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Higher Mortality In HIV-Exposed/Uninfected vs. HIV-Unexposed Infants, Botswana

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Background

- HIV-exposed uninfected (HEU) infants have been found to have higher rates of mortality compared with HIV-unexposed (HU) infants in resource limited settings. Higher mortality rates persists, even with breastfeeding.
- Unknown whether this excess mortality persists when mothers have access to effective antiretroviral treatment (ART) for their own health
- We compared rates of 2-year infant mortality in HEU vs. HU infants in Botswana to assess outcomes in an era where maternal ART was available

Methods

- Prospective observational study comparing health (and neurodevelopmental) outcomes among HEU vs. HU children at 24 months of age
- Enrolled HIV-infected and HIV-uninfected mothers in 2 sites (1 urban and 1 rural) in Botswana from May 2010-July 2012.
- Inclusion criteria:
  - ▪Maternal age >= 18 years, Botswana citizen
  - ▪Willingness and ability to provide written consent
  - ▪Pregnant or within 7 days of delivery of a live born child
- Infants followed for 24 months postpartum
  - Study clinic visits monthly during pregnancy; at delivery; and at 1, 6, 12, 18, and 24 months postpartum
  - DNA PCR at birth,1 mo (6, 12 mo if breastfed); 18 mo ELISA
  - Participant medical care from usual clinics (not study)
- Data on socio-demographic factors, health, and psychosocial characteristics were collected at baseline and approximately every 6 months, and infant health outcomes ascertained.
- Mothers chose infant feeding method with counseling; per Botswana guidelines, HIV-infected mothers choosing replacement feeding could receive free formula.

Results

- Enrolled 949 mothers (474 HIV-infected, 475 HIV-uninfected) and 910 live born infants (453 HIV-exposed, 457 HIV-unexposed)
- 10 (2.2%) infants were HIV-infected (among HIV-exposed)
  - 23 infants had unknown HIV status (16 of whom were **not** likely to be HIV-infected or to have died of HIV-related illness)
- 436 HEU and 457 HU infants were followed prospectively
- 24 month infant vital status known for 431 (99%) HEU and 457 (100%) HU infants
- HEU infants experienced nearly 3-fold higher mortality compared with HU babies (HR 2.9, 95% CI 1.3-6.6)
  - Other predictors with p<0.2 on univariate, in Table 3

Table 1: Maternal and Infant Baseline Characteristics

Maternal Characteristics	HIV-Infected Mothers N=443	HIV-Uninfected Mothers N=451
Age (median years)	29	25
Highest education level		
Primary/None	70 (16%)	22 (5%)
Secondary	339 (77%)	345 (76%)
Tertiary	30 (7%)	83 (18%)
No personal earnings	240 (54%)	312 (69%)
Maternal self-rated health		
Excellent, no worries	269 (59%)	247 (55%)
Good, some worries	155 (35%)	184 (41%)
Fair or poor, worried or very worried	18 (4%)	18 (4%)
Enrollment CD4 count (median cells/uL)	410	
Took 3-drug ART antepartum	143 (32.8%)	
Selected Infant Characteristics	**HEU Infants N=453**	**HU Infants N=457**
Gestational Age (median, weeks)	40 (IQR 39-42)	40 (IQR 39-42)
Birthweight (median, kg)	3 (2.7 - 3.4)	3.2 (2.9 - 3.5)
Low birthweight (≤2500g)	85 (19%)	44 (10%)
Initial infant feeding method		
Breastfed	35 (8%)	451 (98.7%)
Formula fed	394 (90.4%)	5 (1%)
Never fed	7 (1.6%)	1 (0.3%)

Table 2: Mortality in HIV-infected, HEU, and HU children through 24 months

	HIV-infected		HEU		HU		Overall	
Initial Feeding Method	n	Number (%) died	n	Number (%) died	n	Number (%) died	n	Number (%) died
Breastfed	1	0	34	1 (2.9%)	451	5 (1.1%)	486	6 (1.2%)
Formula fed	9	4 (44.4%)	395	14 (3.5%)	5	2 (40.0%)	409	20 (4.9%)
Never fed	0	N/A	7	7 (100%)	1	1 (100%)	8	8 (100%)
Total	**10**	**4 (40.0%)**	**436**	**22 (5.1%)**	**457**	**8 (1.8%)**	**903**	**34 (3.8%)**

HEU infants had significantly higher risk of death by 24 months compared with HU infants (HR 2.9, p = 0.009, 95% CI 1.3-6.6)
6 infants died with unknown HIV status and are excluded from analysis.

Table 3: Univariate Predictors of Mortality

Predictor	All Mothers/babies HR (95% CI), p value	HIV+ Mothers/HEU babies only HR (95% CI), p value
Maternal HIV status (reference = uninfected)	2.9 (1.3 - 6.6) 0.009	
Clinic site (urban vs rural)	1.7 (0.8 - 3.4) 0.16	1.5 (0.6 -3.4) 0.37
Drinking water source: (reference = piped into home)	1.4 (0.5 - 3.7) 0.47	1 (0.3 - 3.1) 0.95
Primary cooking method: (reference = gas, electric, kerosene stove)	1.2 (0.5 - 2.6) 0.69	1.8 (0.8 - 4.4) 0.17
Baseline food security (HFIAS): (ref= secure)	1 (0.5 – 2.1) 0.91	1.6 (0.7 – 4) 0.28
Mother died	67.7 (14.8 - 309.6) <0.0001	29.4 (3.7 - 235.1) 0.001
Antiretrovirals during pregnancy (ref = 3-Drug ART)		
None		13.6 (1.6 - 117.5) 0.02
ZDV		1.6 (0.6 - 4.4) 0.36
Never Breastfed (vs.breastfed)	4.9 (2 – 12.1) 0.001	1.8 (0.2 – 13.7) 0.55
Low birthweight (≤2.5kg)	3.5 (1.6 – 8) 0.003	2.2 (0.8 – 5.9) 0.11
Preterm delivery (<37 weeks)	3.2 (1.5 – 6.9) 0.003	2.7 (1.1 – 6.6) 0.03
Congenital abnormality present	7.1 (2.1 – 23.5) 0.001	10 (2.9 – 34) 0.0002

Conclusions

- HEU infants were nearly three-fold more likely to die before 24 months than HIV-unexposed infants.
- The small number of breastfed HEU infants does not permit conclusions about the independent effects of HIV-exposure vs. formula-feeding on infant mortality
- Mortality was very high in HIV-infected infants, despite access to ART