No Effect of Maternal HIV and *in utero* cART on Infant Leukocyte Telomere Length

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Introduction

- Current **combination antiretroviral therapies (cART) have been highly successful** in preventing mother-to-child-transmission in the 1.5 million children born to HIV+ mothers each year.
- However, such exposure to maternal cART during pregnancy could have long term effects on HIV-exposed uninfected (HEU) infants.
- Many **cART drugs can cross the placenta and could affect cellular processes** in the developing fetus, but so could exposure to maternal HIV "milieu", as both cART drugs and HIV proteins are reported to inhibit telomerase.
- **Leukocyte telomere length (LTL)** reflects cellular replication history and is an important marker of cellular aging.
- We previously reported shorter LTL in HIV+ adults compared to HIV- controls but saw no association with duration of cART[1].
- Among children (0-19y) and infants (0-3d) however, no difference in LTL was seen between HIV+, HEU and HIV-unexposed uninfected (HUU) controls, although among HIV+ children, being on cART was associated with longer LTL[2], and HEU cord blood trended toward shorter LTL[3].

Objective and Hypothesis

Objective: To compare HEU and HUU infant LTL at birth and over the first three years of life, as well as investigate any relationship to maternal HIV/cART exposure *in utero.*

Hypothesis: Infants born to HIV+ mothers who started cART late in pregnancy (2nd and 3rd trimesters) will have shorter LTL compared to infants with less HIV milieu exposure such as:

(a) HEU infants born to HIV+ mothers who conceived on cART

(b) HEU infants born to HIV+ mothers who started cART in the 1st trimester

(c) HUU control infants born to uninfected mothers.

Materials & Methods

- Study subjects included 324 HEU infants aged 0-3y enrolled in the CARMA cohort study; most (n=215) with ≥2 blood samples collected, and 308 HUU controls (0-3y), each with a single blood sample.
- LTL was measured on whole blood DNA via monochrome multiplex qPCR.
- A subset of 0-3y HEU and HUU children (n=214 distinct children per group) were randomly age- and sex-matched 1:1.
- Univariable linear regressions were used to examine the relationship(s) between infant LTL at birth and HIV exposure status, infant sex, gestational age, birth weight, maternal age, ethnicity and smoking ever in pregnancy. Factors significantly associated with LTL were included in the multivariable analyses.

Results

- In a cross-sectional multivariable analysis of all participants that had a birth sample (0-3d, n=193; HEU=114, HUU=79) only **male sex** was associated with **shorter LTL at birth** (p=0.017, ANCOVA).

Demographic Characteristics	HEU n=115	HUU n=91	P
Infant Characteristics			
Male sex	64 (56)	49 (54)	0.80
Gestational age at birth, weeks	38.3 (31.3 - 41.6) (n=115)	39.4 (28.9 - 42.1) (n=88)	<0.01
<34 weeks	4 (3)	1 (1)	
<37 weeks	19 (17)	8 (9)	
Birth weight, kg	3.1 (1.6 - 4.1) (n=115)	3.4 (1.4 - 5.2) (n=88)	< 0.01
Maternal Characteristics			
Maternal age, years	31.2 (17.4 - 45.2) (n=115)	32.5 (21.3 - 43.0) (n=88)	0.09
Maternal ethnicity			< 0.01
Aboriginal, First Nation, Metis, Inuit	33 (29)	7 (8)	
Black/African Canadian	28 (24)	2 (2)	
White	39 (34)	55 (60)	
Asian, South, East or Western Asian	10 (9)	16 (18)	
Other or Missing	5 (4)	11 (12)	
Maternal substance use			
Smoking ever in pregnancy	64 (56)	38 (43)	0.08

N (%) or median (range) and n subjects for whom data was available

Table 1. Demographic characteristics of all infants with a birth sample (0-3d)

- There was a significant interaction between **HEU/HUU status and maternal smoking** (p=0.009) with the latter being associated with **longer LTL in HUU and shorter LTL in HEU.**

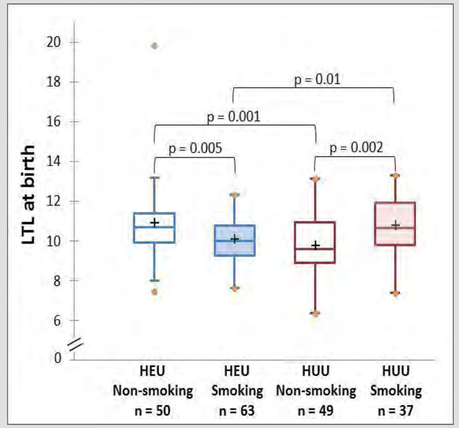

Figure 1. Univariable relationship between HEU/HUU status and maternal smoking in pregnancy on LTL at birth.

- Among age and sex-matched children (n=214:214), leukocyte telomere length attrition rate was not significantly different between groups (p=0.69, Mann Whitney test) .

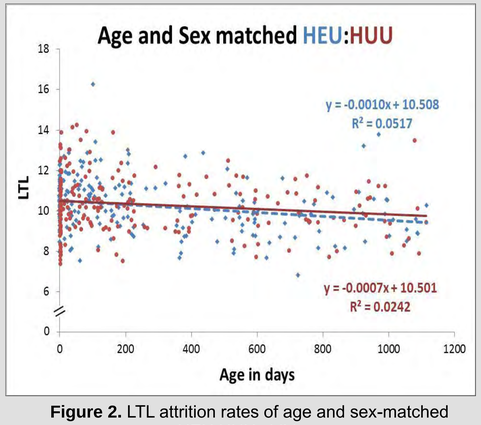

Figure 2. LTL attrition rates of age and sex-matched HEU:HUU children

- However there was a significant sex by age effect with **males having slower attrition than females** (p=0.03, Mann Whitney test).

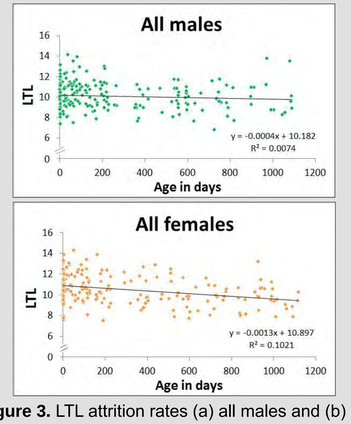

Figure 3. LTL attrition rates (a) all males and (b) all females, irrespective of HIV exposure status

- In another model that included HEU children only (n=114) and investigated cART parameters, duration of cART exposure *in utero* and type of cART did not show any relationship with LTL at birth.
- There was also no relationship between trimester of maternal cART start and LTL at birth.

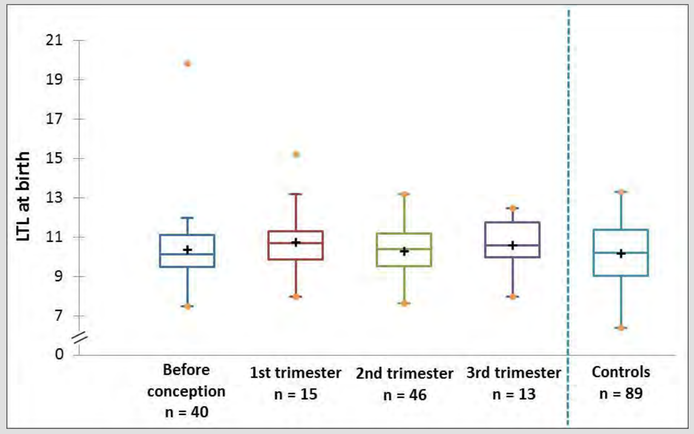

Figure 4. LTL at birth vs. trimester of maternal cART start

- Finally, irrespective of HIV exposure status, **maternal smoking** was significantly associated with **lower infant birth weight** (p=0.003, Mann Whitney test).

	Non-smoking n = 208	Smoking n = 128	P value
Birth weight (kg)	3.16 ± 0.63	2.99 ± 0.59	0.003

Table 1. Relationship between maternal smoking in pregnancy and infant birth weight

Conclusions

- These results further support that exposure to maternal HIV/cART *in utero* does not affect infant LTL, a reassuring finding.
- The contrasting effects of maternal smoking on LTL at birth in the two groups is a novel finding and could possibly be related to cytogenetic damage leading to slower cell replication rates or may represent a surrogate for other factors.

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