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PI-Based HAART Was Associated with Preterm Delivery, but Not Adverse Infant Outcomes, in a Randomized MTCT Prevention Study in Botswana

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Abstract

Background: Protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) use in pregnancy has been associated with preterm deliveries in some observational studies, but not others. We studied this question in the first randomized trial comparing antiretroviral regimens among pregnant women.

Methods: HIV-infected, HAART-naive pregnant women with CD4 cell counts ≥ 200 cells/mm³ were randomized between 26 and 34 weeks gestation to PI-based (lopinavir/ritonavir/zidovudine/lamivudine) or triple nucleoside reverse transcriptase inhibitor (NRTI)-based (abacavir/zidovudine/lamivudine) HAART as part of a clinical trial to prevent mother-to-child HIV transmission (PMTCT). Inclusion criteria for this analysis required delivery of a live, singleton infant. Spontaneous preterm labor or rupture of membranes was a requisite for all deliveries taking place preterm (< 37 weeks gestational age). Risk factors for preterm delivery were evaluated by logistic regression. Weight gain in pregnancy and infant outcomes through 6 months were compared by maternal randomization arm.

Results: In total, 530 women (267 in PI and 263 in NRTI groups) received a median of 11.3 weeks (IQR 8.3-12.9 weeks) of HAART before delivery. Preterm delivery rates were higher in the PI group (21.4% vs. 11.8%, p=0.003). PI-based HAART was a significant risk factor for preterm delivery [odds ratio (OR) 2.03, 95% confidence interval (CI) 1.26 – 3.27]. Weight gain during late pregnancy, measured by mean change in maternal body mass index (BMI) in the first month after HAART initiation, was lower in the PI vs. the NRTI group (0.3 vs. 0.5 kg/m², p <0.001); however, change in BMI one month after HAART initiation was not significantly associated with preterm delivery. Neither infant hospitalization (13.5% for PI vs. 15.2% for NRTI exposed infants) nor mortality (2.6% for PI vs. 1.9% for NRTI exposed infants) in the first six months of life differed by maternal HAART regimen (p=0.62 and 0.77, respectively).

Conclusions: PI-based HAART was associated with a modest increase in preterm delivery but no increase in infant morbidity or mortality through 6 months of life. The importance of lower maternal weight gain in the PI group is uncertain. In resource limited settings utilizing PI-based HAART for PMTCT, additional obstetrical and neonatal care may be needed to avoid adverse consequences from preterm deliveries.

Background

- HAART is highly efficacious as a PMTCT option during pregnancy and breastfeeding
- Many uncertainties remain regarding potential obstetric complications of HAART, including the association of PI-based regimens with preterm delivery (PTD) (< 37 weeks gestation).
- Prior observational studies, predominantly from developed countries, have providing conflicting results on the association between use of PI's in pregnancy and preterm delivery.
- Most women requiring HAART in pregnancy reside in resource limited settings, where access to neonatal care is limited and where increased PTD might contribute to infant mortality.

Methods

- Women included in this analysis were HIV-1 infected pregnant women in Botswana enrolled in the Mma Bana study, a randomized trial investigating the safety and efficacy of either a triple NRTI-based regimen or a PI-based HAART regimen. HAART regimens were initiated between 26-34 weeks gestation among women with CD4+ cell counts ≥ 200 cells/mm³, and continued throughout breastfeeding up to six months postpartum. Women who delivered a live, singleton infant were included in the PTD analysis. Only women experiencing spontaneous PTDs were eligible for this analysis.
- Gestational age was calculated based upon an algorithm combining last reported menstrual period and an ultrasound dating of the pregnancy. The ultrasound was conducted prior to study enrollment. Preterm delivery was defined as < 37 weeks gestation.
- Univariate logistic regression was used to assess the association between maternal randomized HAART treatment, maternal and infant characteristics, as well as known risk factors for PTD delivery and the occurrence of deliveries before 37 weeks gestation.
- Multivariate logistic models were developed for variables found to have a p-value ≤ 0.10 in univariate analysis.
- Analyses of morbidity & mortality of infants in the first 6 months of life by delivery timing (preterm versus term) and by study arm were conducted.

Results

Preterm Deliveries

- Of the 560 women in the randomized treatment arms of the Mma Bana Study, 530 women qualified for the preterm risk factor analysis, with 88 (16.7%) experiencing spontaneous preterm deliveries.
- Baseline demographic and clinical characteristics did not differ by randomized treatment arm.
- Women randomized to the PI-based regimen had a significantly higher rate of PTD (21.4%) compared with women randomized to the triple NRTI treatment regimen (11.8%) [p= 0.003] regardless of gestational age at HAART Initiation.

Rates of PTD by Treatment Arm & Gestation at HAART Initiation

Gestational Age at HAART Initiation	TZV[1] (n)	% Preterm	CBV-KAL[2] (n)	% Preterm
26 to 28 weeks	177	10.2%	180	21.7%
29 to 31 weeks	44	13.6%	63	19.1%
32 to 34 weeks	42	16.7%	24	25.0%
Total	**263**	**11.8%**	**267**	**21.4%**

[1]TZV: Trizivir (Abacavir/Zidovudine/Lamivudine) [2]CBV-KAL: Combivir (Zidovudine/Lamivudine)-Kaletra

Univariate Risk Analysis of Preterm Deliveries

- Use of a PI-based HAART regimen, compared to an NRTI regimen, was significantly associated with a two fold increased risk of preterm delivery in univariate analysis (OR 2.03; 95% CI 1.26 – 3.27).
- Lower maternal income was the only other factor significantly associated with preterm delivery (p=0.002).

Multivariate Risk Analysis of Preterm Deliveries

- After adjustment for maternal income, initiation of PI-based HAART in late pregnancy was associated with a 2-fold increase in preterm delivery (AOR 2.02; 95% CI 1.25 – 3.27).
- Introduction of baseline maternal viral load or CD4+ cell count did not produce evidence of confounding or collinearity within this model.

Change in Maternal Body Mass Index (BMI)

- Median change in BMI one month after treatment initiation among women initiating TZV was 0.5 kg/m² compared to 0.3 kg/m² among women treated with the PI-based regimen. However, no significant association was found between change in BMI one month after treatment initiation and odds of preterm delivery (OR 0.81, 95% CI 0.53-1.24 for each 1 kg/m² increase in BMI).

Infant Morbidity and Mortality Through 6 Months of Life

Event	Preterm (N,%)	Term (N, %)	p-value[1]	TZV (N, %)	CBV-KAL (N, %)	p-value[1]
Resp Tract Infect	8 (9.1%)	9 (2.0%)	**0.003**	10 (3.8%)	7 (2.6%)	0.47
Diarrheal Disease	0 (NA)	12 (2.7%)	0.23	9 (3.4%)	3 (1.1%)	0.09
Meningitis	1 (1.1%)	4(0.9%)	1.0	5 (1.9%)	0 (NA)	**0.03**
Sepsis	4(4.6%)	11 (2.5%)	0.29	10 (3.8%)	5 (1.9%)	0.20
Hospitalization	20 (22.7%)	56 (12.7%)	**0.02**	40 (15.2%)	36 (13.5%)	0.62
Death	6 (6.8%)	6 (1.4%)	**0.002**	5 (1.9%)	7 (2.6%)	0.77

[1]P-value from Fisher's exact test

Conclusions

- PI-based HAART initiated in the 3rd trimester of pregnancy was associated with a 2-fold higher PTD compared with triple NRTI-based treatment
  - Slower BMI increase after treatment initiation was observed with PI-based HAART, and requires further study
- Hospitalizations were 2-fold higher and mortality was 5-fold higher in the first 6 months of life among infants born preterm, but no difference in hospitalizations or mortality was noted by maternal treatment regimen in this clinical trial setting
- PTD should be an expected complication when PI-based HAART is used during pregnancy

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