

The association between mother-to-child transmission and antenatal and neonatal antiretroviral regimen

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Background and Objectives

- In 1994, the ACTG 076 trial demonstrated the efficacy of a three-part regimen of zidovudine (ZDV) monotherapy given antenatally from 14 to 34 weeks gestation, intrapartum and neonatally for 6 weeks in reducing the risk of mother-to-child transmission (MTCT)¹
- MTCT rates have now significantly declined with use of antiretroviral therapy, and management of pregnant HIV-infected women has changed substantially, with widespread use of highly active antiretroviral therapy (HAART)
- Only a few combinations of antiretroviral drugs taken antenatally have been formally evaluated in clinical trials, mostly involving short-courses antiretroviral prophylaxis in less developed country settings²
- Clinical trial data are not available regarding the relative efficacy of different approaches to neonatal prophylaxis (type and duration) for infants born to women taking HAART in pregnancy
- There is increasing recognition of the need to find a balance between reducing the risk of MTCT and minimizing the intensity of fetal/neonatal exposure to antiretrovirals, which may be associated with untoward effects in the uninfected, exposed children³⁻⁵
- We investigated observational data on the use of antenatal and neonatal antiretroviral prophylaxis and MTCT risk in a large European cohort of HIV-infected pregnant women and their children

1. Connor et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Eng J Med* 1994; 331:1173-1180. 2. World Health Organisation. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Guidelines for care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. 2004. Geneva. 3. Le Chenade et al. Perinatal antiretroviral treatment and haematopoiesis in HIV - uninfected infants. *AIDS* (2003) 17:2053-2061; 4. European Collaborative Study. Levels and patterns of neutrophil counts in children born to HIV infected mothers: association with HIV, ART, gender and race. *AIDS* (2004) 18: 2009-2017; 5. Barret et al. Persistent mitochondrial dysfunction in HIV-1 exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS* 2003; 17:1769-1785.

Methods

- The European Collaborative Study is an ongoing prospective cohort study, set up in 1985, in which HIV-infected women identified during pregnancy and their infants are followed up according to a standard clinical and laboratory protocol
- Local ethics approval has been granted and informed consent is obtained before enrolment
- Data collected includes maternal clinical and immunological status, timing of initiation and type of antenatal ART, neonatal prophylaxis (regimen and duration) and infant infection status
- Antenatal ART was classified as "short" if initiated at 28 weeks gestational age or later, and "long" if started before pregnancy and up to 28 gestational weeks. Neonatal prophylaxis was classified as "short" if its duration was less than 6 weeks, otherwise was considered to be "long"
- Infection status definition: infants with a positive virological or serological marker of infection and/or persistence of antibody beyond 18 months of age were included as infected; if a child was HIV antibody-negative and no virus or antigen had ever been detected, (s)he was classified as uninfected, regardless of age.
- Statistical analysis: Univariable comparisons for categorized variables were tested with the χ^2 test or χ^2 test for trend. Univariable and multivariable logistic regression analysis was used to obtain odds ratios (OR) and adjusted odds ratios (AOR) and 95% confidence intervals.

Results 1

- By January 2005, data on 5780 mother-child pairs from ten countries were available for analysis, of whom 2034 received no antenatal or neonatal prophylaxis for prevention of MTCT (most delivering before 1994)
- Most mother-child pairs enrolling since 1994 received long antenatal zidovudine monotherapy and 6 weeks of neonatal zidovudine prophylaxis, but an increasing number of infants whose mothers took HAART in pregnancy are receiving a combination of two or more drugs as neonatal prophylaxis (Table 1)
- Most neonates receiving ZDV monotherapy received this orally for a median of 6 weeks (range 2-12 weeks), but in one centre ZDV was given intravenously for 10 days (194 neonates)
- A total of 225 infants received a combination of two or more antiretroviral drugs as neonatal prophylaxis (Figure 2), for a median of 4 weeks (range 2-7 weeks)

Figure 1: Patterns of use of antiretroviral prophylaxis among 3482 mother-child pairs receiving antenatal and/or neonatal prophylaxis

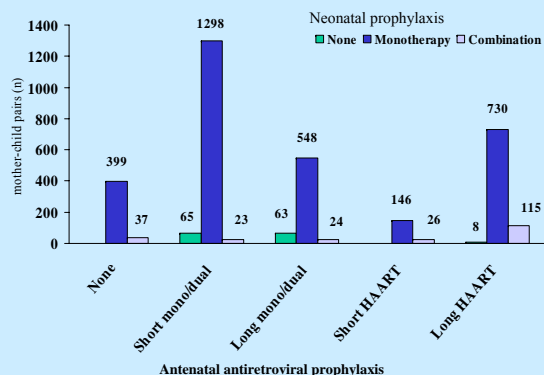


Figure 2: Type of combination neonatal antiretroviral prophylaxis (n=225)

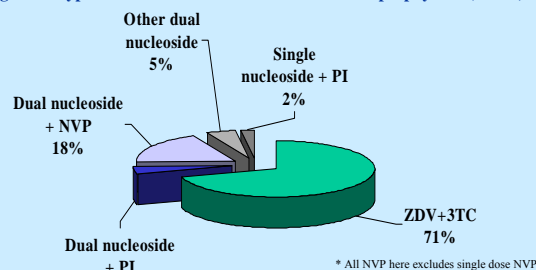


Table 1: Multivariable analysis of risk of MTCT of HIV (n=2439)

	Unadjusted OR (95% CI)	Adjusted OR
Maternal CD4 count		
≥ 500 cells/mm ³	1.00	1.00
200-499	1.58 (1.13-2.21)*	1.94 (1.37-2.76)*
<200	1.60 (1.01-2.52)#	2.05 (1.27-3.31)*
Mode of delivery		
Vaginal delivery	1.00	1.00
Emergency CS	0.59 (0.38-0.91)*	0.91 (0.57-1.44)
Elective CS	0.18 (0.12-0.27)*	0.34 (0.22-0.53)*
Antenatal ART		
None	1.00	1.00
Short mono/dual therapy	0.37 (0.22-0.64)*	0.51 (0.24-1.08)
Long mono/dual therapy	0.27 (0.16-0.47)*	0.39 (0.19-0.80)*
Short HAART	0.05 (0.01-0.33)*	0.06 (0.01-0.44)*
Long HAART	0.04 (0.01-0.10)*	0.05 (0.02-0.17)*
Neonatal prophylaxis		
None	1.00	1.00
Short	0.14 (0.07-0.28)*	1.16 (0.48-2.89)
Long	0.19 (0.13-0.29)*	0.86 (0.45-1.62)

p<0.05 * p<0.02

Results 2

- There were distinct centre differences in use of combination neonatal prophylaxis, with 69% of cases coming from two centres
- Combination neonatal prophylaxis was significantly more common in infants whose mothers received no antenatal ART (AOR 2.65, 95% CI 1.65-4.25) and in those whose mothers were on HAART (AOR 1.80, 95% CI 1.23-2.64) compared with those whose mothers were on mono- or dual therapy antenatally
- Infants who were the second or more child enrolled in the study were nearly one and a half times more likely to receive combination therapy than other children, after adjusting for time period and antenatal ART (AOR 1.42, 95% CI 0.99-2.04, p=0.06)
- Crude MTCT rates (95% CI) stratified by use of antiretroviral prophylaxis were:

no antenatal or neonatal prophylaxis	15.1% (13.6-16.8)
only neonatal prophylaxis	12.7% (9.39-16.7)
short antenatal monotherapy + short neonatal	3.70% (1.21-8.43)
short antenatal monotherapy + long neonatal	7.16% (5.31-9.41)
long antenatal monotherapy + short neonatal	4.11% (0.04-7.60)
long antenatal monotherapy + long neonatal	5.41% (3.49-7.94)
short antenatal HAART + short neonatal	3.13% (0.38-10.8)
short antenatal HAART + long neonatal	1.06% (0.03-5.79)
long antenatal HAART + short neonatal	0% (0 - 1.42)
long antenatal HAART + long neonatal	0.73% (0.20-1.85)
- Risk of MTCT was significantly associated with maternal CD4 count, mode of delivery and antenatal ART in multivariate analysis, but not with neonatal prophylaxis (Table 2)

Discussion

- There has been considerable variation across Europe in the prescribing of antenatal and neonatal antiretroviral prophylaxis, both over time and between centres
- Increasing numbers of women are already on HAART at the time they become pregnant, and long duration of HAART in pregnancy was found here to be associated with a 95% decreased risk of MTCT, independent of other risk factors (mode of delivery and maternal CD4 count)
- Combination neonatal prophylaxis is increasingly being used in Europe, not only as post-exposure prophylaxis for those infants whose mothers did not receive antenatal antiretroviral therapy, but in some centres as a general policy for infants born to HIV-infected women receiving HAART antenatally

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