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* Article

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Antiretroviral therapy in pregnant women with advanced HIV disease and pregnancy outcomes in Abidjan, Côte d'Ivoire

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ABSTRACT

Background: Pregnancy outcomes in women receiving highly active antiretroviral treatment (HAART) in Africa are not well described.

Methods: HIV-1 infected pregnant women in the ANRS Ditrame Plus and the MTCT-Plus projects were included. Between March 2001 and July 2003, when HAART was not yet available, eligible women for HAART received a short-course antiretroviral regimen (sc-ARV) zidovudine (ZDV) or (ZDV + lamivudine) and single-dose of nevirapine (sdNVP) for PMTCT (PMTCT group). Between August 2003 and August 2007, eligible women for HAART received it (HAART group). The frequencies of low birth weight (LBW) (<2500 g), stillbirth and infant mortality are reported. Risk factors associated with LBW were investigated using a logistic regression model.

Results: Of the 326 HIV-infected pregnant women, 175 women received sc-ARV (median CD4 count 177 cells/mm^3) and 151 received HAART (median CD4 count 182 cells/mm^3). At 12 months, 3 paediatric infections (2.3%) occurred in the HAART group vs. 25 (16.1%) in the PMTCT group (p<0.001). The rate of LBW was 22.3% in the HAART group and 12.4% in the PMTCT group (p=0.02). In multivariable analysis (n=309) after adjustment on maternal CD4 count, WHO stage, age and maternal body mass index (BMI), HAART initiated before pregnancy (aOR=2.88, 95% confidence interval [CI] 1.10–7.51) and during pregnancy (aOR=2.12, 95%CI 1.15-4.65) and maternal BMI at delivery (aOR=2.43, 95%CI 1.20-4.91) were associated with LBW.

Conclusions: HAART in pregnant African women with advanced HIV disease substantially reduced mother-to child transmission, but was associated with LBW.

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Introduction

The association between HAART use during pregnancy and adverse infant outcomes, particularly preterm delivery (PTD), has been hotly debated over the last decade, particularly in developed countries where HAART is frequently used for prevention of mother-to-child transmission (1-3). Studies from Europe and the United Kingdom have reported an increased risk of PTD among women receiving HAART during pregnancy (1, 2). However, studies from the United States (3) , Latin American and the Caribbean (4) as well as a recent meta-analysis of 14 perinatal studies (5-6) did not show any significant association between HAART during pregnancy and PTD in developed countries. To date, experience with HAART during pregnancy in Africa has been relatively limited and information about pregnancy outcomes is lacking (7). Our aim was to evaluate pregnancy outcomes in women with advanced HIV disease who were treated with HAART during pregnancy in Abidjan, Côte d'Ivoire.

Methods

Study design and setting

This study was conducted within two sequential PMTCT programs located in the same antenatal clinics in Abidjan: the Ditrame Plus study, March 2001-July 2003 (8) and the MTCT-Plus program, August 2003-August 2007 (9).

Patients and ARV regimens

Pregnant women identified as HIV-1 infected were referred for enrolment in these two programs and all eligible women for HAART and their infants were included. In the Ditrame Plus study, HAART was not yet available for pregnant women and they received for PMTCT intrapartum sdNVP after short-course (sc) ZDV initiated at 36 weeks gestation or sc(ZDV+3TC) initiated at 32 weeks gestation until three days postpartum (referred as the

PMTCT group). In the MTCT-Plus program, we included women on HAART before pregnancy and pregnant women who meet eligibility criteria (WHO clinical stage 2 or 3 and lymphocytes T CD4+ (CD4) count <350 cells/mm^3, or WHO 4 or CD4 count <200 cells/mm^3). They received HAART (ZDV or stavudine (d4T) + 3TC + NVP) in antepartum and continued it in labor and after delivery (HAART group).

In both groups, infants received ZDV syrup for seven days + sdNVP syrup on Day 2 or 3. Women were counselled to either replacement feed or to practice exclusive breastfeeding for 4-6 months. The breast-milk substitutes were free of charge in the PMTCT group but were purchased by the mothers in the HAART group. All women initiated multivitamin supplementation at their enrolment in the programme (10).

Inclusion and follow-up procedures

Maternal socio-demographic, clinical and biological characteristics were recorded at the enrolment. During follow-up, clinical information, drug intake and tolerance data were collected. At delivery, anthropometric data of infants was collected in the maternity ward by the midwife who was neither aware of the women's HIV status nor of their ARV regimen.

Laboratory procedures

Plasma HIV-1 RNA viral load (VL) testing for early diagnosis of paediatric HIV-1 infection was performed using a quantitative real-time RT-PCR technique targeted in the HIV-1 LTR gene, as previously validated (11). The quantification limit of this method was 300 copies/ml with 200 µl of plasma. The algorithm used for defining HIV infection in infants was reported previously (8, 9). CD4 cell counts were measured by a dual-platform flow cytometry technique with an automated blood cell counter (MaxM, BeckmanCoulter, Miami, FL, USA)

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Outcomes

The following pregnancy outcomes were investigated. Stillbirth was defined as the death of a foetus at any time after the 20th week of pregnancy. Infant mortality was defined as born-alive infants who died before their first birthday. LBW, and very(V) LBW were defined as the birth weight <2, 500 grams and <2, 000 grams, respectively.

Statistical analysis

All singleton infants were included in the following analyses (12). Group comparisons used Student's t-test or non-parametric Mann-Whitney U-test for continuous variables, and Chi-2 test or Fisher's exact test for categorical variables. Univariable and multivariable Logistic regression analyses were used to study relation between LBW and explanatory variables. A survival analysis was conducted to estimate infant mortality with Kaplan-Meier probabilities. Determinants of survival were explored using a Cox model.

Results

Description of the study population and ARV regimens

Overall, 358 HIV-infected pregnant women eligible for HAART were included in this study (figure 1). At enrolment the median maternal age was 28 years, inter-quartile range (IQR: 25-32) years, median CD4 count was 179 cells/mm^3 (IQR: 120-252) and median maternal BMI at delivery was 23.8 Kg/m^2 (IQR: 21.8-26.3). There were no statistically significant differences between women receiving HAART *vs.* women eligible for HAART but who did not receive it, except for WHO stage (p<0.001), parity (p=0.001) and age (p=0.039).

The median duration on HAART was 11.7 weeks whereas the median exposure time to sc ARV prophylaxis was 4.9 weeks. The most common antiretroviral regimen used was ZDV+3TC+NVP (87%) in the HAART group and ZDV+sdNVP (54.2%) in the PMTCT group.

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Adverse pregnancy outcomes

Among the 326 singleton infants, the overall stillbirth rate was 3.1% (CI 1.5-5.6%) (Figure 1). There was no significant difference between the HAART and PMTCT groups (3.3% vs 2.9%; p=0.85).

Anthropometric data were available for 309 infants. The median birth weight was 3000 grams, IQR [2700-3250 grams]. Overall, 52 (16.8%) infants had LBW, with a significantly higher proportion in the HAART group compared with the PMTCT group (22.3% vs 12.4%; p=0.020). In the PMTCT group, the frequency of LBW did not vary by sc-ARV regimen (12.3% with sc (ZDV+3TC)+sdNVP and 9.4% with scZDV + sdNVP; p=0.60). Similarly, in the HAART group, the frequency of LBW was not different between women who initiated HAART before pregnancy and those who initiated HAART during pregnancy (25.0% vs 21.5%, p=0.68). The rate of VLBW was similar between groups (p=0.974). There were no significant difference between groups for height or head circumference at birth (p=0.279).

Risk of HIV transmission

Among the 305 infants tested for HIV-infection, 28 infants were identified as HIV-infected at 12 months (Kaplan-Meier estimates: 9.6%, 95%CI [6.7-13.7]). In the HAART group, 65% of the women initiated breastfeeding for 4.7 months in median (IQR: 3.3-6.3), while this proportion was 48% in the PMTCT group, but with a similar duration (4.3 months in median, IQR: 3.5-6.5). The estimated transmission risk was 2.3% (95%CI: 0.7-6.9) in the HAART group, and 16.1% (95%CI: 11.2-22.9%) in the PMTCT group (p<0.001).

Factors associated with low birth weight

A multivariable analysis (Table 1) demonstrated that HAART initiated before pregnancy (aOR=2.88 CI [1.10-7.51]) and during pregnancy (aOR=2.12, CI [1.15-4.65]) and maternal BMI (<25 kg/m^2) (aOR=2.43, 95% CI [1.20-4.91]) were associated with LBW.

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Infant mortality

At age one year, overall infant survival rate was 0.93, CI [0.87-0.96]) among HIV-uninfected infants and was similar in the HAART and PMTCT groups (p=0.78). Neither LBW (aOR=1.5, p=0.38) nor the maternal exposure to HAART (aOR=1.1, p=0.85) were statistically associated with infant mortality in HIV-uninfected infants. The only factor associated with infant mortality was paediatric HIV infection (aOR=11.9, 95%CI: 4.8-29.5) in the Cox model after adjustment on infant feeding practices, LBW, exposure to HAART regimens and maternal characteristics at enrolment.

Discussion

In this West-African study, HAART for pregnant women with advanced HIV disease demonstrated a very low rate of mother-to-child HIV transmission, 2.3%, in comparison to 16.1% in an historical cohort of HAART eligible women who only received short-course PMTCT regimens. At the same time, the frequency of LBW was significantly higher in the HAART group, 22.3% compared with 12.4% in PMTCT group. The impact of HAART on infant outcomes has been examined in multiple studies in developed countries where most women received HAART for PMTCT as well as maternal treatment. One study from the UK noted that the birth weight was significantly lower in infants exposed to HAART in utero compared to those exposed to short-course ARV prophylaxis (13). Also, in a study from US noted, babies born to women initiating PI-based HAART had twice the risk for LBW in comparison to those exposed to other ARV combinations (3). However, others studies from Europe, US, Latin America and Caribbean did not find this association (14, 15, 4). We believe that these are the first data from Africa associating HAART during pregnancy with LBW.

In our analysis, babies born to women receiving HAART were at higher risk for LBW compared with those mothers who received sc-ARV with only 1 or 2 NRTI. The complexity as well as the duration of treatment may contribute to this finding. Women were exposed to

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HAART for 11.7 weeks during pregnancy compared with 4.9 weeks of sc-ARV. Due to the nature of the data set we were unable to examine the relationship between duration of exposure and LBW. We were also unable to study PTD rates because the majority of HIV-infected women did not know the date of their last menstruation and did not have an obstetrical ultrasound examination in the first trimester. Also the association between HAART and PTD was inconsistently reported (1-3). Differences in methodologies, HAART regimens and care practices, make these studies difficult to compare (16). There are few data on biological mechanisms explaining the potential effect of HAART on the occurrence of preterm delivery or LBW. One hypothesis is that could be the consequence of the effect of HAART on the modulation of Th1 and Th2 response (17).

In addition, low maternal BMI was risk factor for having infant with LBW, this is consistent with data already reported in Rwanda (18).

Infant mortality rates for uninfected infants in these cohorts were comparable for women receiving HAART and those receiving ARV prophylaxis. This differs from findings in a study in Uganda which reported a high incidence of mortality in infants born to women who received HAART (25.7 per 100 person-years vs 7.7 in children exposed to maternal sdNVP) (19). We believe that there are several reasons for our good infant outcomes. First, despite an increased rate of LBW, the rate of VLBW was not increased. Second, the transmission rate was low in the HAART cohort diminishing the risk of infant death. Finally, infants born to mothers enrolled in both cohorts were closely followed with a full array of comprehensive services which likely contributed to low mortality rates.

The strength of this study is that we had adequately controlled for WHO stage and maternal CD4 count although we compared two sequential cohorts of women with advanced HIV disease and so, were unable to take into account changes in HIV care over the time and could not assess variables such as smoking, alcohol, and drug abuse which contribute to poor birth outcomes. Also, 87% of women in HAART group received the same regimen:

AZT/3TC/NVP. Finally all HIV-infected women were followed in the same clinical sites by the same clinical teams since 2001.

Further larger scale international pharmacovigilance systems should be established to assess pregnancy outcomes in the context of this wider use of ART in pregnant women.

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