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Soluble CD14 is Associated With Endothelial Dysfunction in South African Youth on ART

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BACKGROUND

There is evidence for endothelial dysfunction in youth living with perinatally acquired HIV (YLPHIV), however little data exist on its mechanisms. We assessed whether markers of inflammation and intestinal integrity were associated with endothelial dysfunction in South African YLPHIV well established on ART.

OBJECTIVES

1. Assess the associations between biomarkers of inflammation and gut integrity and measures of endothelial function
2. Explore independent predictors of endothelial function

MATERIALS AND METHODS

Study design: longitudinal analysis of YLPHIV enrolled in the Cape Town Adolescent Antiretroviral Cohort (CTAAC) and age-matched HIV uninfected youth (HIV-)

Subjects:

YLPHIV: children living with perinatally acquired HIV aged 9-14 years, on stable ART for at least 6 months with HIV-1 RNA< 400 copies/mL.

- **HIV-**: HIV uninfected children age, sex and ethnicity matched.

Serum Biomarkers at baseline and 24 months:

- Plasma markers of systemic inflammation: sTNFRII, hsCRP, IL6
- Plasma markers of monocyte activation: sCD14 and sCD163
- Plasma marker of oxidized lipids: oxLDL
- Marker of intestinal integrity : I-FABP

Endothelial function at 24 months:

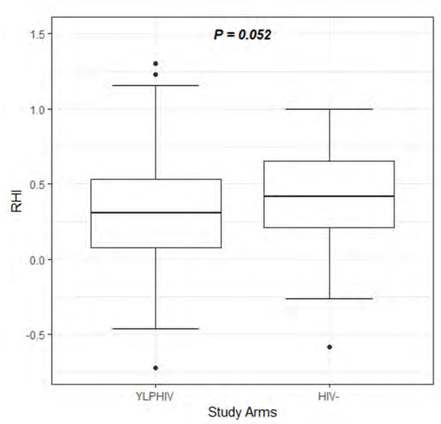
- Reactive hyperemic index (RHI) measured by endoPAT
- RHI <1.35 defined as endothelial dysfunction

TABLE 1: BASELINE CHARACTERISTICS

	YLPHIV n=283	HIV- N=69	p
Female (%)	147 (52)	39 (56)	0.583
Tanner (=>3 ,%)	80 (29)	25 (37)	0.248
Age (years)	11.89	12.01	0.863
Current smoking (%)	2 (0.7)	0 (0)	0.659
CD4 cell count (cells/mm3)	744.00		
CD4 %	31.07		
Viral load (copies/mL)	39.00		
ART regimen			
NRTI:			
AZT	42 (15%)		
ABC	214 (76%)		
D4T	22 (8%)		
3TC	267 (94%)		
NNRTI:			
EFV	176 (62%)		
NVP	5 (2%)		
PI (LPV/r)	96 (34%)		
INSTI (RAL)	2 (0.7%)		
ART duration (years)	8.18		
BMI (kg/m2)	17.18	18.59	**0.004**
Waist hip ratio	0.87	0.81	**<0.001**
Total cholesterol (mmol/L)	4.10	3.80	**<0.001**
LDL (mmol/L)	2.20	2.00	**0.015**
HDL (mmol/L)	1.50	1.45	0.275
Triglycerides (mmol/L)	0.90	0.60	**<0.001**
HOMA IR	1.96	1.24	**0.042**

RESULTS

FIGURE 1: ENDOTHELIAL FUNCTION AT 24 MONTHS



- ***YLPHIV have worse endothelial function as measured by RHI***

FIGURE 2: BIOMARKERS AT BASELINE AND 24 MONTHS

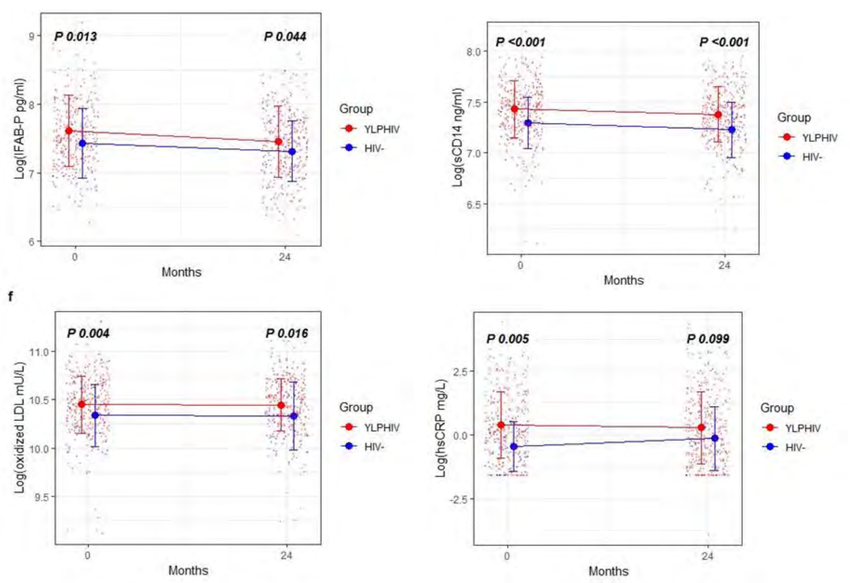


Figure 1: Graph showing biomarkers in YLPHIV and HIV- at baseline and 24 months. Biomarkers were log transformed. P values represent differences between YLPHIV and HIV- at each time point

- ***2 years of continued ART and viral suppression did not lead to a normalization in biomarkers***

TABLE 2: REGRESSION MODEL OF THE ASSOCIATION WITH ENDOTHELIAL DYSFUNCTION IN YLPHIV

RHI < 1.35 (endothelial dysfunction) in YLPHIV		
	Estimate (95% CI)	P
sCD14 (ng/mL) (24 months)	-0.046 (-0.081, -0.010)	**0.013**
Waist hip ratio	-0.193 (-0.985, 0.599)	0.630
Age (years)	0.003 (-0.026, 0.032)	0.819
Sex (Female ref)	-0.080 (-0.160, 0.000)	**0.049**
Tanner (>3)	0.053 (-0.037, 0.143)	0.243
Viral load at 24 months	0.018 (-0.026, 0.062)	0.429
ART duration (years)	-0.010 (-0.024, 0.003)	0.125

- ***Only sCD14 remained independently associated with endothelial dysfunction in YLPHIV***

SUMMARY

- YLPHIV had higher waist-to-hip ratio and worse lipid profiles at baseline which persisted at 24 months. (Table 1)
- BMI and CD4 cell count significantly increased over 24 months in YLPHIV.
- YLPHIV had worse endothelial function at 24 months compared to HIV- participants. (Figure 1)
- hsCRP, sCD14, I-FABP and oxidized LDL were higher at baseline in YLPHIV compared to HIV- participants (Figure 2).
- All biomarkers remained elevated in YLPHIV at 24 months, except for hsCRP. (Figure 2)
- In Spearman correlation**, higher baseline IFAB-P** (r=0.17, p=0.04), and **sCD14** at 24 months (r=0.23, p=0.007) correlated with endothelial dysfunction at 24 months.
- None of the other biomarkers of traditional risk factors correlated with poor RHI (p≤0.78).
- After adjusting for confounders**, higher sCD14** at 24 months remained associated with endothelial dysfunction in YLPHIV. (Table 2)

CONCLUSION

- YLPHIV show evidence of endothelial dysfunction.
- YLPHIV in South Africa have evidence of monocyte activation and intestinal damage which persist over time despite viral suppression
- Enterocyte damage and monocyte activation may play a role in endothelial dysfunction in this population
- Our findings highlight the potential CVD risk in YLPHIV as they are advancing into adulthood and the mechanisms underlying this risk in the absence of traditional risk factors.

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