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Vascular Disease, Immune Activation, and Gut Dysfunction in HIV+ Ugandan Children

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BACKGROUND

Sub-Saharan Africa is facing new challenges in HIV care including management of non-communicable diseases and a growing younger generation. The risk of cardiovascular disease (CVD) and its mechanisms in children living with perinatally acquired HIV (PHIV) in sub-Saharan Africa has been understudied.

OBJECTIVES

1) To evaluate subclinical vascular disease using carotid intima media thickness (IMT) and pulse wave velocity (PWV) in PHIV compared to HIV uninfected children (HIV-) in Uganda
2) To investigate the relationship between inflammation and immune activation and vascular disease
3) To assess the relationship between markers of gut integrity and CVD markers

MATERIALS AND METHODS

Study design: cross sectional analysis of baseline data from an observational cohort of PHIV and HIV- children cohort prospectively enrolled at the JCRC in Kampala, Uganda

Subjects:

HIV+: children living with perinatally acquired HIV aged 10-18 years years, on stable ART for at least 6 months with HIV-1 RNA< 400 copies/mL.
- **HIV-**: HIV unexposed uninfected children age and gender matched.

Vascular disease measures:
- Carotid intima media thickness (IMT)
- Pulse Wave velocity (PWV)

Plasma Biomarkers:
- Plasma markers of systemic inflammation: sTNFRI and II, hsCRP, IL6
- Plasma markers of monocyte activation: sCD14 and sCD163
- Plasma marker of oxidized lipids: oxLDL
- Marker of fungal and microbial translocation: BDG and LBP
- Marker of intestinal integrity and permeability: zonulin and I-FABP

Cellular markers of monocyte and T cell activation:
- T cells phenotyped by flow cytometry: co-expression of CD38 and HLA-DR
- Monocytes phenotyped by flow cytometry: expression of CD14 and CD16

TABLE 1: BASELINE CHARACTERISTICS

	PHIV n=101	HIV- N=96	p
Age (years)	12.93	12.67	0.24
Female sex (%)	54 (53)	50 (52)	0.96
HIV Variables			
Viral load < 20 copies/mL (%)	84 (86%)		
CD4 nadir (cells/µL)	619.50		
CD4 cell count (cells/µL)	988		
ART Duration (years)	9.88		
Nucleotide Reverse Transcriptase Inhibitor (%)			
Abacavir	42 (47)		
Lamivudine	1 (1)		
Tenofovir	12 (14)		
Zidovudine	33 (37)		
Nevirapine (%)	18 (27)		
Efavirenz (%)	46 (44)		
Lopinavir/ritonavir (%)	27 (28)		

RESULTS

FIGURE 1: VASCULAR MEASURES

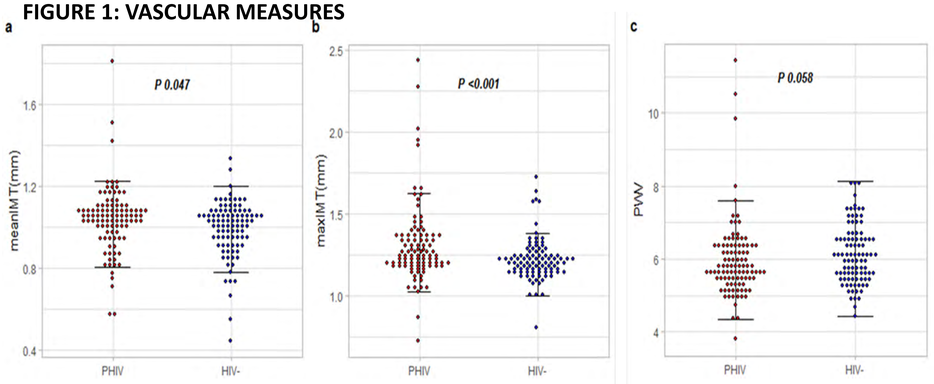


Figure 1a: Dot plot of Mean-Mean IMT (mm) between groups, ***Figure 1b***: Dot plot of Mean-Max IMT (mm) between groups, ***Figure 1c***: Dot plot of PWV (m/s) between groups
Dot plots showing the median mean IMT (mm), max IMT (mm) and PWV (m/s)

FIGURE 2: MONOCYTE ACTIVATION

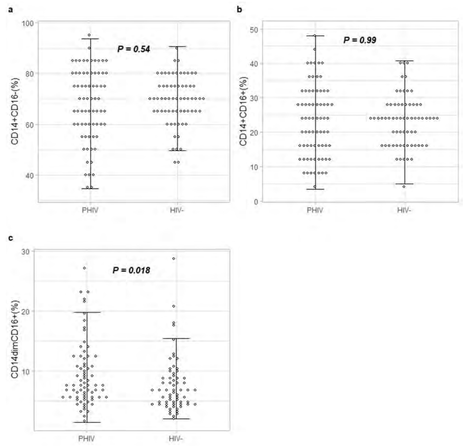
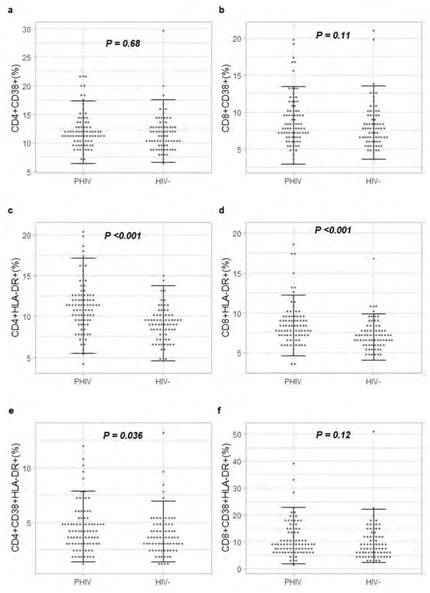


FIGURE 3: T CELL ACTIVATION



SUMMARY

- PHIV had higher CVD risk factors including waist hip ratio, triglycerides and insulin resistance.
- Mean IMT was slightly thicker in PHIV.
- PHIV have higher monocyte and T-cell activation.
- Markers of systemic inflammation (hsCRP), fungal translocation (BDG), intestinal permeability (zonulin) and oxidized lipids (ox LDL) correlated with monocyte and T cell activation in PHIV .
- Zonulin also correlated with IMT in PHIV.
- After adjusting for covariates, and separately adding sCD164, sCD14 and hsCRP, higher levels of zonulin remained associated with IMT

FIGURE 4: CORRELATION BETWEEN MONOCYTE AND T CELLS ACTIVATION AND INFLAMMATION AND GUT MARKERS

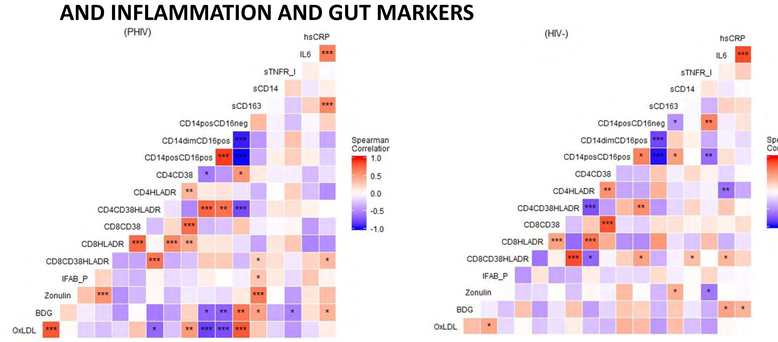


Figure 4: Heat map showing the correlation between T cells and monocyte activation and measures of inflammation, gut integrity and oxidized lipids in A) HIV negative children and B) children living with perinatally acquired HIV (PHIV).
*for p <0.05; ** for p<0.01; *** for P<0.001

TABLE 2: REGRESSION MODEL OF MEAN IMT

	MEAN IMT PHIV	
	Estimate (95% CI)	P
Zonulin (mg/mL)	0.017 (0.002,0.03)	**0.027**
Age (years)	0.01 (0.003, 0.019)	**0.006**
Sex (male)	0.004 (-0.027, 0.035)	0.802
BMI (kg/m2)	-0.030 (-0.047, -0.013)	**0.001**
Triglycerides (mg/dL)	0.025 (0.008, 0.041)	**0.003**
CD4 cell count (cells/uL)	0.034 (0.0168, 0.0518)	**<0.001**
sCD14 (pg/mL)	0.004 (0.017, 0.018)	0.621

CONCLUSION

- We show for the first time that African PHIV have evidence of CVD risk and structural vascular changes despite viral suppression.
- They also have ongoing immune activation.
- Intestinal barrier dysfunction may be involved in chronic immune dysfunction and in the pathogenesis of subclinical vascular disease in this population.
- Longitudinal follow-up of this cohort is ongoing and may yield further insights in CVD risk and its pathophysiology.

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