Open access • Journal Article • DOI:10.1097/QAD.0B013E3282F3D63C

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Published on: 11 Jan 2008 - AIDS (AIDS)

Topics: Viral load, Cohort, Population, Prospective cohort study and Cohort study

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TITLE

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Word count: 3495 words / Version: Novembre, 14th, 2007

ABSTRACT

Objective: To identify factors associated with mother-to-child HIV-1 transmission (MTCT) from mothers receiving antenatal antiretroviral therapy.

Design: The French Perinatal Cohort (EPF), a multicenter prospective cohort of HIV infected pregnant women and their children.

Methods: Univariate analysis and logistic regression, with child HIV status as dependant variable, were conducted among 5271 mothers who received antiretroviral therapy during pregnancy, delivered between 1997 and 2004 and did not breastfeed.

Results: The MTCT rate was 1.3% (67/5271 ; 95% confidence interval [CI], 1.0 -1.6). It was as low as 0.4% (5/1338 ; 95% CI, 0.1 - 0.9) in term births with maternal HIV-1 RNA level at delivery below 50 copies/mL. MTCT increased with viral load, short duration of antiretroviral therapy, female gender and severe premature delivery: 6.6% before 33 weeks versus 1.2% at 37 weeks or more ($p<0.001$). The type of antiretroviral therapy was not associated with transmission. Intrapartum therapy was associated with 4-fold lower MTCT ($p=0.04$) in case of virological failure (> 10 000 copies/mL). Elective cesarean section tended to be inversely associated with MTCT in the overall population, but not in mothers who term delivered with viral load < 400 copies/mL (OR: 0.83; 0.29-2.39; $p=0.37$). Among them, only duration of antenatal therapy was associated with transmission (OR by week: 0.94; 0.90-0.99; $p=0.03$).

Conclusions: Low maternal plasma viral load is the key factor for preventing mother-to-child transmission. Benefits in term of MTCT may be expected from early antiretroviral prophylaxis. Potential toxicity of prolonged antiretroviral use in pregnancy should be evaluated.

Key words: HIV, prevention of mother-to-child transmission, epidemiology, cohort, public health

Over the decade following the landmark PACTG076/ANRS024 American-French trial in 1994, a spectacular decrease in mother-to-child transmission of HIV-1 (MTCT) has been obtained in industrialized countries [1]. Transmission rates on the order of 1 – 2% have been reported for several years [2-5]. While these results were first obtained using zidovudine with elective cesarean section, or a combination of zidovudine and lamivudine, the more recent consensus [6, 7] is to use highly active antiretroviral therapy (HAART) for the prevention of transmission, even in women without an indication for themselves. A number of specific considerations concerning the use of such aggressive regimens during pregnancy still need to be addressed, including optimal use of HAART in reducing the risk for perinatal transmission, effects on pregnancy outcome,[8-14] and whether elective cesarean is required in women receiving active therapy who have an undetectable plasma viral load at delivery [4, 12, 15-18]

Our objective was to estimate the MTCT rate and to evaluate the role of the various components of prophylaxis in the HAART era. At the opposite of most of the studies which included mothers who failed to receive any prophylaxis, the large number of mother-child pairs included in the French Perinatal Cohort provided the opportunity to focus on exclusively women who received antiretroviral therapy (ART) during pregnancy, especially with no obvious potential risk factors such as prematurity or virological failure at delivery.

Subjects and Methods

The French Perinatal Cohort (EPF)

Since 1986, the EPF has prospectively enrolled HIV-infected women who delivered in 90 centers throughout France, except in case of parental refusal. Children were followed up according to recommended standards of care [7], including clinical and biologic examination at birth, 1, 3, 6, 12 and 18-24 months, and then every 6 months for infected children, as previously reported [19]. No specific recommendation for HIV treatment and obstetrical care was made for women included in the cohort, although French national guidelines for prevention of MTCT were regularly published and updated[7]. The national policy since 1993 is to offer universal

voluntary HIV testing as a part of prenatal care. Antenatal prophylaxis was initially based on zidovudine monotherapy or on dual nucleosidic therapy since 1997, with elective cesarean section according to risk/benefit evaluation. HAART was recommended to mothers with viral load above 10 000 copies/mL in 2002 and to all mothers in 2004. Since 2002, elective cesarean section was not recommended for those who delivered under HAART with viral load below 400 copies/mL. In all cases, intrapartum zidovudine infusion and neonatal prophylaxis were recommended. This cohort study was approved, according to French laws, by the Hôpital Cochin IRB and the French computer database watchdog commission (Commission Nationale de l'Informatique et des Libertés).

Study population

All HIV-1 infected women who delivered in mainland France EPF sites between January 1, 1997 and December 31, 2004 were included if they met the following criteria: (1) they received at least one antenatal ART at any time during pregnancy (except exclusive intrapartum prophylaxis); (2) they did not breastfeed (99.8% of treated mothers); (3) the child's infection status was documented. Breastfeeding status was recorded during the postnatal hospitalization, and at each protocol visit. An infant was considered as infected if HIV-1 was detected by virologic tests on two separate samples (HIV1-PCR DNA or HIV RNA or PBMC viral culture or p24 antigenemia) or if anti-HIV1 antibodies detected by ELISA and Western Blot persisted after 18 months of age. An infant was considered as non infected if virologic tests were negative on two separate samples, of which at least one taken after termination of the neonatal prophylactic treatment or if serological testing was negative after 18 months. Laboratory tests were done on sites. HIV-1 RNA quantification in plasma were assessed by either the Roche Amplicor Monitor Test version 1.5 (Roche Diagnostic Systems, Basel, Switzerland) or branched DNA (Quantiplex, Versant, Bayer HealthCare, Tarrytown, USA); HIV-1 PCR DNA in PBMC were performed using the Roche Amplicor Monitor Test with modifications as described [20], or using the real time PCR following the ANRS method [21]. Lastly, for few specific cases, PBMC viral culture was performed as described[22].

Among the 6587 HIV-1 infected women who delivered in the study period, 219 declined enrollment or terminated pregnancy, 118 were infected by HIV-2 exclusively, 226 did not receive antenatal ART (including 124 who received intrapartum ART prophylaxis), 12 breastfed. For 472 mothers, ART or breastfeeding status were missing, mostly due to delay in the return of questionnaires not related to maternal or children characteristics. Among the 5540 mothers who received ART and did not breastfeed, the child's HIV status could not be established for 42 stillbirths, 14 neonatal deaths, and for 213 (3.8%) children because of incomplete virological data. For 117 multiple pregnancies, only the first born was included for estimation of the transmission rate. Overall, 5271 mother-child pairs, from 77 sites, were enrolled in analysis performed on data updated in January, 2007.

Variables

We recorded demographics including geographical origin, gestational age at booking visit in the obstetrical center, levels of plasma HIV1 RNA and CD4 cell count nearest to the time of delivery no more than 7 days after delivery, type and number of antiretroviral combinations received during pregnancy, mode of delivery (vaginal, emergency cesarean section or elective cesarean section, defined as before labor and before rupture of the membranes), and gestational age at delivery. Adherence was not recorded.

The last combination of ART prescribed before delivery was considered for analysis. It was categorized into three classes: monotherapy of nucleoside reverse transcriptase inhibitor (NRTI), almost exclusively with zidovudine, dual-drug therapy (two NRTI, mostly zidovudine-lamivudine), or HAART (three or more drugs of any class). The antenatal ART duration was calculated as the number of weeks between the first initiation of antenatal ART and delivery. When a treatment interruption of at least 15 days was prescribed for women who were receiving ART at the onset of pregnancy, the antenatal ART duration was calculating beginning at reintroduction of ART.

Maternal intrapartum prophylaxis was classified as none versus intravenous zidovudine and/or single-dose nevirapine. Neonatal prophylaxis initiated within 3 days, was classified as: none or zidovudine monotherapy or 2 or more antiretroviral drugs.

Statistical analysis

We first studied whether viral load and prematurity were related to transmission, independently of one another and of other factors likely to play a part in the maternal transmission of HIV. Percentages were estimated with their exact 95% confidence intervals and compared by using Chi-square or 2-tailed Fisher exact test and continuous variables by Student or Wilcoxon rank test. Interaction between prematurity and viral load was investigated in stratified analysis. We assessed, for all births, term births and term births with viral load <400 copies/mL, the validity of linear assumption between transmission rate and duration of ART by fitting a generalized additive model (GAM) with S+ software [23], estimated by smoothing cubic splines [24].

A backward stepwise logistic regression was performed with the child's HIV status as the dependant variable. The significance p-value level for removal was fixed to 0.25, using the likelihood-ratio test. The initial model included four groups of non collinear variables. The first group represented each component of prophylaxis strategy: duration of antenatal ART, type of last ART, mode of delivery, intrapartum prophylaxis, and type of neonatal prophylaxis. Type of first antenatal ART and time of initiation, number of changes during pregnancy, or duration of last antenatal ART were analyzed but not included in the final model because of colinearity. The second group of variables included the last viral load and CD4 cell count, which depended not only on the antenatal prophylaxis but on their level at starting pregnancy, unrecorded for most of these women. The third group included prematurity and gender of neonate. The fourth group comprised available characteristics potentially related to access or adherence to care management: year of delivery, parity, maternal age, geographical origin, active drug use and gestational age at booking.

We then excluded premature births (<37 weeks) to perform stepwise logistic regressions in two subgroups, according to virological failure (viral load $\geq$ 10 000 copies/mL) or success at

delivery (< 400 copies/mL), which represented respectively 7% and 54% of the whole study population.

Analyses were conducted using the STATA software [25] . P<0.05 was used to determine statistical significance.

Results

Characteristics of the population

Overall, 5271 eligible mother-child pairs with deliveries between 1997 and 2004 were enrolled. At end-point, the median follow up for included children was 19 months (interquartile range:15-24). The use of HAART increased from 3% in 1997 to 53% in 2001 and 79% in 2004, while low maternal viral load at delivery (< 400 copies/ml) increased from 47% to 79%. During that period, CD4 cell count remained stable (10% below 200 cells/mm^3 and 68% for 350 or over). In 2004, 54% of mothers who were receiving HAART as last antenatal ART delivered with undetectable HIV-RNA level (<50 c/mL). Overall, 19% of treated women were receiving monotherapy, 33% dual-drug therapy, and 48% HAART at delivery (Table 1). The HAART combination included two NRTI and a Protease inhibitor (PI) in 73% of cases, two NRTI and a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) in 17%, NRTI, PI and NNRTI in 3% and three or more NRTI exclusively in 7%. The proportion of elective cesarean increased from 14% in 1997 to 56% in 2000 and tended to decrease to 41% in 2004, whereas if was stable for emergency cesarean section (29%). Ninety six percent received intrapartum prophylaxis, which was intravenous zidovudine alone or associated with single dose of nevirapine in 6% of cases. All neonates, except 0.7 %, started within the 3 days after birth a 4 to 6 weeks course of postnatal prophylaxis, mainly zidovudine monotherapy (76%). Characteristics according viral load at delivery are presented in table 1.

Risk factors according to gestational age at delivery

Among the 5271 neonates, 67 were infected, an overall MTCT rate of 1.3% (95% CI: 1.0 -1.6). The univariate analysis (Table 2) showed a significant association with prematurity (p<0.001), HIV1 RNA level (p<0.001), CD4 cell count (p<0.001), and duration of ART during the pregnancy (p<0.001). The transmission rate was 6 times higher for neonates born before 33 weeks (6.6%; 95%CI: 2.9-12.5) than for full-term infants (1.1%; 95%CI: 0.8-1.5), but was not increased for those born between 33 and 36 weeks (1.2%; 95%CI: 0.5-2.5). The rate increased with delivery viral load in term (p<0.001) as well in premature births (p<0.001), with no significant interaction between viral load and prematurity (p=0.18; fig 1): overall, the rate was 0.6% (95%CI: 0.4-0.9) below 400 c/mL, reached 1.5% (95%CI: 0.8-2.5) between 1,000 and 10,000 c/mL, and 6.8% (95%CI: 4.6-9.6) over 10,000 c/mL; however, among severe premature births, the rate passed from 1.7% below 400 c/mL to more than 11% for each categories over 400 c/mL (fig 1). The median duration of ART during pregnancy was significantly shorter in mothers of infected than non infected children (9.5 versus 16 weeks globally, p<0.001 ; 11 versus 16 weeks in term births, p=0.001; 5 versus 17 weeks in premature births, p=0.002). The relationship between transmission rate and ART duration was significantly non linear in the whole population (p=0.003), with a strong decreasing transmission rate between 0 and 12 duration weeks, more slightly beyond 12 weeks (fig 2). Excluding premature births, only the linear term was significant, overall (p=0.003), as well as in the subgroup of mothers who delivered with viral load below 400 c/mL (p=0.02).

MTCT was also associated with the time at booking visit to the obstetrical center (p=0.001), the lack of intrapartum prophylaxis (p=0.025), sub-Saharan African origin (p=0.009) and child gender (p=0.022). The higher rate of infection in female than male neonates was not due to a difference in perinatal mortality in males (24/2708 ; 0.7%) vs females (17/2569 ; 0.9%, p=0.4), or in proportion with missing HIV status. Neither maternal age, parity, mode of delivery (p=0.13), knowledge of HIV status before pregnancy, type of maternal ART, nor the type of postnatal prophylaxis were associated with MTCT.

Severe prematurity, HIV RNA level, global duration of ART, and child gender remained independently associated with MTCT in the final model of the stepwise logistic regression (Table 3). The adjusted odds ratio (ORa) for severe prematurity versus term delivery was 3.37 (95%CI: 1.40-8.11) ; however, it was not significantly different from one in mothers who delivered below 400 copies/mL (2.30; 95%CI: 0.29-18.48) whereas it passed to 4.60 (95%CI, 1.78-11.84) beyond 400 copies/mL. Elective cesarean section, not significantly associated with transmission in the initial model, became significantly linked to a lower risk of transmission in the final model.

Risk factors of MTCT in term births with virological failure

In the 364 women who term delivered with viral load $\geq$ 10 000 copies/mL, the MTCT rate was: 6.6 % (95%CI, 4.3 – 9.7%). Intrapartum prophylaxis was strongly associated with a lower risk of transmission: 5.3% (18/339) vs 22.7% (5/22) without intrapartum prophylaxis (p=0.009) (Table 2). Mothers who booked in the first trimester had a lower transmission risk (1.9%) than those booking in the second (9.9%) or third trimester (10.9%) (p=0.03). These two factors remained associated with MTCT after adjustment in both initial and final stepwise logistic regression models (Table 3). The adjusted OR associated with no intrapartum therapy was: 4.72 (95%CI, 1.42-15.71; p=0.011).

Risk factors of MTCT in term births with virological success

In the 2856 mothers who term delivered with viral load below 400 copies/mL, the MTCT rate was 0.6% (95%CI, 0.3 – 1.0%). The rate was as low as 0.4% (5/1338; 95%CI, 0.1-0.9) in women who delivered with viral load below 50 c/mL. Global duration of ART was the only significant risk factor which remained in the initial and final models issued from stepwise logistic regression. The OR for each increment week was: 0.94 (95%CI, 0.90-0.99; p=0.031). Included in the model instead of global ART duration, time at initiation of ART or duration of last ART were also correlated with transmission (p=0.011 and 0.013 respectively). Including children with missing HIV status, as non infected, conducted to similar results. Among the more

homogenous subgroup of 780 women who booked at first trimester and received HAART, the transmission rate was: 0/392 for women already treated at the onset of pregnancy, 1.0% (2/192) when ART was started in the first trimester, 0.9% (1/113) in the second trimester, and 3.6% (3/83) in the third trimester (p=0.006). It is of interest to note that the five mothers who transmitted despite viral loads below 50 c/mL started therapy relatively late, between 32 and 33 weeks. Among the infected children term born to mothers having less than 400 c/mL at delivery, 43% had a positive HIV1 PCR in the first 3 days, suggesting in utero transmission. This proportion was 21% at 10 000 c/ml or more (fig 1).

Discussion

The objective of this study, the largest to date of HIV-1 mother-to-child transmission in the HAART era, was to identify risk factors for persistent cases of transmission despite the use of antiretroviral therapy during pregnancy. During the period 1997-2004, the rate of HIV-1 transmission from mothers receiving any antiretroviral therapy during the pregnancy was 1.3% (95% CI: 1.0 -1.6). Similar rates are reported during the same period in other studies from industrialized countries [2, 4, 26]. Three main factors were independently related to transmission: high maternal plasma viral load near delivery, short duration of antenatal antiretroviral therapy and very premature delivery. We also found an independent association with gender as previously reported [27, 28, 29].

Maternal viral load clearly stands out as the key determinant of mother-to-child transmission risk, as has been consistently reported in all studies [2, 6, 30-37]. In term births, the MTCT rate was 10 times higher when last maternal plasma HIV1 RNA was above rather than below 10,000 c/mL (7.2% vs 0.8%, p<0.01). The rate was 0.5% below 400 c/mL and as low as 0.4% below 50 c/mL.

In French guidelines issued in the study period, zidovudine monotherapy was restricted to women who did not require therapy for their own health and had pre-therapeutic plasma viral loads below 10 000 copies/mL [38]. Thus monotherapy was indicated in women at lower risk of

transmitting the virus, which was likely to explain that MTCT rate did not differ according to the antiretroviral regimen. Be that as it may, our data confirmed that good control of maternal viral load is a key method to prevent MTCT, whatever the type of antiretroviral strategy used to obtain it.

Maternal viral load above 10 000 c/mL at term delivery should not occur according to accepted guidelines [6, 38]. This situation concerned less than 10% of mothers, but contributed to half of the infected children. It occurred even though 45% delivered with HAART and 27% with dual-drug therapy, and may be due to poor adherence, multidrug resistance or treatment interruptions related to poor tolerance, or late access to adequate prenatal care, significantly associated with transmission. Intrapartum prophylaxis appeared to have a strong protective effect in case of virological failure. In contrast, among women with viral loads below 10 000 copies/ml, there was no case of transmission among the 125 women who did not receive intrapartum prophylaxis.

MTCT rate was inversely related to duration of antenatal therapy. Relation with very short zidovudine monotherapy was previously demonstrated in Thailand [8]. The non linear increasing risk in our survey reflected the high rate of transmission in very premature births with low duration: poorer control of HIV viral load due to an unexpectedly short time between the start of maternal therapy and delivery may partly explain the association between transmission and severe prematurity. Overall, the rate was 6-fold higher when deliveries occurred before 33 weeks than at 37 weeks or more. Two results suggest that other factors, not collected in EPF during the study period, may increase perinatal exposure to HIV in severely preterm delivery, such as preterm premature rupture of the membranes, abruption, and chorio-amnionitis: the association remained significant after adjusting for duration of ART, maternal plasma viral load, mode of delivery and intrapartum prophylaxis ; the transmission rate was not increased in case of moderately premature deliveries.

In term births, the increasing risk of transmission with duration of therapy seemed more related to a very low transmission in women who were receiving ART since the first weeks of pregnancy. The time needed to achieve undetectable HIV RNA by the time of delivery may partly account for this finding, as it is generally obtained in non pregnant adults by 10 to 16 weeks [39]. In addition, in utero transmission may occur before therapy is initiated or effective. Presumed in utero transmission occurred in near one half of the children term born with maternal HIV1 RNA level below 400 copies/mL.

Elective cesarean section tended to be associated with a lower risk of MTCT in the overall population. However we observed no significant difference in transmission risk according to the mode of delivery among women who delivered with viral load below 400 c/mL (crude OR: 0.83; 0.29-2.39; p=0.37). A protective effect of elective cesarean section was established in our cohort [16] and others [17, 18], in the absence of antiretroviral prevention and in a period when standard care was zidovudine monotherapy. It is unclear whether such a protective effect persists in women receiving ART with low viral load at delivery. Data from the PACTG [26, 40] failed to show a difference in transmission rate according to mode of delivery in treated women with low viral loads. A recent study reported an association between the mode of delivery and mother-to-child HIV-1 transmission risk, although the association was not statistically significant in the subgroup of women receiving antenatal HAART [4]. In our study, women who received HAART and delivered with viral load below 400 c/mL had a transmission rate of 0.4 % (3/747) with elective caesarean and 0.5 % (3/574) with vaginal delivery (p=0.35). But the power to show a 2-fold decrease was only 18%. The potential benefit of systematic cesarean delivery would have to be balanced with the risks, in a scenario where at least several hundred operations would be required to avoid one case of transmission [11, 41].

The methods available today are able to reduce mother-to-child HIV transmission to well below one percent. Our data confirm the major impact of achieving an undetectable maternal plasma viral load, with only 0.4% transmission among term-born children whose mothers had viral

loads below 50 c/mL at delivery. The most consistent means available to obtain such a control of viral replication is the use of triple combination therapy. Furthermore, our findings strongly suggest that antiretroviral therapy should be started relatively early, at the latest by 28 weeks, to obtain maximum efficacy. However, any incremental benefit of more aggressive and/or longer antiretroviral exposure has to be evaluated against the risks of toxicities, such as adverse events during pregnancy, prematurity, neonatal malformations or mitochondrial dysfunctions in uninfected infants [11 , 42, 43]. The key challenge is to improve early access to specific care and treatment as well as adherence in pregnant women in order to achieve viral suppression during the last trimester of the pregnancy.

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Acknowledgments

This study was supported by the French National Agency for AIDS Research (ANRS), Paris, France. We thank Valerie Benhammou, Karima Hamrene, Yassine Benmebarek, Corinne Laurent, Elisa Ramos, Marlène Peres.

The persons and institutions who participated in the ANRS French Perinatal Cohort (EPF) are listed in the annexe.

Josiane Warszawski declare to be independent of any commercial funder, to have performed the statistical analysis and have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

APPENDIX

The following persons and institutions participated in the ANRS French Perinatal Cohort (EPF):

Hôpital d'Aix en Provence* (Tadrist B.); **Hôpital Nord, Amiens** (Schmit J.L., Horlé B.); **Hôpital d'Angers** (Fournié A.); **Hôpital Victor Dupouy, Argenteuil** (Brault D.); **Hôpital Paris La Roseraie***, **Aubervilliers** (Rozan M.A.); **Hôpital Robert Ballanger, Aulnay** (Zakaria A.); **Hôpital Saint Claude, Basse-Terre*** (Sibille G.); **Hôpital de Bastia** (Pincemaille O.); **Hôpital de la Côte Basque, Bayonne** (Cayla C.); **Clinique du Blanc Mesnil*** (Balde P.); **Hôpital Saint Jacques, Besançon** (Estavoyer J.M.); **Hôpital Avicenne, Bobigny** (Bentata M.); **Hôpital Jean Verdier, Bondy** (Lachassine E., Rodrigues A.); **Hôpital Pellegrin, Bordeaux** (Roux D., Douard D.); **Hôpital Ambroise Paré*, Boulogne Billancourt** (Zenaty D.); **Hôpital Clémenceau, Caen** (Brouard J.); **Hôpital André Rosemon, Cayenne** (Elenga N.); **Hôpital Beaujon*, Clichy** (De Curtis A.); **Hôpital de Creil** (Kingue-Ekollo C.); **Hôpital Intercommunal, Créteil** (Garrait V., Lemerle S., Pichon C.); **Hôpital Béclère, Clamart** (Chambrin V., Labrune P., Clech L.); **Hôpital Louis Mourier, Colombes** (Crenn-Hebert C., Floch-Tudal C.); **Hôpital de Compiègne*** (Lagrue A.); **Hôpital d'enfants, Dijon** (Reynaud I.; Martha S.); **Hôpital de Dourdan*** (Ercoli V.); **Hôpital de Dreux*** (Denavit M.F.); **Hôpital des Feugrais*, Elbeuf** (Lahsinat K.); **Hôpital Intercommunal, Evreux** (Touré K.); **Hôpital Francilien Sud, Evry-Corbeil** (Devidas A., May A., Granier M.); **Hôpital de Fontainebleau** (Routier C.); **Hôpital Victor Fouche, Fort de France** (Hatchuel Y.); **Hôpital de Gonesse*** (Balde P.); **Hôpital Jean Rostand, Ivry** (Jault T.); **Hôpital de Lagny** (Chalvon Demersay A.); **Hôpital du Lamentin*** (Monlouis M.); **Hôpital Les Oudairies, La Roche sur Yon** (Perré P); **Hôpital de La Seyne sur Mer** (Chamouilli J.M.); **Hôpital Louis Domergue, La Trinité*** (Hugon N.); **Hôpital André Mignot, Le Chesnay** (Hentgen V., Messaoudi F.); **Hôpital de Bicêtre, Le Kremlin-Bicêtre** (Peretti D., Fridman S); **Hôpital Jeanne de Flandres, Lille** (Mazingue F., Hammou Y.); **Hôpital Dupuytren*, Limoges** (De lumley L.); **Hôpital de Longjumeau** (Seaume H.); **Hôpital Hôtel Dieu-Hôpital Debrousse, Lyon** (Cotte L., Kebaïli K.); **Hôpital François Quesnay, Mantes La Jolie** (Doumet A.); **Hôpital la Conception, Marseille** (Cravello L., Thuret I.); **Hôpital de Meaux** (Karaoui L.); **Hôpital de Meulan*** (Seguy D.); **Hôpital Marc Jacquet, Melun** (Le Lorier B.); **Hôpital Intercommunal, Montfermeil** (Talon P.); **Hôpital Arnaud de Villeneuve, Montpellier** (Benos P., Lalande M.); **Hôpital Intercommunal, Montreuil** (Heller-Roussin B.); **Maternité Régionale A. Pinard, Nancy** (Hubert C.); **Hôpital de Nanterre*** (Karoubi P.); **Hôpital de Nantes** (Reliquet, V., Brunet-François C.); **Hôpital de Neuilly sur Seine*** (Berterottiere D.); **Hôpital l'Archet-Fondation Lenval, Nice** (Monpoux F., Bongain A., Deville A.); **Hôpital Caremeau, Nîmes** (Dendale J.); **Hôpital Orléans** (Arsac P.); **Hôpital d'Orsay** (De Gennes C.); **Hôpital Bichat, Paris** (Matheron S., Batallan A.); **Hôpital Boucicaut*, Paris** (Lafay Pillet M.C.); **Hôpital Cochin-Port Royal, Paris** (Firtion G., Pannier A); **Hôpital Lariboisière, Paris** (Ciraru-Vigneron N.); **Hôpital des Métallurgistes*, Paris** (Rami M.); **Institut Mutualiste Montsouris*, Paris** (Carlus Moncomble C.); **Hôpital Necker, Paris** (Parat S., Blanche S., Rouzioux C.); **Hôpital Notre Dame du Bon Secours, Paris** (Ayral D.); **Hôpital Pitié Salpêtrière, Paris** (Tubiana R.); **Hôpital Robert Debré, Paris** (Levine M., Faye A., Ottenwalter A.); **Hôpital Rothschild, Paris** (Wallet A.); **Hôpital Saint-Antoine, Paris** (Carbonne B.); **Hôpital Hôpital Saint Michel, Paris** (Aufrant C.); **Hôpital Tenon, Paris** (Lebrette M.G.); **Hôpital Trousseau, Paris** (Dollfus C.); **Hôpital Marechal Joffre, Perpignan** (Medus M.); **Hôpital Les Abymes, Pointe-à-Pitre** (Bataille H.); **Hôpital de Poissy-Saint-Germain en Laye*** (Rousset M.C.); **Hôpital René Dubos, Pontoise** (Mouchnino G.); **Hôpital Américain, Reims** (Munzer M.); **Hôpital Charles Nicolle, Rouen** (Brossard V.); **Hôpital de Saint-Denis** (Allemon M.C., Ekoukou D., Khuong M.A.); **Hôpital Nord, Saint Etienne** (Billiemaz K.); **Hôpital de Saint Martin** (Bissuel F.); **Hôpital Esquirol*, Saint-Maurice** (Robin M.); **Hôpital de Sèvres*** (Segard L.); **Hôpital de Haute Pierre-Hôpital Civil, Strasbourg** (Partisani M., Favreau, J. J, Entz-Werle N.); **C.M.C. Foch, Suresnes*** (Botto C.); **Hôpital Chalucet,Toulon** (Hittinger G.); **Hôpital La Grave, Toulouse** (Berrebi A., Tricoire J.); **Hôpital Bretonneau, Tours** (Besnier J.M.); **Hôpital Brabois, Vandoeuvre les Nancy** (Neimann L.); **Hôpital Paul Brousse*,Villejuif** (Dussaix E.); **Hôpital de Villeneuve Saint Georges** (Guillot F., Chacé A.).

Legends of figures

Fig 1 - MTCT rates according to HIV RNA level at delivery - The ANRS French Perinatal Cohort (1997-2004)

Estimations were based on 5074 available data among the 5271 included mother-child pairs who received antenatal ART and did not breastfed

HIV-1 PCR in the first 3 days was not available for 12 among 52 term born infected neonates and 7 among 15 premature infected neonates

Fig 2 - Relationship between duration of ART during pregnancy and MTCT rate. The ANRS French Perinatal Cohort (1997-2004)

The curve was estimated by a generalized additive model (GAM) with a non linear term (splines). The model was based on 5235 available data among the 5271 included mother-child pairs who received antenatal therapy and did not breastfed.

Plain line: all births (N=5 235)

Dotted line: term births (37 weeks or more) (N = 4 554).

Bold dotted line : term births (37 weeks or more) and maternal HIV-1 RNA < 400 c/mL (N = 2840).

Table 1 – Characteristics of HIV-1 mother-child pairs according to maternal HIV RNA level at delivery 1997-2004† – The ANRS French Perinatal Cohort

	Total		Maternal HIV-1 RNA at delivery, copies/mL					
			< 400		400 - 9 999		≥ 10 000	
	N	%	N	%	N	%	N	%
Year of delivery								
1997-98	1024	19.4	510	15.7	361	26.2	93	21.1
1999-00	1293	24.5	660	20.3	438	31.8	161	36.6
2001-02	1549	29.4	1030	31.6	348	25.3	122	37.7
2003-04	1405	26.7	1056	32.4	231	16.8	64	14.6
Active drug use								
Yes	144	2.7	68	2.1	50	3.6	21	4.8
Geographical origin								
Sub-Saharan Africa	2935	55.9	1845	56.8	734	53.6	244	55.6
Gestational age at booking, wk								
3rd trimester (≥ 28)	536	10.4	270	8.5	167	12.7	66	15.4
2nd trimester (14-27)	2165	42.0	1323	41.5	583	43.2	177	41.4
1st trimester (<14)	2450	47.6	1592	50.0	600	44.4	185	43.2
Gestational age at delivery, wk								
<33	122	2.3	60	1.8	30	2.2	24	5.5
33-36	563	10.7	339	10.4	147	10.7	52	11.8
≥ 37	4583	87.0	2856	87.7	1201	87.2	364	82.7
Maternal CD4 cell count at delivery								
<200 cells/mm^3	520	10.2	269	8.4	139	10.2	104	24.2
200-349	1134	22.2	655	20.4	319	23.5	130	30.2
≥ 350	3459	67.7	2284	71.2	899	66.3	196	45.6
Gender of neonate								
Male	2684	51.3	1604	49.7	754	54.9	214	49.0
Mode of delivery								
Elective Caesarean	2438	46.5	1409	43.5	719	52.4	230	52.6
Emergency Caesarean	1046	20.0	633	19.5	256	18.7	117	26.8
Vaginal delivery	1758	33.5	1201	37.0	396	28.9	90	20.6
Initiation of antenatal ART, median wk (IQ)	22 (0-29)		21 (0-28)		24 (12-30)		23 (9-29)	
Duration of antenatal ART, median wk (IQ)	16 (9-33)		17 (10-35)		14 (8-26)		14 (8-29)	
Last antenatal ART								
HAART	2513	47.8	1842	56.7	391	28.4	196	44.6
Dual-drug therapy	1745	33.2	1045	32.1	526	38.3	119	27.1
Monotherapy	1003	19.1	364	11.2	458	33.3	125	28.4
Intrapartum prophylaxis								
Yes	5006	95.6	3120	96.2	1300	95.0	407	95.6
Postnatal child prophylaxis								
Dual or HAART	1204	23.0	651	20.2	396	28.9	122	28.0
Monotherapy	3990	76.3	2551	79.0	966	70.5	314	72.0
None or late	37	0.7	28	1.0	8	0.6	0	0

† Eligible population: HIV-1 infected women who delivered between January 1, 1997 and December 31, 2004, and : (1) received at least one antenatal ART at any time during pregnancy, (2) did not breastfeed and (3) with child's infection status documented.
IQ = interquartile range
ART=antiretroviral therapy, HAART=highly active antiretroviral therapy.

Table 2 – Mother-to-child transmission (MTCT) in women receiving antiretroviral therapy during the pregnancy – univariate analysis - The ANRS French Perinatal Cohort (1997-2004)

	All births				Term births							
					Maternal HIV-1 RNA at delivery < 400 cp/mL				Maternal HIV-1 RNA at delivery ≥ 10 000 cp/mL			
	N †	n †	%	p #	N †	n †	%	p #	N †	n †	%	p #
Total	5271	67	1.3		2856	17	0.6		364	24	6.6	
Gestational age at delivery, wk												
<33 week	122	8	6.6	<0.001								
33-36	563	7	1.2									
≥ 37	4583	52	1.1									
Maternal HIV-1 RNA at delivery												
≥ 10 000 copies/mL	440	30	6.8	<0.001								
1000-9999	938	14	1.5									
400-999	440	3	0.7									
<400	3256	19	0.6									
Active drug use												
Yes	144	2	1.4	0.71	49	0	0	1.00	20	2	10.0	0.63
No	5125	65	1.3		2806	17	0.6		344	22	6.4	
Geographical origin												
Sub-Saharan Africa	2935	48	1.6	0.009	1642	12	0.7	0.28	199	17	8.5	0.103
Other origin	2318	19	0.8		1208	5	0.4		164	7	4.3	
Gestational age at booking, wk												
3rd trimester (≥ 28 week)	536	15	2.8	0.001	229	2	0.9	0.45	55	6	10.9	0.003
2nd trimester (14-27)	2165	30	1.4		1169	5	0.4		142	14	9.9	
1st trimester (<14)	2450	21	0.9		1393	10	0.7		157	3	1.9	
Maternal CD4 cell count at delivery												
<200 cells/mm^3	520	16	3.1	<0.001	228	3	1.3	0.19	83	6	7.2	0.80
200-349	1134	17	1.5		572	4	0.7		110	8	7.3	
≥350	3459	33	1.0		2015	10	0.5		164	9	5.5	
Gender of neonate												
Female	2552	42	1.7	0.022	1423	10	0.7	0.48	185	16	8.7	0.11
Male	2684	25	0.9		1411	7	0.5		177	8	4.5	
Mode of delivery												
Elective Caesarean	2438	23	0.9	0.13	1296	7	0.5	0.90	203	10	4.9	0.37
Emergency Caesarean	1046	18	1.7		464	3	0.7		86	8	9.3	
Vaginal delivery	1758	25	1.4		1083	7	0.7		72	5	6.9	
Initiation of antenatal ART, wk												
Non stopped from onset	1356	10	0.7	0.044	759	1	0.1	0.108	82	6	7.3	0.96
4-20	1115	10	0.9		619	3	0.5		77	4	5.2	
21-28	1117	17	1.5		606	4	0.7		71	4	5.6	
>28	1647	29	1.8		856	9	1.1		132	9	6.8	
Median infected/non infected	27 / 22			<0.001	29 / 21			0.014	25 / 24			0.46
Duration of antenatal ART, wk												
Median infected/non infected	9.5 / 16			<0.001	10 / 17			0.023	13 / 15			0.30
Duration of last antenatal ART, wk												
Median infected/non infected	7 / 11			<0.001	8 / 12			0.013	8 / 10			0.47
Last antenatal ART												
HAART	2513	30	1.2	0.77	1585	9	0.6	0.94	155	13	8.4	0.48
Dual-drug therapy	1745	22	1.3		938	6	0.6		105	6	5.7	
Monotherapy	1003	15	1.5		328	2	0.6		104	5	4.8	
Intrapartum prophylaxis												
No	230	7	3.1	0.025	95	0	0	1.00	22	5	22.7	0.009
Yes	5006	59	1.2		2750	17	0.6		339	18	5.3	
Postnatal child prophylaxis												
Dual or HAART	1159	21	1.8	0.084	546	3	0.6	1.00	103	7	6.6	0.95
Monotherapy	3975	46	1.2		2231	14	0.6		257	17	6.8	
None or late	*37*	*0*	-									

† n indicates the number of infected children among N mother-child pairs included in the analysis

P-value was obtained by Fisher exact test for active drug use, gestational age, maternal HIV-1 RNA level and intrapartum prophylaxis, by Wilcoxon rank test for ART duration and time at initiation and by Chi-square test for all other variables. ART=antiretroviral therapy, HAART=highly active antiretroviral therapy.

Table 3 – Mother-to-child transmission (MTCT) in women receiving antiretroviral therapy during the pregnancy – Stepwise logistic regression†† - The ANRS French Prenatal Cohort (1997-2004)

	All births N=4713 †					Term births								
						Maternal HIV-1 RNA at delivery < 400 cp/mL N=2659 †					Maternal HIV-1 RNA at delivery ≥ 10 000 cp/mL N=340 †				
	Initial model ††		Final model			Initial model ††		Final model			Initial model ††		Final model		
	OR a	95% CI	OR a	95% CI	p	OR a	95% CI	OR a	95% CI	p	OR a	95% CI	OR a	95% CI	p
Gestational age at delivery, wk															
<33 week	3.25	(1.32-8.03)	3.37	(1.40-8.11)	0.019										
33-36	0.84	(0.35-2.03)	0.85	(0.35-2.03)											
≥ 37	1	*	1												
Maternal HIV-1 RNA at delivery															
≥ 10 000 copies/mL	9.36	(4.90-17.87)	9.82	(5.24-18..37)	<0.001										
1000-9999	2.46	(1.19-5.09)	2.52	(1.25-5.11)											
400-999	1.13	(0.33-3.90)	1.14	(0.33-3.90)											
<400	1	**	1												
Active drug use						§									
Yes	1.11	(0.24-5.13)									2.11	(0.31-14.48)			
No	1	NS									1	*NS*			
Geographical origin															
Sub-Saharan Africa	1.70	(0.94-3.10)	1.61	(0.92-2.83)	0.094	1.20	(0.39-3.69)				1.69	(0.53-5.40)			
Other origin	1	$$	1			1	*NS*				1	*NS*			
Gestational age at booking, wk															
3rd trimester (≥ 28 week)	1.97	(0.93-4.15)	1.95	(0.93-4.04)	0.18	0.64	(0.13-3.19)				6.54	(1.32-32.31)	8.53	(1.93-37.59)	0.010
2nd trimester (14-27)	1.17	(0.64-2.13)	1.15	(0.64-2.09)		0.40	(0.13-1.21)				5.30	(1.36-20.72)	6.08	(1.66-22.26)	
1st trimester (<14)	1	$				1	*NS*				1	*	1		
Maternal CD4 cell count at delivery															
<200 cells/mm^3	1.79	(0.88-3.62)	1.92	(0.98-3.79)	0.17	3.4	(0.8-14.1)				0.79	(0.23-2.72)			
200-349	1.15	(0.61-2.18)	1.22	(0.65-2.27)		1.7	(0.5-5.7)				1.35	(0.45-4.04)			
≥ 350	1	*NS*	1			1	*NS*				1	*NS*			
Gender of neonate															
Female	1.98	(1.16-3.35)	1.98	(1.17-3.35)	0.011	1.39	(0.52-3.69)				2.30	(0.84-6.29)	2.21	(0.86-5.71)	0.10
Male	1	*	1			1	*NS*				1	$	1		
Mode of delivery															
Elective Caesarean	0.56	(0.29-1.06)	0.49	(0.26-0.89)	0.059	0.72	(0.24-2.16)				1.46	(0.37-5.80)			
Emergency Caesarean	0.90	(0.46-1.76)	0.81	(0.42-1.56)		0.95	(0.23-3.89)				2.59	(0.65-10.32)			
Vaginal delivery	1	$	1			1	*NS*				1				
Duration of antenatal ART, wk															
For each increment week ‡	0.96	(0.94-0.99)	0.97	(0.94-0.99)	0.010	0.93	(0.88-0.99)	0.94	(0.90-0.99)	0.031	0.98	(0.94-1.02)			
		**					*					*NS*			

Last antenatal ART								
HAART	1.22	(0.56-2.67)	1.20	(0.22-6.67)	4.01	(0.98-16.38)		
Dual-drug therapy	1.09	(0.48-2.47)	1.31	(0.23-7.44)	2.08	(0.45-9.71)		
Monotherapy	1	*NS*	1	*NS*	1	$		
Intrapartum prophylaxis								
No	1.60	(0.66-3.89)	§		3.99	(1.09-14.65)	4.72 (1.42-15.71)	0.011
Yes	1	*NS*			1	*	1	
Postnatal child prophylaxis								
Dual or HAART	1.33	(0.68-2.62)	1.12	(0.22-5.71)	0.96	(0.30-3.04)		
Monotherapy	1	*NS*	1	*NS*	1	*NS*		

† N indicates the number of subject included in final logistic regression. ORa = adjusted odds ratio ; 95%CI = "95% confidence interval" .

† † The initial model included all variables listed in the table and also birth date, maternal age and parity.

P-values in the initial models are indicated by: ** $p<0.01$ * $0.01\leq p<0.05$ $$ $0.05\leq p<0.10$ $ $0.10\leq p<0.25$ *NS* $p>0.25$

§ The variable could not be included in the initial model since no transmission occurred in one category

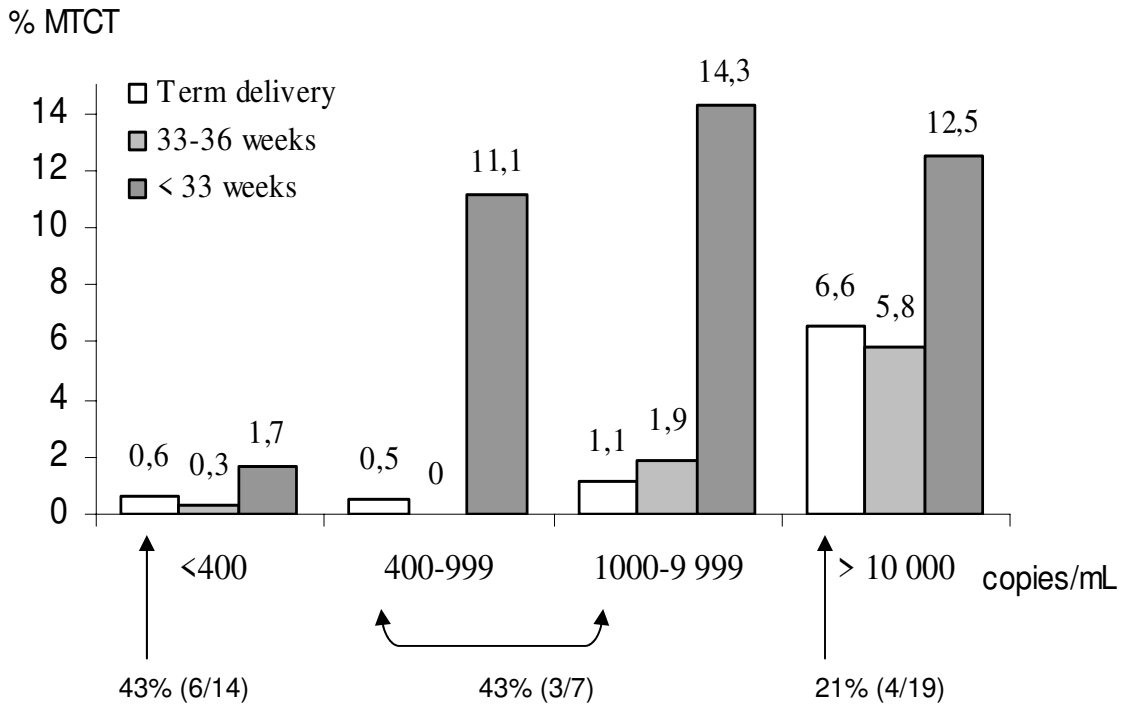
‡ Odds ratio was given for each increment week

ART=antiretroviral therapy, HAART=highly active antiretroviral therapy.

Fig 1 - MTCT rates according to HIV RNA level at delivery - The ANRS French Perinatal Cohort (1997-2004)

Estimations were based on 5074 available data among the 5271 included mother-child pairs who received antenatal ART and did not breastfed

HIV-1 PCR in the first 3 days was not available for 12 among 52 term born infected neonates and 7 among 15 premature infected neonates



Percentage of in utero transmission in term delivery (based on positive HIV1 PCR within 3 days after birth available for 40 of 52 term births)

Fig 2 - Relationship between duration of ART during pregnancy and MTCT rate. The ANRS French Perinatal Cohort (1997-2004)

The curve was estimated by a generalized additive model (GAM) with a non linear term (splines). The model was based on 5235 available data among the 5271 included mother-child pairs who received antenatal therapy and did not breastfed.

Plain line: all births (N=5 235)

Dotted line: term births (37 weeks or more) (N = 4 554).

Bold dotted line : term births (37 weeks or more) and maternal HIV-1 RNA < 400 c/mL (N = 2840).