Maternal and cord plasma bioactive eicosanoid profile differ in HIV+ and HIV- women

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Background

- Pregnant women with HIV on antiretroviral therapy (ART) are at an increased risk of developing adverse birth outcomes including preterm birth and fetal growth restriction. The mechanisms that underlie these are not fully known.
- Eicosanoids play important roles in the maintenance of pregnancy and the growth and development of the fetus
- Lipid abnormalities are common in HIV+ patients and are accentuated in those receiving ART, and HIV infection has been associated with altered production of eicosanoids however, no data exist in the context of pregnancy.

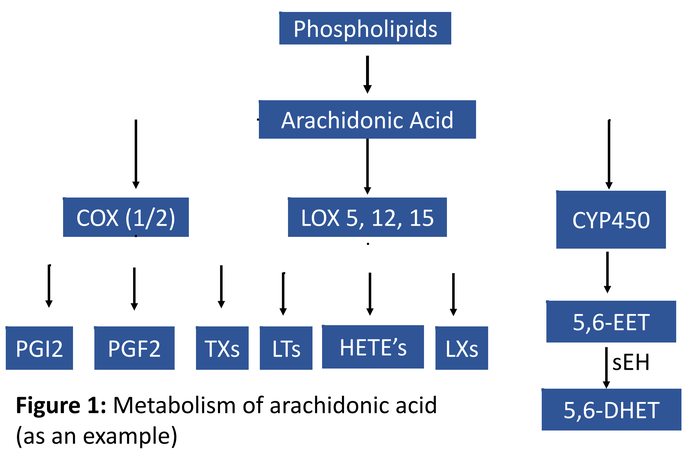


Figure 1: Metabolism of arachidonic acid (as an example)

Hypothesis

Levels of bioactive eicosanoids will be dysregulated in pregnancy complicated by HIV and ART.

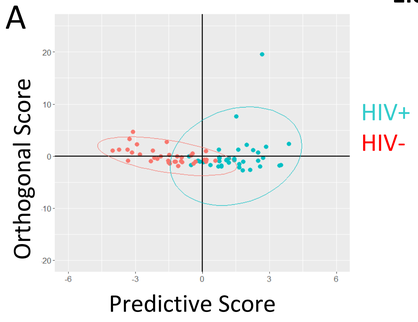
Methods

76 maternal samples at gestational week 33-38 (39 WHIV, 37 HIV-) and 55 cord samples (31 WHIV, 24 HIV-) were included. All WHIV received protease inhibitor (PI)-based ART. Levels of 139 eicosanoids were measured using liquid chromatography-mass spectrometry and quantified against standard curves with a lower limit of 0.025ng. Differences between groups for each eicosanoid were assessed using Mann-Whitney test and corrected for multiple comparisons using a false discovery rate of 0.05. Orthogonal partial least squares discriminant analysis (OPLS-DA) was used to differentiate groups by maternal HIV status. Correlations between eicosanoids in maternal and cord plasma were examined by Spearman r.

Results

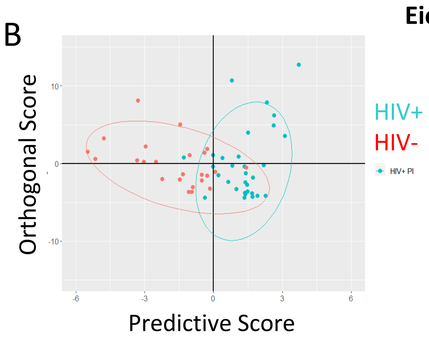
Table: Levels of bioactive eicosanoids in maternal and cord blood that differed significantly by HIV status. Also shown the pathway leading to each metabolite

Pathway	Factor in Maternal Plasma GW33-38 (ng/ml)	HIV+ n=39	HIV- n=37	Adjusted p-value
	AA	861 (521-1193)	484 (389-668)	0.0053
	EPA	80.2 (51-182)	46.6 (33-68)	0.0044
	DHA	784 (409-1139)	444 (360-610)	0.028
DHA/CYP/epoxygenase /epoxide hydrolase	19,20-DiHDPA	0.55 (0.46-0.68)	0.71 (0.61-0.97)	0.0026
AA	5,6-dehydro_Arichidonate	4.1 (2.4-7.0)	2.3 (1.7-3.1)	0.0053
AA/LOX	11-HETE	0.25 (0.15-0.42)	0.17 (0.12-0.25)	0.031
AA/LOX	15-HETE	0.73 (0.51-1.36)	0.47 (0.39-0.78)	0.034
AA/LOX	5-HETE	0.57 (0.44-1.03)	0.45 (0.33-0.58)	0.046
AA/LOX	12-HETE	0.84 (0.57-2.06)	0.63 (0.38-1.05)	0.046
DHA/LOX	14-HDoHE	0.30 (0.14-0.48)	0.14 (0.09-0.21)	0.0053
DHA/LOX	13-HDoHE	0.14 (0.11-0.21)	0.09 (0.07-0.13)	0.0053
DHA/CYP/w-hydrolase	20-HDoHE	0.44 (0.28-0.61)	0.29 (0.19-0.42)	0.026
DHA/LOX	11-HDoHE	0.13 (0.02-0.29)	0.04 (0-0.11)	0.049
EPA/LOX	12S-HEPE	0.08 (0.06-0.19)	0.06 (0.05-0.08)	0.022
aLA/LOX	13(S)-HOTrE(gamma)	0.11 (0.07-0.17)	0.09 (0.06-0.11)	0.048
AA/CYP/epoxygenase /epoxide hydrolase	14,15-EET	0.28 (0.23-0.41)	0.22 (0.18-0.27)	0.029
Pathway	**Factor in Cord Plasma (ng/ml)**	**HIV+ n=31**	**HIV- n=24**	**Adjusted p-value**
AA/CYP/epoxygenase /epoxide hydrolase	11,12-DHET	0.85 (0.63-1.09)	1.2 (1.0-1.53)	0.00019
AA/CYP/epoxygenase /epoxide hydrolase	8,9-DHET	0.38 (0.26-0.48)	0.73 (0.61-0.87)	0.00029
AA/CYP/epoxygenase /epoxide hydrolase	5,6-DHET	1.38 (1.03-3.38)	1.68 (0.94-3.65)	0.00058



Eicosanoids important for separation

Eicosanoids	Maternal
19,20-DiHDPA	1.61754
ARA	1.5552
14-HDoHE	1.554716
12S-HEPE	1.538438
11-HETE	1.453736



Eicosanoids important for separation

Eicosanoids	Cord
8,9-DHET	3.085719
11,12-DHET	2.830295
5,6-DHET	2.5517
14,15-DHET	2.1489
19,20-DiHDPA	1.810645

Figure: Orthogonal partial least squares discriminant analysis (OPLS-DA) data for maternal (A) and cord (B) samples

Demographics and Birth Outcomes

Maternal and birth characteristics for maternal plasma samples

Characteristic	HIV + (n=39)	HIV – (n=37)	P Value
Maternal Age, years	33 [29-36]	32 [30-35]	0.65
Pre-pregnancy BMI	25 [22·9-30]	24.4 [21.6-29.7]	0.41
Race, n [%]			0.33
Black	30 [77%]	26 [70%]	
White	6 [15%]	10 [27%]	
Other	3 [8%]	1 [3%]	
Gestational age at birth, wk	39·1 [38-40]	40.1 [39.1-40.9]	0.0014
Pre-term birth, n [%]	0 [0%]	0 [0%]	
SGA, n [%]	9 [23%]	0 [0%]	0.0024
Birth weight, g	3020 [2841-3575]	3468 [3192-3721]	0.004
BWZ score (intergrowth)	-0.06 [-0.75-0.83]	0.42 [-0.17-0.88]	0.025
ART-regimen			
Lopinavir	21 [54%]		
Atazanavir	13 [33%]		
Darunavir	5 [13%]		

Maternal and birth characteristics for cord plasma samples

Characteristic	HIV + (n=31)	HIV – (n=24)	P Value
Maternal Age, years	31.5 [29-34.2]	31 [28-34]	0.66
Pre-pregnancy BMI	25 [22.4-30.5]	24.8 [22-30]	0.65
Race, n [%]			0.86
Black	24 [77.4%]	18 [75%]	
White	5 [16.1%]	5 [21%]	
Other	2 [6.5%]	1 [4%]	
Gestational age at birth, wk	38.9 [37.9-40.1]	40 [39.2-40.7]	0.0027
Pre-term birth, n [%]	4 [13%]	0 [0%]	0.12
SGA, n [%]	5 [%]	0 [0%]	0.002
Birth weight, g	3130 [2695-3575]	3468 [3192-3721]	0.0008
BWZ score (intergrowth)	-0.21 [-0.60-0.71]	0.42 [-0.17-0.88]	0.0052
ART-regimen			
Lopinavir	14 [45%]		
Atazanavir	13 [42%]		
Darunavir	4 [13%]		

Summary

- A total of 53 and 58 eicosanoids were identified in maternal and cord plasma samples respectively
- Cord and maternal eicosanoid profiles differed, with only 3 correlating between compartments among HIV- women and none among WHIV.
- The HIV+ group maternal plasma had higher levels of circulating AA, EPA, and DHA, and elevated levels of lipoxygenase pathway-derived bioactive compared to the HIV- group including several HETEs, which have been associated with inflammatory and vasoconstrictive properties.
- In cord plasma, only 3 eicosanoids differed significantly between groups. All were vasodilating and pro-angiogenic DHETs (CYP/epoxygenase/soluble epoxide hydrolase metabolites of AA), and were lower in the HIV+ group.
- OPLS-DA analysis showed group separation by eicosanoids with maternal and cord specimens

Conclusions

Bioactive eicosanoid profiles differ in maternal and cord plasma, and are altered in pregnant WHIV. Elevated maternal levels of inflammatory lipoxygenase metabolites and lower cord levels of DHETs in the context of HIV and PI exposure may be indicators of, or contributors to, poor placenta function. Our findings also indicate an altered in utero environment that could contribute to fetal programming.

Thank you!

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Abbreviations: COX, cyclooxygenase; LOX, lipoxygenase; CYP450, cytochrome P450; PG, prostaglandin, TX, thromboxane; LT, leukotriene; HETE, hydroxyeicosatetraenoic acid; LX, lipoxin; EET, epoxyeicosatrienoic acid; DHET, dihydroxyeicosatrienoic acid; sEH, soluble epoxide hydrolase; HEPE, hydroxyeicosapentaenoic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDoHE, hydroxydocosahexaenoic acid; GW, gestational week; DiHDPA, dihydroxy-docosapentaenoic acid; AA, arachidonic acid, LC-MS-MS, liquid chromatography-tandem mass spectrometry; UHPLC, ultra-high-performance liquid chromatography.