

Is Intrapartum Intravenous Zidovudine still Beneficial to Prevent Mother-to-child HIV-1 Transmission ?

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ABSTRACT

Background
An annual residual mother-to-child HIV-1 transmission (MTCT) rate of 1 to 2% persists in the French Perinatal Cohort. Although MTCT was high among women who did not receive antiretroviral therapy (ART), 96% of HIV-1-infected women, enrolled in the period 1997-2002, received ART during their pregnancy and accounted for 80% of the cases of MTCT. The objective of this study was to identify factors associated with HIV-1 transmission among treated women.

Methods
HIV-1 infected women delivering between January 1, 1997 and December 31, 2002 in the 77 sites of the French Perinatal Cohort were included for this analysis if they received ART during pregnancy and did not breast-feed (n=3711).

Results
MTCT was strongly correlated with late access (third trimester) to obstetrical center (p<0.01), with high plasma HIV-1-RNA (≥1000) closest to the delivery (p<0.01) and with preterm (before 37 weeks) delivery (p=0.03). MTCT occurred in 2.8% (13/458) of premature infants versus 1.3% (43/3253) of full-term infants. Among full-term infants, the rate of MTCT was 0.7% (13/2150) if the mothers HIV-1-RNA was less than 1000 c/ml and was 3.0% (30/984) if the mothers HIV-1-RNA was greater than or equal to 1000 c/ml. In the latter case, the lack of intrapartum prophylaxis was significantly associated with a higher risk of transmission after adjustment, in a logistic regression, for maternal viral load (≥10,000 versus 1000-10,000), mode of delivery, duration of antenatal ART, last combination of ART (monotherapy, dual-drug therapy, or HAART), type of neonatal prophylaxis (zidovudine alone or with another NRTI, single dose nevirapine), and maternal geographic origin: adjusted OR = 3.1 (95% CI: 1.0-9.5). Intrapartum prophylaxis was intravenous zidovudine exclusively in most cases, or associated with single dose nevirapine (7%). Only 5% of women did not receive any intrapartum prophylaxis.

Conclusion
MTCT increased with late access to obstetrical center, duration of antenatal ART, maternal viral load, and preterm delivery. In full term neonates born to treated mothers whose last HIV-1-RNA was higher than 1000 c/ml, the lack of intrapartum prophylaxis appeared to be independently associated with a higher risk of MTCT.

INTRODUCTION

Background

In developed countries, the mother-to-child HIV-1 transmission (MTCT) rate has been dramatically reduced by preventive interventions. The benefit of elective caesarean section, intrapartum prophylaxis and type of neonatal prophylaxis remains to be evaluated in the context of HAART era.

Objectives

To identify factors associated with HIV-1 mother to child transmission among women who received antenatal antiretroviral therapy (ART) in the HAART era.

PATIENTS AND METHODS

The French Perinatal cohort (EPF)

- Prospective multicenter national cohort of mothers and infants established since 1986.
- Children examined at birth, 1, 3, 6, 12, and 24 months ; Infected infants followed on a long term basis.

Study population

All HIV-1 women who delivered between January 1997 and December 2002 were included if:

- they received antenatal ART at any moment of the pregnancy,
- they did not breastfeed,
- the child infection status was documented

RESULTS

During the 1997-2002 period :

- HAART increased from 4 % in 1997 to 60 % in 2002
- Low maternal viral load before delivery (<1000 copies/ml) increased from 60% in 1997 to 80% in 2002.
- Nearly one half of treated women delivered by elective caesarean section, 5% received no intrapartum prophylaxis and only 0.3% of neonates did not receive postnatal prophylaxis.
- Intrapartum prophylaxis was intravenous zidovudine exclusively in most cases, and associated with single dose nevirapine in 7% of cases.**

The MTCT rate among women who received antenatal ART was 1.5% (95% CI: 1.1 to 1.9), which contrasts with 15.0% (95% CI: 18.5 to 21.5) among non treated women.

Among ART treated women, the proportion of infected infants was higher in lack of intrapartum prophylaxis, whatever the year of delivery (Fig 1)

RISK FACTORS OF MTCT AMONG WOMEN WHO RECEIVED ANTENATAL ART

(a) Overall, independent risk factors were (Table 1) :

- Low gestational term delivery (< 32 weeks),
- short antenatal ART duration,
- high maternal viral load.

(b) Among full term infants, maternal viral load and late access to the obstetrical center were the main risk factor of MTCT

- The MTCT rate was 3.0% with maternal viral load ≥ 1 000 cp/ml versus 0.6% with maternal viral load < 1000 cp/ml

For MATERNAL VIRAL LOAD < 1 000, no risk factors were identified.

For MATERNAL VIRAL LOAD ≥ 1 000, independent risk factors were (Table 2) :

- late access to the obstetrical center,
- high maternal viral load (≥ 10, 000),
- ART combination before delivery,
- lack of intrapartum prophylaxis

There was a trend towards lower transmission following elective caesarean section (ECS), though the association was not statistically significant.

(1) The association with the lack of intrapartum prophylaxis concerned exclusively women with maternal viral load ≥ 10,000 cp/ml (Table 3) ; the adjusted OR is 3.7 (95% CI: 1.1-12.0).

(2) The paradoxical association with receipt of HAART as last ART concerned exclusively women with maternal viral load ≥ 10,000 cp/ml (Table 3). It may reflect the choice of a more intensive treatment for at risk women.

TABLES - Factors associated with MTCT in ART treated women - EPF 1997-2002

Table 1 – ALL TREATED WOMEN

	UNIVARIATE ANALYSIS			LOGISTIC REGRESSION		
	% of infected infants			HIV child status as dependent variable		
	N	%	p*	ORa **	95% CI	p
TOTAL	3711	1.5				
First visit to obstetrical center						
Third trimester (≥ 28 weeks)	376	2.9	<0.01	2.2	(0.9-5.2)	0.14
Second trimester ([14-28 w [)	1445	2.0		1.7	(0.9-3.3)	
First trimester (< 14 w)	1801	0.9		1		
Duration of antenatal ART by week						
≥ 10 000				0.97	(0.94-0.99)	0.03
Gestational age at delivery, weeks						
< 32	61	9.8	0.03	3.7	(1.2-11.1)	0.06
[32-37[397	1.8		1.3	(0.5-2.8)	
≥ 37	3253	1.3		1		
Viral load (copies/ml)						
≥ 10 000	632	4.4	<0.01	12.1	(5.8-25.1)	<0.01
[1000-10 000[774	1.7		3.1	(1.4-7.0)	
[400-1000[343	0.6		1	(0.2-4.7)	
< 400	2091	0.6		1		
Elective Caesarean section						
No	1976	1.8	0.11	1.5	(0.8-2.7)	0.2
Yes	1709	1.2		1		
Maternal ART at delivery						
HAART	1351	1.7	0.7	1.4	(0.6-3.2)	0.7
Dual-drug therapy	1493	1.3		1.1	(0.5-2.6)	
Monotherapy	805	1.6		1		
Intrapartum prophylaxis						
No	179	3.9	<0.01	1.7	(0.7-4.3)	0.2
Yes	3507	1.4		1		
Neonatal antiretroviral prophylaxis						
Dual-drug therapy	1112	1.7	0.8	1.4	(0.7-2.9)	0.3
Monotherapy	2563	1.4		1		
No or late	23	0.0				
Single dose nevirapine received by neonate						
Yes	388	1.0		0.7	(0.2-2.0)	0.5
No	3310	1.5	0.4	1		

* Chi2 test, exact test or Wilcoxon rank-sum test

** ORa : odds ratios adjusted for variables listed here, geographical origin, and CD4 cell count

Table 2 – FULL TERM INFANTS AND MATERNAL VIRAL LOAD ≥ 1,000 c/ml

	UNIVARIATE ANALYSIS			LOGISTIC REGRESSION		
	N	%	p	ORa *	95% CI	p
TOTAL	984	3.0				
First visit at obstetrical center						
Third trimester (≥ 28 weeks)	121	5.0	<0.01	3.4	(0.9-12.6)	0.04
Second trimester ([14-28 w [)	384	4.9		3.8	(1.3-10.6)	
First trimester (< 14 w)	451	1.1		1		
Duration of antenatal ART by week						
≥ 10 000						
[1000-10 000[0.97	(0.93-1.00)	0.13
Elective Caesarean section						
No	453	4.0	0.13	1.7	(0.7-3.9)	0.2
Yes	524	2.3		1		
Maternal ART at delivery						
HAART	249	6.0		3.2	(1.1-9.8)	0.07
Dual-drug therapy	337	1.8	<0.01	1.3	(0.4-4.7)	
Monotherapy	369	2.4		1		
Intrapartum prophylaxis						
No	54	9.3	0.02	3.1	(1.0-9.5)	0.04
Yes	923	2.7		1		
Neonatal antiretroviral prophylaxis						
Dual-drug therapy	308	3.6		1.4	(0.5-3.6)	0.5
Monotherapy	671	2.8	0.6	1		
Single dose nevirapine received by neonate						
Yes	107	1.9	0.9	0.5	(0.1-2.3)	0.4
No	875	3.2		1		

* Chi2 test, exact test or Wilcoxon rank-sum test

** ORa : odds ratios adjusted for variables listed here, geographical origin, and CD4 cell count

Table 3 – FULL TERM INFANTS AND MATERNAL VIRAL LOAD ≥ 1,000 c/ml

	MATERNAL VIRAL LOAD (copies/ml)					
	[1,000 - 10,000]			≥ 10,000		
	N	%	p*	N	%	p*
Maternal ART at delivery						
Monotherapy	249	1,2	0.9	88	3,4	0,08
Dual-drug therapy	273	1,1		96	6,3	
HAART	137	1,5		112	11,6	
Intrapartum prophylaxis						
No	33	0,0	1	21	23,8	0,02
Yes	641	1,2		282	6,0	

* Chi2 test or Fisher exact test

CONCLUSION

(1) In ART treated women, MTCT increased with short ART duration, maternal viral load, and preterm delivery.

(2) For full term infants born to ART treated mothers:

- The maternal viral load and the late access to the obstetrical center were the main risk factors of MTCT
- No risk factors were identified when maternal viral load was < 1,000 c/ml
- The lack of intrapartum prophylaxis was associated with a higher risk of MTCT when maternal viral load was not well controlled (≥ 10,000 c/ml).

Fig 1 – MTCT according to intrapartum prophylaxis among ART treated women – EPF 1997-2002

