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Effect of Breastfeeding on Mortality and Morbidity in HIV-Exposed Uninfected Children in Uganda

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Background

- Children born to HIV-infected mothers, who remain HIV-uninfected have a higher risk of morbidity and mortality than children born to HIV-uninfected mothers.
- The mechanisms underlying this relationship are multi-factorial, including: (1) HIV-exposed uninfected (HEU) children have impaired immune responses compared to HIV-unexposed uninfected children (HUU) and (2) indirect effects, such as increased poverty, parental mortality, and exposure to infectious pathogens.
- The impact of age and breastfeeding on the relationship between HIV exposure and morbidity remains unclear.

Hypothesis: Early weaning among HIV-exposed uninfected children may account for the excess risk of mortality and morbidity associated with HIV-exposure.

Methods

Study Population and Procedures

- Secondary analysis of 186 HEU (257 person years) and 389 HUU (542 person years) children in Tororo, Uganda who were participating in a trial evaluating the effect of antimalarial chemoprevention.
- Children were randomized to: trimethoprim sulfamethoxazole, dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine, or no chemoprevention.
- Children were seen in a dedicated study clinic for routine monthly visits and any acute illness. They were diagnosed and managed in accordance with standardized protocols.

Analysis

- Multivariate generalized estimating equations with robust standard errors adjusting for repeated measures in the same study participants were used to generate relative risks of morbidity and mortality outcomes.

Methods (cont'd)

Primary outcomes of interest:

(1) **Death**

(2) **Hospitalizations:** all-cause and non-malarial

(3) **Severe febrile illness/pneumonia:** composite of sepsis syndrome (fever and toxic appearance) or severe pneumonia (pneumonia with severe respiratory distress or ill appearance)

(4) **Malaria:** positive blood smear and fever

(5) **Severe malnutrition:** weight-for-height z-score<-3 SD and/or kwashiorkor and/or marasmus

Primary exposure variables of interest:

(1) HIV-exposure

(2) Breastfeeding status (any or none), collected at clinic visits and assigned for every day at risk. HIV-infected mothers were initially counseled to stop breastfeeding at 6 months. Midway through the trial the Ugandan Ministry of Health guidelines changed and HIV-infected mothers were counseled to breastfeed their children for 12 months. HIV-uninfected mothers were counseled to breastfeed for up to two years or beyond.

Examining interactions between HIV exposure and breastfeeding:

- Age-stratified analysis was performed with three HIV-exposure and breastfeeding risk categories. Due to lack of person-time, HUU non-breastfeeding children were excluded from the analysis for the 6-11 month age group and HEU breastfeeding children were excluded from the analysis for the 12-24 month age-group.
- There were no interactions in the model assessing malaria. Thus, results were presented in aggregate and adjusted for age, breastfeeding, wealth index, and chemoprevention.

Results

Baseline Characteristics

- The proportion of children breastfeeding differed between HEU and HUU children: at 6 months 82.5% vs. 99.5%, (p<0.001), at 12 months 29.4% vs. 98.6%, (p<0.001), and at 24 months 0% vs. 24.7% (p<0.001), respectively.
- There was no difference in gender and household wealth index between HIV-exposure groups.
- At enrollment 85% of HIV-infected mothers reported taking trimethoprim-sulfamethoxazole and 38% taking combination anti-retroviral therapy.

Mortality and Non-Malarial Morbidity

- 7 deaths among HEU and 1 death among HUU. HEU compared to HUU had a higher risk of death (RR 13.5, 95% CI: 1.12-167.3, p=0.04), adjusting for age (months), wealth index, breastfeeding, and chemoprevention.
- HEU children had an higher risk of: hospitalizations (RR: 1.80, 95% CI: 1.00-3.23, p=0.048), non-malarial hospitalizations (RR: 2.25, 95% CI: 1.11-4.56, p=0.024), severe febrile illness (RR: 2.39, 95% CI: 1.39-4.13, p=0.002), severe diarrhea (RR: 3.23, 95% CI: 1.52-6.85, p=0.002), and severe malnutrition (RR: 4.31, 95% CI: 1.90-9.78, p<0.001), adjusting for wealth index and chemoprevention. However, the association was no longer significant when breastfeeding was added to the model.

Table 1: Associations between HIV exposure and breastfeeding status with morbidity outcomes among infants 6-11 months of age

Outcome	HUU breastfeeding[a] (189 PY of follow-up)		HEU breastfeeding (43 PY of follow-up)				HEU not breastfeeding (48 PY of follow-up)			
	Events	Incidence[b]	Events	Incidence[b]	RR (95% CI)[c]	p	Events	Incidence[b]	RR (95% CI)[c]	p
All hospitalizations	6	0.032	2	0.046	1.27 (0.22-7.39)	0.79	17	0.354	**10.1 (3.70-27.6)**	<0.0001
Non-malarial hospitalizations	2	0.011	1	0.023	1.50 (0.14-16.4)	0.74	12	0.250	**19.6 (4.95-77.3)**	<0.0001
Severe febrile illnesses	17	0.09	5	0.116	1.34 (0.44-4.07)	0.61	13	0.271	**3.84 (2.06-7.17)**	<0.0001
Severe diarrhea	11	0.058	3	0.07	0.78 (0.17-3.58)	0.75	22	0.458	**6.37 (2.32-17.4)**	<0.0001
Severe malnutrition	3	0.016	1	0.023	2.55 (0.18-35.5)	0.49	15	0.312	**18.4 (4.68-72.0)**	<0.0001

Table 2: Associations between HIV exposure and breastfeeding status with morbidity outcomes among children 12-24 months of age

Outcome	HUU not-breastfeeding[a] (261 PY of follow-up)		HUU breastfeeding (92 PY of follow-up)				HEU not breastfeeding (166 PY of follow-up)			
	Events	Incidence[b]	Events	Incidence[b]	RR (95% CI)[c]	p	Events	Incidence[b]	RR (95% CI)[c]	p
All hospitalizations	24	0.092	11	0.119	1.14 (0.54-2.43)	0.73	16	0.097	0.97 (0.54-2.43)	0.94
Non-malarial hospitalizations	14	0.053	3	0.032	0.62 (0.16-2.46)	0.5	6	0.036	0.70 (0.24-2.04)	0.51
Severe febrile illnesses	13	0.05	2	0.217	0.53 (0.13-2.12)	0.37	16	0.097	2.07 (0.93-4.64)	0.08
Severe diarrhea	8	0.031	5	0.043	2.67 (0.64-12.8)	0.17	9	0.054	2.21 (0.79-6.16)	0.13
Severe malnutrition	14	0.054	4	0.043	2.36 (0.32-17.2)	0.4	18	0.108	**2.67 (1.01-7.05)**	0.05

[a] Reference group [b] Per person year [c] Adjusted for age, chemoprevention, and wealth index; PY=person-years; RR=relative risk; CI=confidence intervals.; HEU= HIV-exposed uninfected children and HUU=HIV unexposed uninfected children

Results (cont'd)

Morbidity Due to Malaria

- The incidence of malaria from 6-24 months of age in both HUU and HEU children was 4.5 per person year and 2.8 per person years respectively, p<0.001.
- HEU children had a 37% decreased risk of malaria compared to HUU children (RR 0.63, 95% CI: 0.53-0.73, p<0.001).

Conclusions

In this cohort, HEU have a higher risk of non-malarial morbidity and mortality compared to HUU children, and this association is moderated by breastfeeding status and age.

Breastfeeding:

- Among children 6-11 months, non-breastfeeding HEU have a markedly higher risk of all non-malarial morbidity compared to breastfeeding HUU. Whereas, there is no difference between non-malarial morbidity outcomes among breastfeeding HEU and HUU.
- These data suggests that early cessation of breastfeeding may at least partially account for the excess risk of non-malarial morbidity among HEU.

Age:

- The higher risk of non-malarial morbidity outcomes declined with increasing age. This may be due to maturation of the of the immune system of HIV-exposed uninfected children.
- Among non-breastfeeding children 12-24 months of age, only the risk of severe malnutrition was higher in HEU compared to HUU.

Malaria:

- The lower risk of malaria among HEU compared to HUU may be due to differences in chemoprevention adherence, as HIV infected women may perceive their child's risk of infection to be higher and are more accustomed to taking medications.