UNIQUE EICOSANOID/LIPID PROFILES IN PREGNANT WOMEN LIVING WITH HIV IN BOTSWANA

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BACKGROUND

- Studies have shown that infants born to women living with HIV (WLHIV) have lower insulin sensitivity in the first month of life compared to those born to HIV-seronegative women.
- Few data exist on maternal eicosanoid/lipid profiles in pregnant WLHIV and how this influences the *in utero* environment or infant insulin sensitivity.
- We evaluated maternal eicosanoid/lipid profiles in pregnant WLHIV and pregnant HIV-seronegative women in Botswana and assessed their relationship with infant insulin sensitivity.

METHODS

Study population

- The Tshilo Dikotla study enrolled pregnant WLHIV and HIV-seronegative pregnant women as well as their offspring from 2016-2019 in Botswana to assess metabolic effects of *in utero* HIV and ARV exposure.
- All WLHIV received tenofovir (TDF)/emtricitabine (FTC) plus either dolutegravir (DTG) or efavirenz (EFV)
- This analysis included mother-infant pairs with maternal repository plasma collected between 24-28 wks gestational age (GA) and infant insulin and glucose levels at 1 mo of age.

Primary outcome

- Homeostasis Model Assessment for Insulin Resistance (HOMA) was assessed and log-transformed using infant fasting (collected just prior to a normal feed) insulin and glucose levels at 1 mo of age.

Exposure of interest

- ~800 eicosanoids/lipid subspecies were measured via liquid chromatography mass spectrometry in fasting maternal plasma.

Statistical analysis

- Volcano plots were used to visualize differences in eicosanoids/lipid subspecies by maternal HIV status.
- Lasso regression models were fit to assess maternal factors (age, gestational diabetes) and eicosanoid/lipid subspecies predictive of infant log HOMA at 1 mo of age, stratified by maternal HIV status.

In this Botswana cohort, pregnant WLHIV showed partial compensation of pro-inflammatory eicosanoid mediator production; compared to DTG, EFV was associated with a maternal dyslipidemic profile in pregnancy which was predictive of lower infant insulin sensitivity.

RESULTS

- N=223 mother-infant pairs (n=146 pregnant WLHIV, n=77 HIV-seronegative pregnant women) (Table 1).
- Pregnant WLHIV exhibited an eicosanoid profile indicating the presence of pro-[11-HETE and 12-HETE] and anti- [15-HEPE,14-HDoHE, 11(12) EET, 5(6) DiHET, 16-HDHA, 19(20) DiHDPA] inflammatory mediator production compared to HIV-seronegative pregnant women (Fig A). Findings were similar comparing EFV- and DTG-treated women separately to HIV-seronegative women.
- EFV-treated women had higher levels of complex lipids compared to DTG-treated women (Fig B). This maternal dyslipidemic profile included lipid subspecies (lysophosphatidylcholine 20:4 and 22:4) (Fig B) predictive of infant HOMA at 1 mo of age among WLHIV in lasso regression (Table 2).
- No maternal lipid subspecies were associated with infant HOMA in HIV- women.

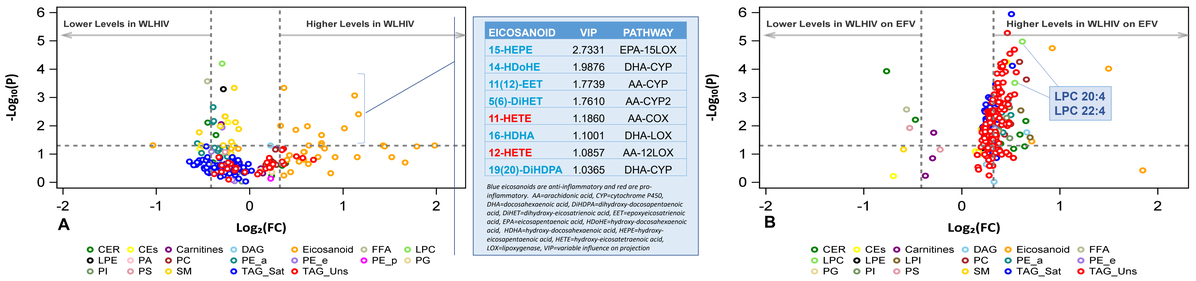

Figure. *Volcano plots visualize the log_{10}(Mann–Whitney P value) on the y-axis and the log_2 (fold change [FC]) on the x-axis for each eicosanoid/lipid subspecies compared between the following groups: (**A**) Pregnant WLHIV vs. pregnant HIV-seronegative individuals and (**B**) Pregnant WLHIV on EFV vs. DTG. Dotted lines represent the significance thresholds with FC >1.25 and <0.75 on x-axis and p value >0.05 on y-axis. Cer=ceramides; CE=cholesterol ester; DAG=diacylglycerol/diglyceride; DTG=dolutegravir; EFV=efavirenz; FFA=free fatty acid; LPC= lysophosphatidylcholine; LPE=lysophosphatidylethanolamine; LPI=lysophosphatidylinositol; LPG=lysophosphatidylglycerol; PA=phosphatidic acid; PC=phosphatidylcholine; PE_a=phosphatidylethanolamine acyl; PE_e=phosphatidylethanolamine ether; PE_p=phosphatidylethanolamine plasmalogen; PI=phosphatidylinositol; PS=phosphatidylserine; Sat=saturated; SM=sphingomyelin; TAG=triacylglycerol/triglyceride; Uns=unsaturated; WLHIV=women living with HIV*

Table 1. Characteristics of Pregnant Women at Enrollment and Their Infants at Birth by Maternal HIV Status

	Women living with HIV (n=146)	HIV-seronegative women (n=77)	*p*-value
WOMEN			
Sociodemographic			
Age (years)	30.0 (25.0 -34.0)	26.0 (21.0 -30.0)	<.0001
Gestational age at OGTT (wks)	26.4 (25.3 -28.3)	25.9 (25.0 -28.0)	0.066
Employed	80 (54.8)	37 (48.1)	0.398
Past obstetric history			
Gravidity	3.0 (2.0 - 4.0)	1.0 (1.0 - 3.0)	<.0001
Chronic hypertension prior to pregnancy	7 (4.8)	1 (1.3)	0.268
Family history of diabetes	0 (0.0)	1 (1.3)	0.345
Alcohol use during pregnancy	6 (4.3)	5 (6.8)	0.518
Tobacco use during pregnancy	0 (0.0)	1 (1.4)	0.344
Height (cm)	160 (155 - 165)	160 (156 - 163)	0.305
BMI[$] (kg/m^2)	26.1 (23.0 -29.6)	25.9 (23.0 -31.0)	0.344
Gestational diabetes	10 (6.8)	7 (9.1)	0.599
Hypertensive at OGTT*	6 (4.1)	2 (2.6)	0.718
Preeclampsia	0 (0.0)	0 (0.0)	
HIV clinical disease at OGTT			
CD4 cell count >500 (cells/mm^3)	68 (46.6)		
HIV RNA level <40 (copies/mL)	134 (91.8)		
On ART prior to pregnancy	89 (61.4)		
ART regimen			
TDF/FTC/DTG	81 (55.5)		
TDF/FTC/EFV	65 (44.5)		
INFANTS			
Preterm birth (<37 weeks gestational age)	21 (14.4)	10 (13.0)	0.841
Gestational age at delivery (weeks)	39.3 (37.9 -40.4)	39.6 (38.6 -40.4)	0.175
Birth weight z score	1.1 (-0.0 - 2.0)	1.2 (-0.0 - 2.3)	0.237
Birth length z score	-0.2 (-1.1 - 0.6)	-0.1 (-0.9 - 0.4)	0.314
Infant feeding in 1st month of life			
Exclusive breastfeeding	106 (72.6)	57 (74.0)	0.875

*Continuous variables shown as median (interquartile range) and categorical variables shown as n (%). *Defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. [$]BMI was obtained during pregnancy. ART=Antiretroviral Therapy; BMI=Body Mass Index; DTG=dolutegravir; FTC=emtricitabine; GA=gestational age; OGTT=Oral Glucose Tolerance Test; TDF=tenofovir; USD=US Dollars*

Table 2. Lasso Regression Results Showing Maternal Analytes Predictive of Infant HOMA by Maternal HIV Status

Analyte	Analyte type
Women living with HIV	
LPC (20:0)	Lysophosphatidylcholine
LPC (20:1)	Lysophosphatidylcholine
LPC (20:4)	Lysophosphatidylcholine
LPC (22:4)	Lysophosphatidylcholine
PE (18:2/16:1)	Phosphatidylethanolamine
17(18)-EpETE (epoxy-eicosatetraenoic acid)	Eicosanoid
HIV-seronegative women	
none	

CONCLUSIONS

- In our cohort, WLHIV showed both pro- and anti-inflammatory eicosanoid mediator production compared to HIV-seronegative pregnant women, suggesting at least partial compensation of HIV-related inflammatory effects.
- Compared to DTG, EFV was associated with a maternal dyslipidemic profile in pregnancy which was predictive of lower infant insulin sensitivity.
- Further studies are warranted to delineate whether enhancement of anti-inflammatory mediator production may benefit maternal/infant metabolic outcomes.

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