1–67.6)		6.7 (0.7–59.7)	
Tri or quadri-therapy >1 month	2/116 (1.7%)	1.0	0.004	1.0	0.02
Mode of delivery					
Vaginal delivery with episiotomy	2/19 (10.5%)	2.0 (0.4–10.4)		0.8 (0.1–11.0)	
Vaginal delivery without episiotomy	4/78 (5.1%)	0.9 (0.3–3.2)		0.4 (0.1–2.4)	
Emergency cesarean section	3/33 (9.1%)	1.7 (0.4–7.0)		1.7 (0.3–9.1)	
Elective cesarean section	7/126 (5.6%)	1.0	0.73	1.0	0.57
Duration between rupture of the amniotic membranes and childbirth					
<4	12/205 (5.9%)	1.0		1.0	
≥4	4/42 (9.5%)	1.7 (0.5–5.5)	0.38	1.4[£] (0.3–6.7)	0.65

OR=odds ratio; CI=confidence interval

*Wald test

[£] Adjusted for age, parity, ethnicity, and other variables presented in the table (duration between rupture of the amniotic membranes and childbirth was not entered in models simultaneously with the mode of delivery because of colinearity)

Table 4 Characteristics of mothers and pregnancies where vertical transmission occurred despite ART prophylaxis being administered for longer than 1 month during pregnancy

Year of birth	Age (years)	Ethnicity	Parity	BF	HIV diagnosis	On delivery			Treatment		Compliance	BF	Delivery mode	First PCR	GA (weeks)
						CDC	VL	CD4	During pregnancy	On delivery					
1994	29	A	1	no	before P	C3	NA	18	ZDV 2nd and 3rd trimester	–	poor	no	ECs	NA	36
1996	30	E	1	no	during P	A1	NA	814	ZDV 3rd trimester	ZDV IV	good	no	VD	neg	41
1999	37	A	1	no	before P	B2	2,400	242	HAART 2nd and 3rd trimester	ZDV IV	good	no	ECs	neg	38
1999	40	A	3	no	during P	A2	19,900	397	HAART 3rd trimester	ZDV IV	poor	no	ECs	neg	38

A=African; E=European; P=pregnancy; VL=viral load; GA=gestational age; BF=breast-feeding; ECs=elective cesarean section; VD=vaginal delivery; NA=not available

HAART compared with mono or dual therapy). These associations, however, were not statistically significant.

Discussion

Since the introduction of antiretroviral prophylaxis during pregnancy, the rate of MTCT of HIV has dramatically decreased in developed countries. In 1994, the PACTG076 study showed that ZDV given to the mother during pregnancy, delivery, and to the newborn could reduce the risk of transmission from 25% to 8% [2]. By 1996, combination ART progressively became the standard of care for the prevention of MTCT. In recent studies, the transmission was shown to be reduced to <2% in mothers treated with HAART [3, 5]. Our study aimed primarily at reviewing the impact of prophylactic measures on vertical transmission in a single reference center cohort of infants born to HIV-1-infected mothers between 1986 and 2002.

The decrease in the vertical transmission rate from 10% in 1986–1993 to 4.7% in 1999–2002 reflects the progressive implementation of newly available means of prevention. Whilst the transmission rate is 4.7% globally for the cohort in the era of HAART, it is lower than 2% in women who received HAART for more than one month during pregnancy.

The timing of the diagnosis has an obvious impact on the feasibility of implementing prophylactic measures to reduce MTCT. During the period 94–02, 43% of the women were diagnosed with HIV infection during pregnancy or at delivery, and 24/261 (9%) had no antenatal ART prophylaxis: the MTCT rate in this small group of patients was 25%. The risk of vertical transmission in untreated women in the era of HAART was four times higher than in the group of mothers followed before 1994 (p=0.05). This suggests that factors such as late diagnosis during pregnancy, poor antenatal care, insufficient implementation of preventive interventions associated or not with social

Table 5 Risk of preterm birth (<37 weeks) according to the administration of ART during pregnancy (1986–2002)

	n (%)	Crude OR (95%CI)	p-value*	Adjusted OR§(95%CI)	p-value*
Type of treatment during pregnancy					
None	15 (12.1%)	1.3 (0.6–3.0)		1.4 (0.5–4.2)	
Mono or dual therapy	10 (9.5%)	1.0		1.0	
Tri or quadri-therapy	20 (15.2%)	1.7 (0.8–3.8)	0.43	2.5 (1.0–6.5)	0.15
Duration of ART during pregnancy					
None	15 (12.1%)	1.8 (0.4–8.3)		2.2 (0.3–19.1)	
Mono or dual therapy ≤1 month	2 (7.1%)	1.0		1.0	
Mono or dual therapy >1 month	6 (9.4%)	1.4 (0.3–7.1)		1.4 (0.1–13.4)	
Tri or quadri-therapy ≤1 month	6 (40.0%)	8.7 (1.5–50.9)		10.1 (1.0–103.2)	
Tri or quadri-therapy >1 month	13 (11.2%)	1.6 (0.4–7.7)	0.04	3.1 (0.4–25.9)	0.08

OR=odds ratio; CI=confidence interval
*Wald test
§Adjusted for age, parity, and ethnicity

precarity play a significant role in vertical transmission. The duration of prophylaxis appeared to play a crucial role in its effectiveness. Among the mothers treated with HAART for <1 month, 13.3% transmitted HIV to their newborn compared with 1.7% in mothers treated for >1 month. Among the women receiving ART for >1 month during pregnancy, those who received a mono or a dual therapy tended to have a higher risk of vertical transmission (3.1%) compared to the women who received HAART (1.7%). Due to the lack of power, this difference was not significant, but it persisted after adjustment for other obstetrical interventions, which indicates that it does not only reflect a more systematic implementation of these preventive interventions in the era of HAART.

In agreement with other studies, we showed that MTCT was correlated with high maternal viral load and low CD4 count at delivery [5, 16]. In our cohort, the rate of transmission was similar in elective cesarean section and in vaginal delivery without episiotomy (6% and 5%, respectively). Current guidelines no longer propose cesarean section in mothers with undetectable viral load [9].

Several studies have suggested that the use of HAART during pregnancy was associated with the increased risk of preterm birth [4, 7, 14], although others could not confirm this observation [15]. We found that HAART administered for a short duration was associated with a higher risk of preterm birth, which could either reflect the lower opportunity of women who deliver preterm in receiving treatment, or represent an acute side-effect of HAART in a subsample of women. Among the women treated for longer periods, the differences between premature delivery between the mother receiving HAART and the mother receiving mono or dual therapy was not significant, and this might possibly be due to lack of the power due to the small sample size. Obviously, there are other maternal factors known to be associated with preterm delivery, including ethnicity, socio-economic factors, illicit drug use, poor quality of the obstetrical follow up, or poor clinical status of the mother. In our cohort, most women were of African origin and living in poor socio-economic situations. The rate of premature birth in this population in Brussels is known to be higher than in the general population (9.7% vs. 7.4%) [8].

In conclusion, HAART given during pregnancy, together with other preventive measures, allows us to dramatically decrease the MTCT of HIV. However, transmission still occurs at a high rate in the subgroup of women who miss the opportunity to benefit from these interventions because of a late diagnosis of HIV infection or poor antenatal care.

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