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BACKGROUND

The relative safety and efficacy of commonly prescribed antiretroviral medications have not been well defined in pregnancy. We initiated a prospective randomized trial, Pediatric AIDS Clinical Trials Group (PACTG) 1022, to evaluate the safety and efficacy of two frequently prescribed antiretroviral regimens for HIV-infected pregnant women.

OBJECTIVES

- ▶ To compare the treatment-limiting toxicity of nevirapin vs. zidovudine
- ▶ To explore the association between nevirapine toxicity and higher CD4 cell counts

METHODS

Study Design:

- Prospective, randomized, open-label trial
- Enrollment May 2002 through August 22, 2003
- Median length of follow-up through January 1, 2004—38 weeks

Participating Centers:

Stony Brook, Columbus Regional Healthcare System, University of Miami, Baylor University, Columbia University, City Hospital at San Juan, University of Tennessee Health Science Center, University of Washington, University of Cincinnati, University of California Los Angeles, Mount Sinai Hospital, University of California San Diego, Yale University, Howard University, Bronx-Lebanon Hospital

Population:

- 38 HIV-1 infected pregnant women at 10–30 wks GA

Eligibility:

- HIV-1 viral load >1000 copies/mL
- Intent to continue antiretroviral therapy after delivery
- Antiretroviral naive (<8 wks prior zidovudine allowed)
- No CD4 cell count entry restrictions

Ineligibility:

- Baseline alanine aminotransferase (ALT) >2.5X upper normal limit
- Active hepatitis B or C
- Other serious concurrent illness

Treatment Arms:

NEBFINAVIR vs. **NEVIRAPINE**
 Zidovudine & Lamivudine vs. Zidovudine & Lamivudine

Toxicity Management:

- Stringent toxicity management guidelines uniformly applied
- Study treatment stopped for the following indications:
 - Confirmed ALT or aspartate aminotransferase (AST) >5X upper normal limit
 - Symptoms of clinical hepatitis at any grade ALT/AST
- Rash accompanied by urticaria, mucous membrane involvement, or constitutional symptoms

Analysis:

- Early interim analysis prompted by ↑ toxicity and changes in nevirapine prescribing information
- Rate of treatment-limiting toxicity compared by treatment arm
- Inten-to-treat analysis
- All subjects and subset with entry CD4 cell count >250 cells/μL
- 2-tailed Fisher's exact used to determine statistical significance

RESULTS

Baseline Demographic and Clinical Characteristics

Demographic Characteristics	NEBFINAVIR (n=21)	NEVIRAPINE (n=17)
Median age	25	28
Race/ethnicity		
White	0 (0%)	1 (6%)
African American	8 (38%)	9 (53%)
Hispanic	12 (57%)	7 (41%)
Asian/Pacific Islander	1 (5%)	0 (0%)
Clinical Characteristics		
Median gestational age at entry	22 wks (15–30 wks)	20 wks (14–28 wks)
Median follow-up as of 1-1-04	37 wks (20–75 wks)	41 wks (6–72 wks)
Entry lab values (median, range)		
Viral load (copies/mL)	7,762 (1,738–85,114)	9,772 (3,388–67,608)
CD4 count (cells/μL)	324 (30–912)	359 (99–371)
CD4 >250 cells/μL	14 (67%)	14 (82%)
ALT (alanine aminotransferase) 1.25–2.5X upper limit normal	0 (0%)	3 (18%)

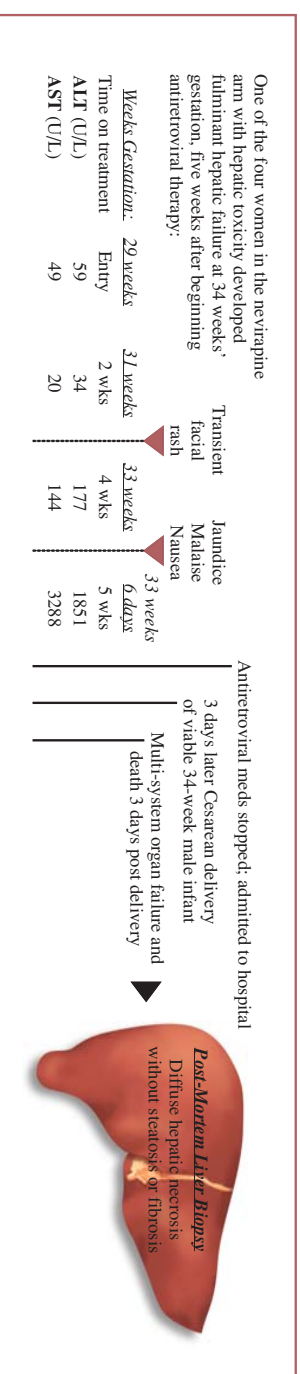
Adverse Events → Treatment Discontinuation

Anti-retroviral	Wks GA @ Entry	Wks GA @ Onset Adverse Event(s)	Entry CD4 Count (cells/μL)	Entry ALT (U/L)	Adverse Event(s)
1 Nevirapine	22	6	239	11	568
2 Nevirapine	17	2	380	11	62
3 Nevirapine	21	4	606	21	135
4 Nevirapine	29			1851	1851
5 Nevirapine	23	22	259	12	41
6 Nevirapine	19	26	510	60	311

Treatment-Limiting Toxicity by Treatment Arm

Subject Group	NEBFINAVIR N (%) (95% CI)	NEVIRAPINE N (%) (95% CI)	p value
All subjects	1/21 (5%) (0–24)	5/17 (29%) (10–56)	.07
Entry CD4 >250 cells/μL	0/14 (0%) (0–23)	5/14 (36%) (13–65)	.04

Treatment-Limiting Toxicity → One Hepatic Failure and Death



DISCUSSION

- ▶ We observed greater than expected toxicity associated with nevirapine during the 1st phase of this randomized trial
- ▶ All adverse events in nevirapine arm occurred in women with entry CD4 cell count >250 cells/μL
- ▶ Hepatic necrosis seen on liver biopsy from the subject who died is consistent with drug-induced hepatic toxicity, possibly direct hepatocellular injury or an immunologic response.
- ▶ It is unclear whether pregnancy poses additional risk for nevirapine-associated hepatic toxicity beyond the risk associated with female gender.

SUMMARY

- ▶ Toxicities observed in this small randomized trial may be clinically relevant even though the sample size is small.
- ▶ These data raise concerns about the safety of continuous nevirapine in pregnancy in women with CD4 cell counts over 250 cells/μL.
- ▶ The safety of nevirapine-containing antiretroviral regimens for pregnant women with lower CD4 cell counts deserves additional investigation, especially since this is rapidly becoming a 1st-line regimen for pregnant women in resource-limited countries.