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Infectious Morbidity and Mortality of Infants HIV-Exposed Uninfected Compared To Infants HIV-Unexposed Uninfected in Botswana

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Background

- In 2020, Botswana had the third highest HIV prevalence worldwide among adults ages 15-49 at ~20%.¹
- Over 95% of pregnant women living with HIV receive antiretroviral treatment, with vertical transmission of HIV to newborns occurring in < 2% of births, and ~ 25% of all births in Botswana involving an infant who is HIV exposed yet uninfected.²
- Studies have shown increased risk for infection-related hospitalizations among infants born to WLHIV, who are HIV-exposed uninfected (HEU), compared to infants born to women without HIV, who are HIV-unexposed uninfected (HUU).³
- Our objectives were:
 - To describe prevalence of infectious morbidity/mortality overall and by infant HIV exposure status, comparing prevalence between infants who are HEU and those who are HUU.
 - To identify risk factors associated with infectious morbidity/mortality among all infants, in addition to specific risk factors among infants who are HEU.

Methods

- Between 2016 to 2022, the Tshilo Dikotla study prospectively enrolled pregnant women ≥ 18 years old, both living with HIV and HIV-seronegative, in Botswana, following children and their mothers up to three years after the child's birth.
- Pregnant WLHIV received tenofovir/lamivudine or emtricitabine and efavirenz or dolutegravir through Botswana's national treatment program.
- The primary outcome of interest was infant infectious morbidity or death in the first year of life, where infectious morbidity was defined as a need for hospitalization due to an infectious cause
- Logistic regression models were fit to identify risk factors for infant infectious morbidity/mortality, including infant HIV exposure status.
- A subgroup analysis among infants who were HEU was performed to assess associations between timing of maternal antiretroviral therapy (ART) initiation (pre-conception vs. during pregnancy), maternal enrollment CD4 and HIV viral load, and the outcome of infant infectious morbidity/mortality.

Results

- Of 464 infants, 314 (67.7%) were HEU. Maternal age was higher among WLHIV (30.3 vs. 24.6 years; p < 0.01), as was gravidity (3.0 vs. 1.0; p < 0.01). (Table 1)
- A total of 35 (7.5%) infants were hospitalized/died due to infectious causes [26 (8.3%) HEU vs. 9 (6.0%) HUU (p=0.38)]. The most frequent reasons for hospitalization were pneumonia and diarrhea/gastroenteritis.
- 2 infectious-related deaths occurred due to sepsis (1 infant with HIV exposure and one without).
- There was no significant difference in infectious morbidity by infant HIV exposure status [adjusted Odds Ratio (aOR): 1.22; 95% Confidence Interval (CI), 0.51, 2.92] after adjusting for maternal age, gravidity, income, and education. (Table 2)
- No association was found between timing of maternal ART initiation and infectious morbidity (aOR 1.68; 95% CI, 0.72, 3.96) among infants who were HEU, after additionally adjusting for maternal CD4 count and HIV viral load at study enrollment.

Results (cont.)

Table 1: Maternal and Infant Characteristics by Infant HIV exposure status

Characteristics	Infants HEU N = 314	Infants HUU N = 150	p-value
Maternal Characteristics			
Maternal age (years)	30.3 [25.8, 35.2]	24.6 [21.3, 29.4]	<0.01
Gravidity	3.0 [2.4]	1.0 [1-3]	<0.01
Monthly household income			0.75
<P200	125 (39.8%)	52 (34.7%)	
P200-1000	34 (10.8%)	18 (12.0%)	
>P1000	147 (46.8%)	76 (50.7%)	
Unsure/Other	8 (2.6%)	4 (2.7%)	
Highest education			<0.01
None/Primary	15 (4.8%)	1 (0.7%)	
Junior/Senior Secondary	266 (84.7%)	102 (68.0%)	
Tertiary	33 (10.5%)	47 (31.3%)	
ART initiation prior to conception	176 (56.1%)	-	-
CD4 count at enrollment (cells/mm³)^a			-
≤200	16 (5.1%)	-	-
201-500	146 (46.8%)	-	-
>500	150 (48.1%)	-	-
HIV RNA level <40 copies/mL at enrollment^b	290 (93.0%)	-	-
Median detectable viral load at enrollment, log₁₀	2.23 [1.85, 3.35]	-	-
Median detectable viral load at enrollment, copies/mL	172 [70, 2261]	-	-
Infant Characteristics			
Male^c	159 (50.6%)	72 (48.0%)	0.69
Preterm birth (<37 weeks)	52 (16.6%)	26 (17.3%)	0.89
Birth weight-for-age Z-score^d	-0.2 [-0.9, 0.6]	-0.1 [-0.8, 0.5]	0.40
Birth length-for-age Z-score^d	1.2 [0.1, 2.1]	1.3 [0.1, 2.4]	0.20
Exclusively breastfed from birth^e	263 (86.2%)	138 (99.3%)	<0.01

Abbreviations: ART, antiretroviral treatment; HEU, HIV-exposed uninfected; HUU, HIV-unexposed uninfected; IQR, interquartile range; P, Pula (10 Pula = 1 USD);
Median and IQR presented for continuous variables. Counts and percentages presented for categorical variables. Wilcoxon Rank Sum test used to derive p-values for continuous variables and Fisher's exact testing used for categorical variables;
^aMissing values for CD4 cell count at enrollment: 2; ^bMissing HIV RNA viral loads at enrollment: 2; ^cNo reported sex for two infants (Anthropometric Z-scores calculated using INTERGROWTH21st software) ^dMissing values for infant feeding status, breast versus formula, at birth: 20.

Table 2: Logistic Regression Models of Risk for Infant Infectious Morbidity/Mortality

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	aOR (95% CI)	p-value
Maternal Characteristics				
Age (per 1 year increment)	1.01 (0.96, 1.07)	0.65	0.99 (0.92, 1.07)	0.82
Gravidity				
1st pregnancy	REF		REF	
≥ 2nd pregnancy	1.50 (0.66, 3.39)	0.33	1.42 (0.53, 3.75)	0.48
Income				
>P1000 per month	REF		REF	
P200-1000 per month	0.46 (0.10, 2.03)	0.30	0.46 (0.10, 2.06)	0.30
None; < P200 per month	0.98 (0.47, 2.03)	0.43	0.98 (0.45, 2.12)	0.45
Education				
Tertiary	REF		REF	
None/Primary/Secondary	1.27 (0.48, 3.38)	0.63	1.13 (0.40, 3.16)	0.82
Infant Characteristics				
HIV Exposure Status				
HIV-unexposed	REF		REF	
HIV-exposed	1.41 (0.65, 3.10)	0.39	1.22 (0.51, 2.92)	0.66

Abbreviations: P, Pula (10 Pula = 1 USD)

Conclusions

- In this small sub-Saharan African cohort, where 93% of WLHIV had achieved viral suppression, no detectable associations were observed between infant HIV exposure status and infant infectious morbidity/mortality.
- Larger studies are needed to confirm these findings.

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References

1. UNAIDS. Botswana. Accessed February 5, 2021. <https://www.unaids.org/en/resources/country-profiles/botswana>
2. World Health Organization. Botswana HIV Country Profile: 2019. Accessed November 15, 2021. <https://cfs.hivcd.org/country-factsheet.html>

3. le Roux, Stanz M et al. Infectious morbidity of breastfed, HIV-exposed uninfected infants under conditions of universal antiretroviral therapy in South Africa: a prospective cohort study. *Lancet Child Adolesc Health*. Published online 2020.

