



Low and Undetectable Breast Milk Interleukin-7 Concentrations are Associated with Reduced Risk of Post-Natal HIV Transmission

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BACKGROUND

Although HIV transmission through breastfeeding is of large public health importance, the mechanisms underlying transmission are not well understood. Interleukin [IL]-7 has been shown to enhance HIV transmission and replication *in vitro*, but its effect on HIV transmission *in vivo* is unknown. We tested whether breast milk IL-7 concentration is associated with postnatal HIV transmission.

METHODS

A nested case-control study was conducted within a cohort of women recruited in Lusaka, Zambia. The cases included 24 HIV-infected women, who transmitted the virus to their infants post partum. The controls were 47 non-transmitters. For comparison, 18 HIV-uninfected women were also included. Breast milk samples were matched by the time of sample collection (70% 1 week post partum, 30% 1 month post partum). Logistic regression was conducted to adjust for possible confounders.

RESULTS

IL-7 levels in all three groups were significantly higher in breast milk than in plasma (non-transmitters: median 153 pg/ml [IQR: 70, 325] versus 12 pg/ml (9, 13) p=0.0005; transmitters: 117 (0.3, 373) versus 10 (4, 21) p=0.0002; HIV-uninfected women : 182 (109, 416) versus 11 (9, 15) p <0.0001). There was no difference in the median or mean breast milk IL-7 levels among any of the three groups (Figure 1). However, the distribution of breast milk IL-7 levels differed between the groups. IL-7 had a bimodal distribution among non-transmitters compared to a normal distribution among transmitters and HIV-uninfected women (Figure 2). Low/undetectable breast milk IL-7 levels below a cut-off of 30pg/ml were significantly associated with fewer HIV transmissions. This effect remained significant after adjusting for possible confounders (Table 2). Predictors of low breast milk IL-7 among the non-transmitters were parity and time of sample collection (Table 3).

CONCLUSION

Low/undetectable levels of IL-7 in breast milk collected at 1 week and 1 month postpartum were associated with protection from HIV transmission through breastfeeding. These observations are consistent with data showing that IL-7 promotes productive infection of quiescent T-cells *in vitro*. Our data suggest that *in vivo* normal or high breast milk IL-7 concentrations may enhance susceptibility of quiescent infant T-cells to HIV infection. The role of IL-7 in HIV transmission through other routes should be investigated.

Table 1: Baseline characteristics of women included in the analysis

	Mother HIV-infected		p-value	Mother HIV-uninfected
	Postnatal Transmitters	Non-Transmitters		
N	24	47		18
<i>Breast Milk</i>				
N (%) HIV RNA >50 copies/ml	16 (70)	19 (41)	0.03	/
Median (IQR) log ₁₀ HIV RNA	2.5 (1.7, 3.9)	1.7 (1.7, 2.2)	0.007	/
N (%) sodium ≥13 mmol	9 (38)	17 (36)	0.91	7 (39)
<i>Maternal Parameters during pregnancy</i>				
Mean (SD) CD4+ counts/μL	215 (107)	390 (197)	<0.001	845 (227)
Mean (SD) log ₁₀ plasma HIV RNA copies/ml	4.9 (0.6)	4.5 (0.9)	0.08	/
<i>Clinical factors</i>				
Mean (SD) age in years at enrolment	27.9 (4.5)	25.9 (4.3)	0.07	26.2 (7.1)
% (SE) still breastfeeding at 4 months ¹	91 (6.0)	91 (4.3)	0.91	94 (5.7)
% (SE) still breastfeeding at 12 months ¹	35 (10.4)	49 (7.9)	0.34	94 (5.7)
Parity [(n (%))]				
Primipara	1 (4)	7 (15)		5 (28)
1-2 Previous live births	8 (33)	25 (53)		5 (28)
3+ Previous live births	15 (63)	15 (32)		8 (44)
Mean (SD) birth weight (grams)	2672 (612)	3028 (497)	0.01	3004 (616)
N (%) preterm births <35 weeks	4 (17)	8 (17)	1.0	3 (17)

¹ Kaplan-Meier estimates with standard error (SE); SD= standard deviation; IQR=inter-quartile range

Figure 1: IL-7 concentrations in breast milk are higher than in plasma in all three groups of women.

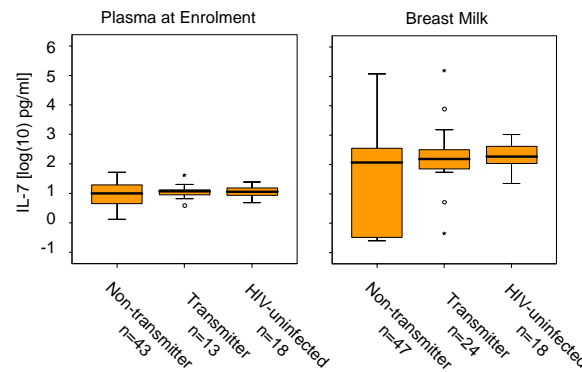


Figure 2: Breast milk IL-7 levels among non-transmitters exhibit a bimodal distribution. Undetectable samples are marked in yellow.

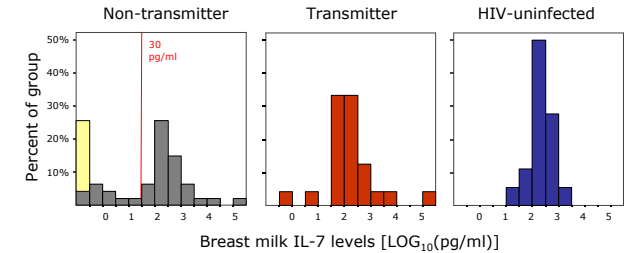


Table 2: Low/undetectable breast milk IL-7 levels are associated with a reduced risk of postnatal HIV-transmission. Shown are the results of logistic regression modeling.

	Unadjusted	95% CI	Adjusted	95% CI
	Odds Ratio		Odds Ratio ¹	
Undetectable or low (<30pg/ml) breast milk IL-7	0.13	0.03 to 0.64	0.10	0.02 to 0.62
Breast milk viral load per log ₁₀ increase	2.32	1.27 to 4.24	2.18	1.06 to 4.46
Plasma CD4+ T-cells per 10 cells increase	0.93	0.89 to 0.97	0.92	0.88 to 0.97
Parity per increase of previous live birth	1.39	0.97 to 2.00		
Time of sample collections (1 mo versus 1 wk)	1.08	0.36 to 3.20		

¹ adjusting for all three variables shown in this column. Adding parity, birth weight, preterm birth, maternal age or time of sample collection does not appreciably change the IL-7 effect. None of these variables remained significant, if added to the model.

Table 3: Time of sample collection and higher parity are associated with low breast milk IL-7 levels among the non-transmitters (N=47).

	Mother HIV-infected Non-transmitters only		p-value
	Low Breast milk IL-7 <30 pg/ml	Normal breast milk IL-7 ≥30 pg/ml	
N	19	28	
<i>Breast Milk</i>			
N (%) one week samples	10 (53)	24 (86)	0.01
N (%) HIV RNA >50 copies/ml	10 (53)	9 (33)	0.19
Median (IQR) log ₁₀ HIV RNA	1.8 (1.7, 2.6)	1.7 (1.7, 2.2)	0.41
N (%) sodium ≥13 mmol	4 (21)	13 (46)	0.08
<i>Maternal Blood</i>			
Mean (SD) CD4+ counts/μL	394 (208)	387 (193)	0.90
Mean (SD) log ₁₀ HIV RNA copies/ml	4.5 (0.9)	4.6 (0.8)	0.63
Mean (SD) log ₁₀ IL-7 ²	1.1 (0.3)	0.9 (0.4)	0.17
<i>Parity N (%)</i>			
Primipara	2 (11)	5 (18)	
1-2 Previous live births	7 (37)	18 (64)	
3+ Previous live births	10 (53)	5 (18)	0.02