DISTINCT CORD C-PEPTIDE, ADIPOKINE, & LIPIDOMIC SIGNATURES BY *IN UTERO* HIV EXPOSURE

POSTER #0802

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BACKGROUND

- **Metabolic derangements early in life of HIV-exposed uninfected (HEU) infants have been reported**
- **Decreased insulin sensitivity and/or altered energy metabolism in the fetus (or mother-placenta-fetus) can lead to negative health outcomes later in childhood or adulthood**
- **Few studies have investigated metabolic parameters and lipidomic signatures in cord blood of HEU infants**

OBJECTIVES

- **Assess the association of *in utero* HIV exposure with insulin sensitivity at birth**
- **Assess differences in cord blood metabolic parameters, adipokines, and lipidomic signatures between HEU and HIV-unexposed uninfected (HUU) infants**

METHODS

Study Design: Cohort study, urban tertiary center, USA

Inclusion Criteria:

- **Singleton live births of women living with HIV (WLHIV) or HIV-uninfected women**

Exclusion Criteria: Without available cord blood, HIV infection

Primary Outcomes: C-peptide, Insulin

Exposure of Interest:

- ***In utero* HIV exposure**
- **Cord blood metabolites and lipid subspecies**

Statistical Analysis:

- **Linear regression models were fit to assess the association between *in utero* HIV/ART exposure and cord C-peptide, adjusting for confounders**
- **Spearman tests were used to assess the correlations of adipokines, inflammatory markers, and ghrelin with C-peptide**
- **Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to identify separation between HEU and HUU infants based on metabolite and lipid subspecies**
- **Elastic net regression was used to identify factors, including metabolites and lipid subspecies most associated with increased cord C-peptide, stratified by *in utero* HIV exposure**

Table 1. Characteristics of Women and Infants at Enrollment

	Women with HIV/ Infants HIV-exposed n=56	Women without HIV/ Infants HIV-unexposed n=62	*p* value
***WOMEN*^**			
Age, years	26 (23-31)	23 (21-27)	*<0.01*
Race/ Ethnicity			*0.24*
White	1 (1.8)	2 (3.2)	
Black/ African American	33 (58.9)	25 (40.3)	
Hispanic	19 (33.9)	30 (48.4)	
Other	3 (5.4)	5 (8.1)	
Employment	16 (28.6)	24 (38.7)	*0.25*
Family history of diabetes	19 (33.9)	33 (53.2)	*0.04*
Pre-pregnancy BMI, kg/m²	26.4 (22.3, 31.5)	25.0 (22.7, 29.4)	*0.39*
CD4 cell count at enrollment, cells/mm³			------
< 50	7 (12.5)	------	
51-200	11 (19.6)	------	
201-500	8 (14.3)	------	
> 500	24 (42.7)	------	
HIV RNA level <50 at delivery	48 (85.7)	------	------
ART during pregnancy			------
NNRTI-based	12 (21.3)	------	
PI-based	29 (52.0)	------	
Integrase Inhibitor-based	5 (8.9)	------	
≥3 classes of ARVs	9 (16.0)	------	
Other	1 (1.8)		
Gestational Diabetes	1 (1.8)	0 (0.0)	*0.29*
INFANTS			
Preterm (<37 weeks GA)	5 (8.9)	3 (4.8)	*0.47*
SGA	12 (15.2)	6 (7.5)	*0.13*
C-section delivery	50 (63.3)	16 (20.0)	*<0.01*
Birth WAZ	-0.50 (-1.10, 0.15)	-0.25 (-0.78, 0.24)	*0.47*
Birth LAZ	-0.26 (-0.82, 0.46)	0.11 (-0.74, 0.60)	*0.28*
Birth HCAZ	-0.15 (-0.78, 0.34)	-0.21 (-0.68, 0.30)	*0.77*
HIV infection	0 (0.0)	---	
Cord Blood Metabolites			
Insulin µIU/mL	14.6 (10.9, 23.8)	12.6 (8.8, 19.1)	*0.03*
C-peptide ng/mL	1.04 (0.80,1.56)	0.88 (0.48, 1.15)	*<0.01*
Adiponectin µg/mL	45.0 (32.3, 83.8)	52.1 (30.2, 73.8)	*0.60*
Ghrelin pg/mL	13.7 (4.7, 13.7)	4.4 (2.7, 13.7)	*0.01*
Leptin ng/mL	11.7 (6.8, 23.2)	12.4 (7.7, 18.2)	*0.84*
Resistin ng/mL	101.9 (56.5, 162.8)	134.7 (81.1, 300.0)	*<0.01*
IL-6 pg/mL	13.7 (13.7, 23.0)	15.9 (7.9, 45.9)	*0.29*
IL-10 pg/mL	1.7 (0.8, 2.8)	1.5 (0.4, 3.3)	*0.58*
TNF-α pg/mL	15.0 (11.9, 18.3)	14.6 (12.1, 17.6)	*0.84*
IFN-γ pg/mL	0.6 (0.6, 1.0)	0.60 (0.6, 0.6)	*<0.01*

^First Enrolled Pregnancy Only; *Continuous variables shown as (Median)(Interquartile Range) and categorical variables shown as (n)(%); *p values* for continuous variables from Wilcoxon tests and for categorical variables from chi-square or Fisher exact tests as appropriate. ART=antiretroviral therapy; BMI=Body Mass Index; GA=gestational age; HCAZ=Head Circumference for Age Z score; LAZ=Length for Age Z score; NNRTI=Non-nucleoside reverse transcriptase inhibitor, PI=Protease Inhibitor; SGA=Small for Gestational Age; WAZ=Weight for Age Z score;

Table 2. Unadjusted and Adjusted Models for the Association between *in utero* HIV exposure and Cord Insulin, C-peptide

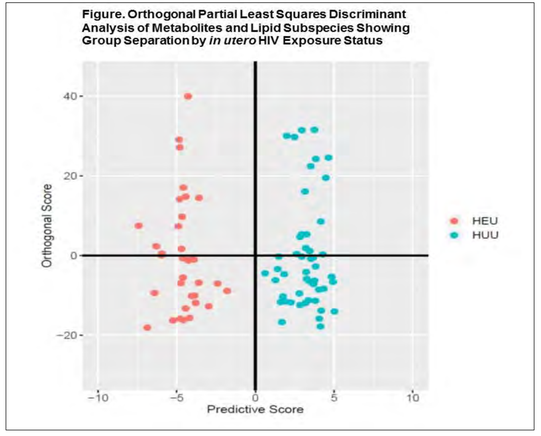
Model Outcome	Unadjusted Coefficient	*p* value	Adjusted Coefficient	*p* value
Log Insulin	0.248	0.05	0.295	**0.03**
Log C-peptide	0.334	0.02	0.522	**<0.01**

All models adjusted for maternal age, maternal gestational diabetes, family history of diabetes, maternal pre-pregnancy body mass index, infant sex, infant preterm birth, infant birth weight z score

Table 3. Spearman Correlations of C-peptide with Adipokines, Inflammatory Markers, and Ghrelin by *in utero* HIV exposure status

	HEU infants (n=56)		HUU infants (n=62)	
Marker	**rho**	***p* value**	**rho**	***p* value**
IL-6	**0.29**	***0.05***	**0.08**	***0.52***
TNF-α	**0.26**	***0.08***	**0.10**	***0.46***
IFN-γ	**0.03**	***0.86***	**0.10**	***0.45***
Resistin	**-0.04**	***0.77***	**-0.40**	***<0.01***
Adiponectin	**0.07**	***0.72***	**0.01**	***0.96***
Leptin	**0.64**	***<0.01***	**0.26**	***0.04***
Ghrelin	**-0.16**	***0.29***	**-0.06**	***0.63***

Figure. Orthogonal Partial Least Squares Discriminant Analysis of Metabolites and Lipid Subspecies Showing Group Separation by *in utero* HIV Exposure Status



RESULTS

- **No differences in maternal race/ethnicity, pre-pregnancy BMI, gestational diabetes (GDM) or infant preterm birth (PTB), birth weight/length were noted (Table 1)**
- **All HEU infants were ART-exposed (52% PI, 21% NNRTI, 9% INSTI)**
- **After adjusting for maternal age, GDM, family diabetes history, pre-pregnancy BMI, as well as infant sex, PTB, and birth weight z score, mean cord insulin (β=0.295, *p*=0.03) and C-peptide (β=0.522, *p*<0.01) were significantly higher in HEU vs. HUU infants (Table 2)**
- **IL-6 correlated positively with C-peptide in HEU (rho=0.30, *p*=0.05) but not HUU infants (rho=0.08, *p*=0.52) while resistin correlated inversely with C-peptide in HUU (rho= -0.40, *p*<0.01) but not HEU. Leptin correlated positively with C-peptide in both groups (rho=0.64, *p*<0.01 in HEU; rho=0.26, *p*=0.04 in HUU) (Table 3)**
- **Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) showed clear group separation by metabolites and lipid subspecies. (Figure)**
- **Elastic net regression identified pre-pregnancy BMI and complex lipids with polyunsaturated side chains to be positively associated with cord C-peptide in both groups**
- **In HEU but not HUU infants, arachidonic acid and microbial derivatives of tyrosine and tryptophan were associated with C-peptide.**

CONCLUSIONS

- **Compared to HUU, HEU infants manifest higher insulin and C-peptide levels suggesting lower insulin sensitivity**
- **Differences in cord metabolite, lipid subspecies, & adipokines are significant between HEU and HUU infants, suggesting altered fetal metabolic programming due to *in utero* HIV exposure**

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