Maternal CMV Urinary Shedding in HIV-Infected Women and Congenital CMV Infection

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Background

- Cytomegalovirus (CMV) is a leading cause of sensorineural hearing loss and a major infectious etiology of developmental delay. Preliminary data indicates CMV is more prevalent in HIV-exposed infants. However, less is known about the role of maternal CMV shedding and risk of congenital CMV for HIV-infected pregnant women.

Objectives

- We evaluated CMV urinary shedding rates in HIV-infected pregnant women to determine if HIV-exposed infants born to mothers with CMV shedding were at increased risk for congenital CMV.

Methods

- The study population was a subset of mother-infant pairs from Brazil, Argentina, South Africa and the U.S., who were enrolled in NICHD HPTN 040, a perinatal trial which enrolled women identified as HIV-infected during labor with no antiretroviral use in pregnancy, for whom maternal and infant urine specimens were available.
- One mL aliquots of maternal urines were tested with qualitative Real-Time PCR for CMV DNA; those with positive results were tested by quantitative CMV PCR.
- Infant urines were similarly tested with mother-infant pair results correlated.

Results

- Urine specimens were available for 260 women.
- 24 (9.2%) women had detectable CMV viruria.
- The majority (91.7%) with viruria had low level detectable CMV (<200 copies/mL). Two had 236 and 53,524 CMV copies/mL urine.
- Significant differences were noted in the number of infants with congenital CMV born to mothers with and without CMV viruria (20.8% vs 2.1%, p=0.0008).
- The two women with higher levels of CMV viruria had infants with congenital CMV.
- Mean CD4 counts and mean HIV viral loads were not significantly different between women with and without CMV viruria.

Maternal Characteristics

Age (yo)	13-24 25-29 ≥30	99 (38.1%) 77 (29.6%) 84 (32.3%)	**Syphilis**	Yes No	20 (7.7%) 239 (92.3%)
Region	Americas Africa	222 (85.4%) 38 (14.6%)	**Chlamydia**	Yes No	40 (15.9%) 212 (84.1%)
Rupture of Membranes Duration (hrs)	<0.5 0.5 - <6 6 - <12 12- <24 >24 Unknown	148 (56.9%) 56 (21.5%) 21 (8.1%) 9 (3.5%) 5 (1.9%) 21 (8.1%)	**Gonorrhea**	Yes No	13 (5.2%) 239 (94.8%)
Mode of Delivery	C-section before rupture Vaginal or C-section after rupture	93 (35.8%) 167 (64.2%)	**Alcohol Use**	Yes No	99 (38.2%) 160 (61.8%)
Any Prenatal Care	Yes No	159 (61.2%) 99 (38.1%)	**Illegal Substance Use**	Yes No	38 (14.7%) 221 (85.3%)

Maternal CMV Urinary Shedding, CMV and HIV Perinatal Transmission, Infant Death, CD4 Count and HIV Viral Load

Maternal CMV in Urine	CMV Transmission Rate to Infants	HIV Transmission Rate to Infants	Infant Death Rate	Mean Maternal CD4 Count (cells/mm³)	Mean Maternal HIV Viral Load (copies/mL)
CMV Positive N=24 (9.2%)	5/24 (20.8%)	7/24 (29.2%)	1/24 (4.2%)	441.8 (SD 178.6) Range (128-778)	94,664 (SD 202,185.2) Range (94-718,900)
CMV Negative N=236 (90.8%)	5/236 (2.1%)	19/235 (8.1%)	2/236 (0.85%)	481.1 (SD 311.1) Range (28-2160)	70,906.8 (SD 253,893.1) Range (0-2,700,000)
Total N=260	10/260 (3.8%)	26/260 (10%)	3/260 (1.2%)	477.4 (SD 301.1) Range (28-2160)	73,108.3 (SD 249,313.4) Range (0-2,700,000)
P-value[1*]	0.0008	0.005	0.25	0.92	0.91

[1]Fisher's exact test for categorical variables or Kruskal-Wallis test for continuous variables; SD: Standard deviation*

Relationship between Maternal CMV Urinary Shedding and Perinatal HIV Transmission

Maternal CMV Urine N=260	Infant HIV Transmission		Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
	HIV-Infected N=26	HIV-Uninfected N=234				
Positive 24 (9.2%)	7 (29.2%)	17 (70.8%)	4.7 (1.7-12.8)	0.002	5.6 (1.9-16.8)*	0.002
Negative 236 (90.8%)	19 (8.1%)	217 (91.9%)	1.00		1.00	

**Adjusted for rupture of membranes and log10 HIV viral load and infant ART study arm*

Relationship between Maternal CMV Urinary Shedding , Gonorrhea, and HIV Viral Load and Congenital CMV

Maternal Risk Factors	Infant CMV Transmission		Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Maternal CMV Urine N=260	**CMV Positive** N=10	**CMV Negative** N=250				
Positive 24 (9.2%)	5 (20.8%)	19 (79.2%)	12.2 (3.2-45.7)	0.0002	29.7 (5.4-164.2)**	0.0001
Negative 236 (90.8%)	5 (2.1%)	231 (97.9%)	1.00		1.00	
Maternal Gonorrhea N=252						
Positive 13 (5%)	2 (15.4%)	11 (84.6%)	6 (1.1-32.5)	0.04	19.5 (2.5-151.3)***	.005
Negative 239 (91.9%)	7 (2.9%)	232 (97.1%)	1.00		1.00	
HIV Log10 Viral Load[2*] N=259	10 (3.9%)	249 (96.1%)	2.8 (1.3-6.3)	0.01	---	---

***Adjusted for mode of delivery, gonorrhea, and log10 HIV viral load.*
****Adjusted for maternal urine CMV, mode of delivery, and log 10 HIV viral load.*
2 For each 1 unit of Log10 HIV viral load increase, without consideration of any other factors.*

- Relationships for HIV transmission and CMV transmission were adjusted based on significant covariates identified in the univariate model analysis.
- Women with CMV viruria were >5 times more likely to transmit HIV to their infants (29.2% vs. 8.1%, p =0.005); aOR 5.6 (95% CI 1.9-16.8).*
- Women with CMV viruria were also nearly 30 times more likely to transmit CMV to their infants (aOR 29.7, 95% CI 5.4-164.2).**
- Higher rates of death were observed for infants of women with versus without CMV viruria (4.2% vs 0.85%, p=0.25), although not significant.
- Maternal gonorrhea was also a risk factor for infant CMV transmission (aOR 19.5, 95% CI 2.5-151.3), but this was not seen with maternal chlamydia or syphilis.***

Conclusions

- High rates of urinary CMV shedding were observed in HIV-infected pregnant women not on antiretrovirals.
- Maternal CMV viruria at the time of birth may be a risk factor for CMV and/ or HIV transmission to infants

Acknowledgements

- NICHD HPTN 040 Study Group
- NIAID/NICHD, HPTN, IMPAACT
- UCLA CDI Harry Winston Fellowship Award
- Bryson Lab: Bonnie Ank, Mary Ann Hausner, Jessica Liu