HIV Exposure Does Not Affect Cytomegalovirus Acquisition Risk in a Setting of Optimized Maternal ART

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Background

- Cytomegalovirus (CMV) is a common human herpesvirus that establishes lifelong latency with possibility of reinfection.
- Though infection is generally asymptomatic, CMV may alter immune responses to other pathogens and vaccines.
- Children who are HIV-exposed, uninfected (CHEU) historically have had higher incidence and earlier acquisition of CMV than children who are HIV-unexposed, uninfected (CHUU), which may contribute to higher morbidity/mortality among CHEU.

Objective: To assess the incidence and risk factors of primary CMV infection among CHEU and CHUU in the current era of optimized, universal maternal ART.

Methods

- This analysis was nested in the Linda Kizazi Study, a birth cohort study designed to evaluate how mother-to-child viral transmission affects child health and development.

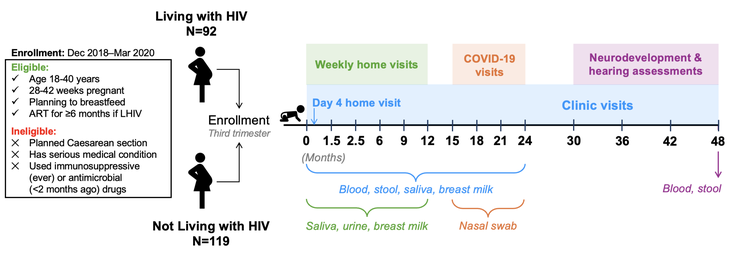


Figure 1. Linda Kizazi Study enrollment and follow-up. Women were recruited from antenatal and HIV care visits at Mathare North Health Centre, a maternal-child health facility serving a densely-populated, low-income area of Nairobi, Kenya. Clinical data collection included current and recent symptoms of illness, diagnoses, medications, immunizations, and infant feeding practices.

- Quantitative PCR was used to measure CMV DNA levels in:
  - Infant urine and saliva (weekly, 0-12 months)
  - Maternal breast milk and saliva (weekly, 0-12 months)
  - Maternal vaginal swab (enrollment)
- **Primary CMV infection** ("CMV acquisition") was defined as the first detectable CMV DNA level in saliva/urine followed by ≥3 subsequent, consecutive visits with saliva CMV ≥3-log or urine CMV ≥0.5-log, confirmed by CMV serology.
- Kaplan-Meier survival analysis was used to compare timing of primary CMV infection between CHEU and CHUU.
- Cox proportional hazards regression was used to assess correlates of CMV acquisition, including HIV exposure; models were stratified by EBF vs not EBF to account for feeding mode.

Results

Uptake of HIV treatment & prevention interventions was high

Table. Selected Participant characteristics.

Characteristic	N	Overall[†] N = 72	CHUU[†] N = 44	CHEU[†] N = 28
Female sex assigned at birth	72	33 (46%)	16 (36%)	17 (61%)
Any siblings <5 years	72	36 (50%)	27 (61%)	9 (32%)
Household crowding	72	48 (67%)	27 (61%)	21 (75%)
Toilet shared with other households	72	65 (90%)	39 (89%)	26 (93%)
Exclusively breastfed for 6 months	65	43 (66%)	21 (55%)	22 (81%)

[†] n (%)

All CHEU received ARV and cotrimoxazole prophylaxis. Most (89%) mothers with HIV initiated ART before pregnancy (89% efavirenz-based).

Over half of CHEU & CHUU acquired CMV in the first 3 months of life.

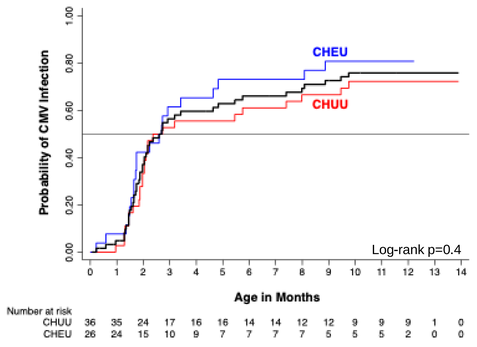


Figure 2. Kaplan-Meier curve for the probability of primary CMV infection. The black line indicates the survival probability among all infants. The horizontal line shows the median survival probability (0.5). One infant with congenital CMV infection was excluded from analyses.

Breast milk CMV DNA level was associated with a two-times greater hazard of CMV acquisition for both CHEU & CHUU despite higher CMV levels among women with HIV.

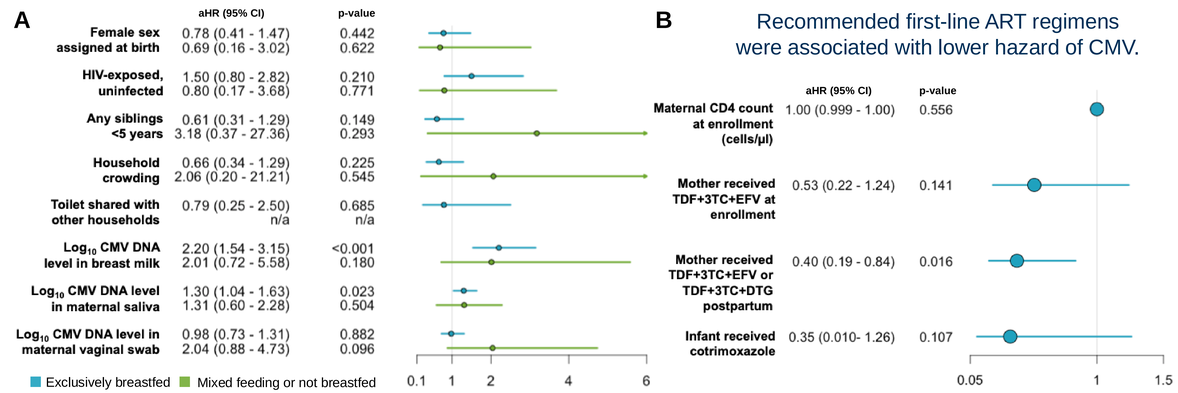


Figure 3. Adjusted hazard ratios for hypothesized correlates of primary CMV infection among (A) all infants and (B) CHEU. Cox proportional hazards models included the correlate and, if applicable, HIV exposure, infant sex, and household crowding. n/a = insufficient sample size to calculate hazard ratio.

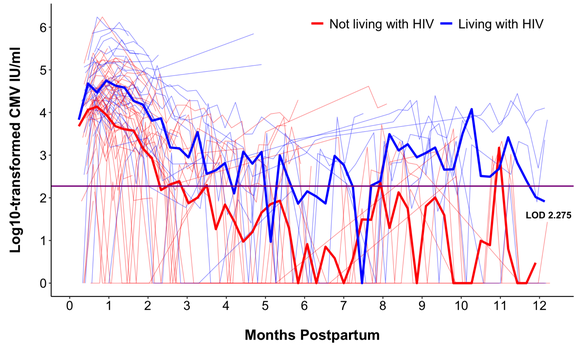


Figure 4. Log10-CMV levels in breast milk, by maternal HIV status. Bold lines represent overall mean $\log_{10}$-CMV DNA levels for each time point. Background lines represent individual patterns of $\log_{10}$-CMV DNA levels.

Conclusions

- Consistent with other populations in low- and middle-income countries, most infants acquired CMV in the first 3 months of life and nearly all by one year.
- The timing and hazard of CMV infection was similar between CHEU and CHUU, suggesting that optimized maternal ART initiated before or in early pregnancy reduces transmission compared to cohorts followed in the pre-universal ART era.
- Breast milk remains a primary source of CMV acquisition for all infants.
- Women with HIV had higher breast milk CMV DNA levels than women without HIV, though this did not translate to greater risk of transmission; further study is needed to understand mechanisms for this finding.

Acknowledgements

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