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MONOCYTE ACTIVATION AND GUT BARRIER DYSFUNCTION IN SOUTH AFRICAN YOUTH ON ART AND THEIR ASSOCIATIONS WITH ENDOTHELIAL DYSFUNCTION

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Abstract

Background: There is evidence for endothelial dysfunction in youth living with perinatally acquired HIV (YLP HIV). However little data exist on its mechanisms.

Methods: YLP HIV and age-matched HIV-uninfected (HIV-) youth enrolled in the Cape Town Adolescent Antiretroviral Cohort (CTAAC) in South Africa between 9–14 years of age were included. YLP HIV were on antiretroviral therapy (ART) > 6 months with viral load <400 copies/mL at baseline and 24 months. Serum biomarkers of systemic inflammation, monocyte activation, intestinal integrity, and oxidized LDL-cholesterol were measured at baseline and after 24 months. Endothelial function was measured at 24 months using reactive hyperemic index (RHI); endothelial dysfunction was defined as RHI < 1.35. Spearman correlation coefficient and quantile regression were used to examine associations between RHI and different biomarkers.

Results: We included 266 YLP HIV and 69 HIV- participants. At baseline, median (Q1, Q3) age was 12 (11, 13) years and 53% were females. YLP HIV had poorer endothelial function compared to HIV- youth (RHI=1.36 vs 1.52, $p < 0.01$). At baseline and 24 months, YLP HIV had

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Author Contributions:

SDF and GAM designed the research. SDF wrote the first draft of the manuscript and assisted with data analysis. JU, ZA and AS provided statistical support. JJ, LM and HZ conducted research (CTAAC team) and reviewed/edited the manuscript.

Competing interests

GAM served as a consultant for Merck, Gilead, Viiv, and Theratechnologies, and has received research funding from Roche, Astellas, Tetrphase, and BMS. All other authors had no conflict of interest.

higher markers of monocyte activation (sCD14), gut barrier dysfunction (intestinal fatty acid binding protein, IFAB-P) and oxidized LDL cholesterol ($p = 0.04$) compared to HIV- youth. Among YLPHIV, sCD14 remained associated with endothelial dysfunction after adjusting for age, sex, Tanner stage, and ART duration ($\beta: -0.05$, $p=0.01$).

Conclusion: Despite viral suppression, South African YLPHIV have poor endothelial function and persistent evidence of monocyte activation and gut barrier dysfunction compared to HIV- youth. The long-term clinical significance of gut integrity and monocyte activation needs to be further assessed in YLPHIV.

Keywords

Pediatric HIV; gut integrity; inflammation; translocation; monocyte activation; vascular function

Introduction

Adolescents and young adults represent a growing share of people living with HIV worldwide. As cardiovascular disease (CVD) is now a leading cause of death in adults living with HIV [1–3], the evaluation of CVD risk in youth who are facing a lifetime of exposure to both HIV and ART is becoming a high research priority.

Changes in the endothelium are one of the earliest alterations of the vessel wall which occur prior to atherosclerosis[4]. Peripheral Arterial Tonometry (endoPAT) measures vascular function in an automated and non-invasive manner by assessing vascular morphology and function through finger pulse volume and infrared light transmission plethysmography[5]. We reported previously that youth living with perinatally-acquired HIV (YLPHIV) both in the US[6] and in South Africa[7] have poorer endothelial function compared to that of uninfected controls as measured by reactive hyperemic index (RHI) using endoPAT.

The association between chronic inflammation and CVD is well documented in adults living with HIV [8–16]. The etiologies for vascular dysfunction in YLPHIV are likely multifactorial, however the specific role of systemic inflammation, immune activation, and intestinal integrity on the vascular process in the setting of few traditional CVD risk factors in this population is unclear. In this study, our objectives were to determine whether markers of inflammation, immune activation and gut integrity were different between YLPHIV and HIV- South African youth; second, to investigate the relationship between these markers and measures of endothelial function as measured by endoPAT and third to explore independent predictors of endothelial dysfunction.

Methods

Study design

The Cape Town Adolescent Antiretroviral Cohort (CTAAC) is an ongoing prospective cohort in South Africa which enrolled YLPHIV aged 9–14 years on ART for >6 months as well as age, sex, and ethnicity-matched HIV-uninfected youth between October 2013 and March 2015 as previously described[17, 18]. Parental written consent was obtained and adolescent assent provided. Children were recruited from primary care and hospital-based

clinics in Cape Town, South Africa. The study was approved by the Faculty of Health Sciences, University of Cape Town Human Research Ethics Committee. For this substudy, only participants with plasma samples available at enrollment and after 24 months were included, and among YLP HIV, only those with an HIV-1 RNA PCR of <400 copies/mL at both timepoints and through the 2-year observation period were included.

Study evaluation

At baseline and 24 months, participants were fasting for > 8 hours and blood draws were obtained for real time measurements of lipid profiles, insulin resistance, high sensitivity C-reactive protein (hsCRP) and CD4 cell count. The derived homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as described [19]. Blood was processed and serum stored. Frozen, never previously thawed serum was shipped to University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA. The samples were used for measurement of soluble and cellular markers of monocyte immune activation, markers of systemic inflammation, gut integrity and oxidized lipids.

Inflammation, soluble immune activation and gut markers

Measurements were performed by the Dahms Clinical Research Unit Core Laboratory [Dr McComsey, laboratory Director]. In this analysis, we selected biomarkers based on prior data in HIV suggesting their association with CVD, metabolic complications, or overall mortality. Intestinal fatty acid binding protein (I-FABP) is considered a marker of enterocyte damage and has been associated with increased mortality[20, 21]. Soluble CD14 (sCD14) is a soluble marker of monocyte activation and microbial translocation and is associated with mortality and progression of atherosclerosis[26]. Oxidized lipids (oxidized LDL) is the form of LDL that has undergone oxidative changes and has been shown to contribute to endothelial cell activation[22]. The remaining biomarkers [soluble CD163 (sCD163), interleukin-6 (IL-6), and soluble tumor necrosis alpha receptor II (sTNFR II)] correlate with cardiometabolic complications, or drive other hallmarks of immune dysregulation in HIV.

I-FABP, sCD14, sCD163, sTNFR II, hsCRP, IL-6 (R & D Systems, Minneapolis, Minnesota, USA) and oxidized LDL (Merckodia, Winston Salem, North Carolina, USA) were measured by ELISA. The intra-assay variability ranged between 4–8% and inter-assay variability was less than 11% for all markers. Laboratory personnel were blinded to group assignments.

Endothelial function

Endothelial function was measured using peripheral arterial tonometry as previously described[6, 23]. Briefly, the device (Itamar Medical Ltd., Caesarea, Israel) consists of two finger probes. The probe allows the application of a constant and evenly distributed near-diastolic counter pressure within the entire probe [24, 25]. The recordings was performed with the patient in a seated position with both hands at the same level. After a period of stabilization, the blood pressure cuff on the study arm was inflated to 60 mm Hg above systolic pressure for 5 min. The cuff was deflated to induce reactive hyperemia and assess PAT. A reactive hyperemia index (RHI) was generated and is the post to pre -occlusion PAT signal ratio in the occluded side normalized to the control side and corrected for baseline vascular tone. An index of >1.35 is considered normal with <1.35 being abnormal [25].

Augmentation index (AI) is calculated from PAT pulses recorded at the baseline period and the result is further normalized to heart rate of 75 beats per minute (AI 75). Lower AI values reflect better arterial elasticity.

Statistical analyses

Demographics, clinical indices and HIV-related factors are presented by group at baseline. Median and interquartile range (IQR) are reported for continuous variables and frequency and percent for nominal variables. Changes from baseline to 24 months in clinical variables and biomarkers were determined. All baseline variables were compared between groups using unpaired t-tests or Wilcoxon Rank Sum tests as warranted by distribution for continuous variables and by Chi-Square tests, Fisher's Exact tests, or Pearson Exact Chi-Square tests as appropriate for categorical variables. Within-group changes of biomarkers were tested using paired t-tests or Wilcoxon Signed Rank tests as appropriate for the distribution. RHI was log transformed to more closely approximate a normal distribution.

Spearman correlation analysis was utilized to assess the relationships between baseline and 24 months clinical variables with biomarkers at both time points and endothelial dysfunction at 24 months. Next, quantile regression was employed to answer what baseline and 24 month biomarkers as well as change in biomarkers are independently associated in YLPHIV with endothelial dysfunction at 24 months as the outcome, after adjusting for confounders. All statistical tests were two-sided and considered significant with $p < 0.05$. Analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Results

Baseline Demographics

Overall, 352 CTAAC participants had stored serum available and were included in the present analysis. Demographic information and baseline characteristics of the participants are displayed in Table 1. Median age (Q1, Q3) was 12 years (10.57, 13.19), 53% were females and 30% were in Tanner stages 3. YLPHIV had higher waist-to-hip ratio, homeostatic assessment of insulin resistance (HOMA) and worse lipid profiles ($p = 0.04$). No participants had cardiovascular disease or were taking lipid-lowering agents.

YLPHIV had a median CD4 cell count of 744 cells/mm³ (603, 951), a median viral load of 39 copies/mL and median ART duration of 8 years (5.42, 9.58). The majority of participants were on efavirenz (EFV, 61%) and the remaining on lopinavir/ritonavir (LPV/r, 30%) with a lamivudine (98%) or stavudine (62%) backbone.

Characteristics at the 24-month visit

Characteristics for the 24 months visit are shown in Table 2. YLPHIV continued to have higher CVD risk factors with higher waist-to-hip ratio and higher LDL and triglycerides ($p = 0.002$). Within each group, over 24 months, the only significant changes were in the waist to hip ratio and BMI. The waist to hip ratio did not change in YLPHIV ($p = 0.12$), but increased by a median of 0.02 (-0.02, 0.05) in uninfected participants ($p = 0.01$) over 24

months. BMI increased by 1.52 (0.57, 2.43, $p<0.01$) kg/m² in YLPHIV and by 1.35 (0.61, 2.33, $p<0.01$) in uninfected participants over 24 months.

In YLPHIV, CD4% increased significantly by a median of 1.4 % (-1.72, 4.07, $p=0.013$). The median viral load remained at 39 copies/mL. Most YLPHIV (76%) had a switch in ART regimen, with the majority being a switch from a stavudine backbone to abacavir.

Changes in Biomarkers

As illustrated in Figure 2, at baseline, hsCRP, sCD14, I-FABP and oxidized LDL were higher in YLPHIV compared to HIV- participants ($p = 0.013$). All biomarkers, except for hsCRP, remained higher in YLPHIV compared to HIV- participants at 24 months ($p = 0.044$, Figure 1).

Within groups, sCD14, and I-FABP decreased significantly within YLPHIV over 24 months ($p = 0.011$, Table 3). There was not significant change within the HIV- arm for any of the biomarkers.

The increase in CD4 % over 24 months in YLPHIV correlated with decreases in sCD163, IL6, sTNFR2, and oxidized LDL ($r=0.15-0.22$, $p<0.01$).

The results of the analyses including all participants did not differ from the sensitivity analyses performed including only participants with endoPAT at 24 months ($n=335$); therefore only the former data are presented.

EndoPAT measures

Of the participants with plasma available at both time points, 335 also had endoPAT measures at 24 months with no differences in the demographic or HIV characteristics. YLPHIV had worse endothelial function as measured by a lower RHI than uninfected participants ($p<0.01$, Figure 2). 43% of YLPHIV vs 30% of uninfected participants ($p=0.21$) had endothelial dysfunction ($RHI<1.35$). Compared to participants with higher RHI, those with endothelial dysfunction were overall more likely to be younger males with lower BMI, have higher waist-to-hip ratio and higher triglyceride levels ($p = 0.01$, data not shown). Among YLPHIV, there was no difference in RHI for the participants on ABC, EFV or LPV/r ($p = 0.69$).

Baseline Predictors of endoPAT at 24 months

In univariate analyses, higher baseline IFAB-P weakly correlated with worse endothelial dysfunction at 24 months ($\rho=0.17$, $p=0.04$). None of the other biomarkers nor variables traditionally associated with CVD risk factors including sex, CD4 cell count, HOMA-IR, blood pressure, BMI, waist hip ratio correlated with endothelial dysfunction ($p = 0.78$, data not shown).

At 24 months, only higher sCD14 at that time point correlated with endothelial dysfunction ($\rho=0.23$, $p=0.007$). Change in each biomarker did not correlate with endothelial dysfunction.

In multivariable analyses, in YLPHIV, after adjusting for confounder including waist hip ratio, age, sex, tanner stage, viral load and ART duration, only higher sCD14 at 24 months remained associated with endothelial dysfunction ($\beta=-0.046$, 95% CI -0.081 , -0.010 , $p=0.013$).

Discussion

These findings provide novel information on the prevalence and pathogenesis of cardiometabolic complications of YLPHIV in Africa, for which there are limited data. We found that YLPHIV virologically suppressed on ART have persistent monocyte activation and gut barrier dysfunction which may contribute to vascular dysfunction seen in this population. This extends our prior observation of increased carotid intima thickness measurements in youth with HIV and the potential role of intestinal barrier dysfunction in the etiology of vascular disease in this population [26, 27].

Despite viral suppression and long term ART, South African YLPHIV have residual systemic inflammation and monocyte activation consistent with findings in adults living with HIV[28] and other pediatric cohorts[29–32]. Several biomarkers (sCD14 and IFAB-P) decreased significantly after 24 months in YLPHIV, however sCD14, IFAB-P and oxidized LDL remained significantly elevated compared to the uninfected participants. In addition, oxidized LDL did not significantly change after 24 months. Oxidized LDL is a marker of oxidative stress and in uninfected adults has been associated with obesity[33], insulin resistance[34] and cardiovascular disease[35] and in HIV has been associated with markers of immune activation[36]. Increased circulating levels of LDL in YLPHIV may be related to multiple factors including HIV disease and ART. The ongoing inflammation in this population may promote pro-inflammatory alterations of lipid particles[37]. Oxidized LDL in turn may play a role in the persistent monocyte activation seen in YLPHIV[37] supporting the bi-directional relationship between inflammation and lipid alteration. IFAB-P, a marker of gut structural damage, has been associated with higher mortality[20] and alteration in body composition specifically fat accumulation in HIV[38]. IFAB-P levels were found to increase in ART-naïve adults, 96 weeks post ART[38], suggesting that despite ART, gut integrity is not completely restored.

CD14 is expressed on monocytes/macrophages, serves as a co-receptor for toll-like receptor and facilitates cellular responses to lipopolysaccharides, the major component of the outer membrane of gram-negative bacteria[39]. The soluble form of CD14 (sCD14) is produced by the liver as an acute phase reactant and can also be shed by activated monocytes as a marker of lipopolysaccharide activation[40]. Studies in children, youth and adults living with HIV randomized to different ART regimens reported that sCD14 levels remain persistently elevated despite ART and viral suppression consistent with our findings [29, 41–44]. Studies in adults suggest that sCD14 decreased only with integrase strand transfer inhibitor (INSTI) use but not with protease inhibitor or NNRTI based regimens[42–44]. One of the mechanisms hypothesized is a higher concentration of INSTI in the enterocytes leading to better control over bacterial translocation[43]. We found that both IFAB-P, a marker of enterocyte necrosis or inflammation, and sCD14, significantly decreased in YLPHIV, however remained elevated over 24 months compared to uninfected participants. This further

supports that despite viral suppression and immunologic improvement (CD4% significantly improved over 24 months in YLPHIV), there likely remains a cycle of ongoing bacterial translocation, monocyte activation and disruption in gut integrity. that does not improve with early viral suppression. Future studies will be needed as more children and youth are initiated and switched to INSTI-based regimen as this drug class is now the preferred first line on the World Health Organization HIV treatment guidelines for adults and children[45].

Chronic intestinal mucosal damage, bacterial translocation, inflammation and monocyte activation can have detrimental health consequences and may play a role in cardiometabolic complications in YLPHIV. To our knowledge, only one study has investigated endothelial function as measured by endoPAT and its relationship with inflammatory biomarkers in Southern African adults living with HIV[46]. Bestawros et al. found that persistent systemic inflammation as measured by hsCRP and sTNFRI was associated with impaired endothelial function over 12 weeks in undernourished HIV-infected adults starting ART[46]. We found that both IFAB-P, a marker of enterocyte necrosis or inflammation, and sCD14, a marker of monocyte activation and an indirect measure of microbial translocation, correlated with endothelial dysfunction in YLPHIV. After adjusting for known confounders, only high levels of sCD14 remained associated with worse endothelial function.

In the general population and in HIV, sCD14 has been associated with vascular disease, a surrogate marker for increased risk of future clinical cardiovascular events in older adults and overall mortality [40, 47–49]. This is the first published study to demonstrate a relationship between sCD14 and endothelial dysfunction in YLPHIV in the setting of lack (or few) traditional CVD risk factors. Our previous reports from youth in the US did not identify a relationship between sCD14 and RHI[6]. We hypothesize that this is largely in part due to the smaller sample size of YLPHIV in the US study but may also be secondary to ongoing microbial translocation and altered intestinal integrity which may be different between US and South African youth, who are exposed to a high burden of infectious diseases. Although future larger studies are warranted, our findings of the association of sCD14 with worsening endothelial function in YLPHIV suggests a common pathway in HIV in which activation of the immune system by microbial products may accelerate the progression of co-morbidities even at a young age.

This analysis leverages a well-defined cohort with an age, sex- and ethnicity-matched control group enrolled in parallel in the same country. There are several limitations in our study, we only had serum samples available which restricted the assays we conducted and were unable to further assess the functional integrity of the gut and quantify measure microbial translocation, however, we were able to assess biomarkers of these in a longitudinal manner over 24 months. In addition, were limited by having only a single measure of endothelial function. We cannot prove causal relationships or exclude the possibility of residual confounding. Our study focused on black youth in South Africa and therefore our findings cannot be generalized to different populations, however the vast majority of the world's population of children/youth with perinatally acquired HIV reside in sub-Saharan Africa[50].

In conclusion, our study showed that YLP HIV in South Africa have evidence of monocyte activation and intestinal damage which persist over time despite viral suppression with ART. In addition, YLP HIV show evidence of subclinical vascular disease. The extent of monocyte activation may play a role in endothelial dysfunction in this population. These findings further highlight the potential early CVD risk factors in YLP HIV as they are advancing into adulthood and the mechanisms underlying this risk in the absence of traditional risk factors emphasizing the need for further investigation.

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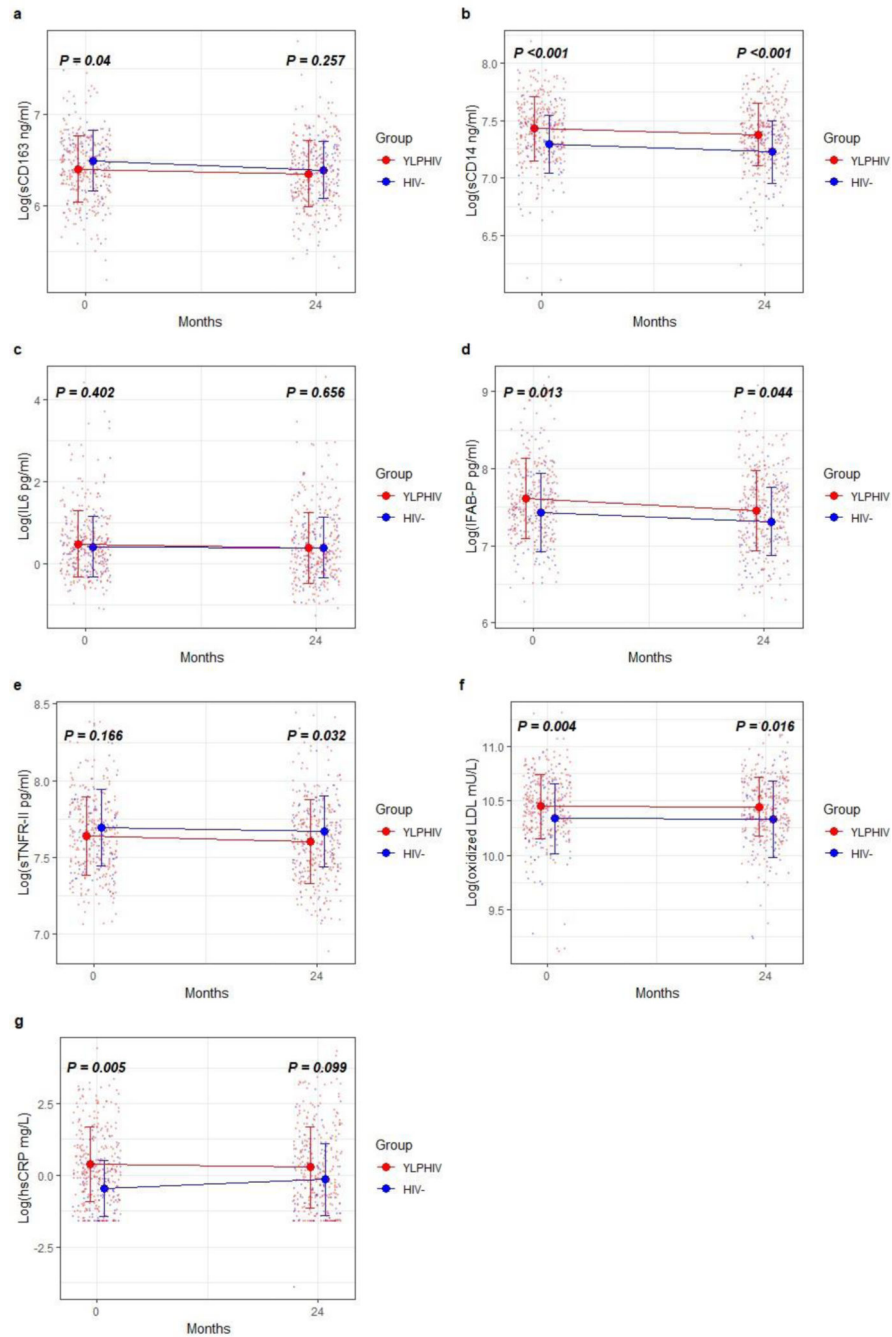


Fig. 1. Changes in biomarkers between the groups at baseline and 24 months. Graph showing median biomarkers with whiskers representing interquartile range, and the colored small dots are all values (a: soluble CD163, b: soluble CD14, c: IL-6, d: intestinal fatty acid binding protein, e: soluble tumor necrosis factor receptor a II, f: oxidized LDL, g: high sensitivity C-reactive protein) in youth living with perinatally acquired HIV and HIV at enrollment and 24 months. Biomarkers were log transformed. Wilcoxon test used, P values represent differences between youth living with perinatally acquired HIV and HIV at each

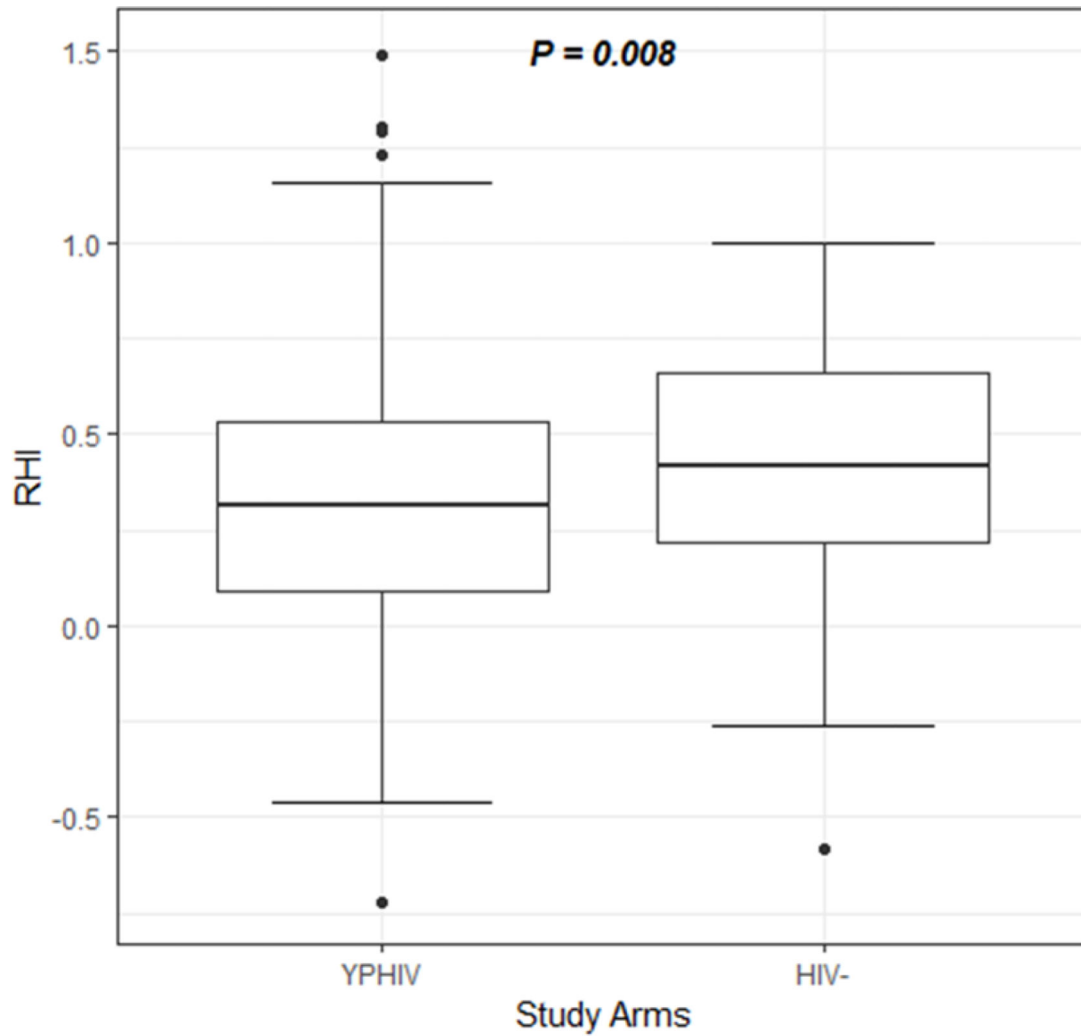
time point. hsCRP, high sensitivity C-reactive protein; IFAB-P, intestinal fatty acid binding protein; IL-6, interleukin 6; sCD14 and 163, soluble CD14 and 163; sTNFRII, soluble tumor necrosis factor receptor a II.

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Group	n	Mean	SD	Median	Q1	Q3	C.V
YLP HIV	266	0.32	0.33	0.31	0.09	0.53	1.05
HIV-	69	0.4	0.31	0.42	0.22	0.66	0.8

Fig. 2. EndoPAT. Box plot of ln reactive hyperemic index in youth living with perinatally acquired HIV and HIV-. The box represents the interquartile range, whiskers represent the range. Wilcoxon test used for comparison.

Table 1:

Characteristics of Participants at Enrollment

	YLPHIV N=283	HIV- N=69	<i>p value</i>
Female (%)	147 (51.9)	39 (56.5)	0.583
Tanner (=>3,%)	80 (28.7)	25 (36.8)	0.248
Age (years)	11.89 [10.65, 13.09]	12.01 [10.24, 13.42]	0.863
Current smoking (%)	2 (0.7)	0 (0)	0.659
CD4 cell count (cells/mm3)	744.00 [603.00, 951.00]	---	
CD4 %	31.07 [26.72, 35.29]	---	
Viral load (copies/mL)	39.00 [39.00, 39.00]	---	
ART regimen			
NRTI:			
AZT	44 (15%)		
ABC	19 (19%)		
D4T	177 (62%)		
3TC	277 (98%)	---	
NNRTI:			
EFV	170 (61%)		
NVP	23 (8%)		
PI (LPV/r)	84 (30%)		
INSTI (RAL)	1 (0.3%)		
ART duration (years)	8.18 [5.42, 9.58]	---	
BMI (kg/m2)	17.18 [16.07, 19.12]	18.59 [16.65, 20.93]	0.004
Waist hip ratio	0.87 [0.82, 0.95]	0.81 [0.79, 0.84]	<0.001
Systolic blood pressure (mm Hg)	105.00 [99.50, 112.00]	106.00 [100.00, 116.00]	0.097
Diastolic blood pressure (mm Hg)	67.00 [62.00, 73.00]	69.00 [64.00, 75.00]	0.144
Total cholesterol (mmol/L)	4.10 [3.70, 4.70]	3.80 [3.40, 4.30]	<0.001
LDL (mmol/L)	2.20 [1.80, 2.60]	2.00 [1.60, 2.32]	0.015
HDL (mmol/L)	1.50 [1.30, 1.80]	1.45 [1.20, 1.73]	0.275
Triglycerides (mmol/L)	0.90 [0.70, 1.20]	0.60 [0.50, 0.80]	<0.001
HOMA IR	1.96 [1.13, 3.14]	1.24 [0.19, 2.52]	0.042

Median [Interquartile Range]. Bold values represent $p < 0.05$

3TC: lamivudine, ART: antiretroviral therapy, ABC: abacavir, AZT: zidovudine, BMI: body mass index, D4T: stavudine, EFV: efavirenz, HDL: high density lipids, HOMA IR: homeostatic assessment of insulin resistance, INSTI: integrase strand transfer inhibitor, LDL: low density lipids, LPV,r: lopinavir boosted ritonavir, NRTI: nucleotide reverse transcriptase inhibitor, NNRTI: non nucleotide reverse transcriptase inhibitor, NVP: nevirapine, PI: protease inhibitor, RAL: raltegravir, YLPHIV: youth living with perinatally acquired HIV

Table 2:

Characteristics of Participants at 24 months of Follow-Up

	YLP HIV N=283	HIV- N=69	<i>p value</i>
Female (%)	147 (51.9)	39 (56.5)	0.583
Tanner (=>3,%)	188 (68.9)	50 (72.5)	0.561
Age	13.95 [12.68, 15.23]	14.04 [12.29, 15.34]	0.765
Current Smoking (%)	6 (2%)	2 (3%)	0.791
CD4 cell count (cells/mm ³)	727.00 [576.00, 905.50]		
CD4 %	32.39 [27.97, 36.86]		
Viral load (copies/mL)	39.00 [39.00, 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%)		
BMI (kg/m²)	18.82 [17.33, 21.14]	20.34 [17.88, 22.30]	0.016
Waist hip ratio	0.87 [0.83, 0.91]	0.84 [0.80, 0.89]	0.002
Systolic blood pressure (mm Hg)	104.00 [98.00, 111.00]	107.00 [103.00, 114.00]	0.015
Diastolic blood pressure (mm Hg)	67.00 [61.00, 71.00]	69.00 [64.00, 73.00]	0.069
Total cholesterol (mmol/L)	4.10 [3.61, 4.78]	3.53 [3.17, 4.05]	<0.001
LDL (mmol/L)	2.18 [1.77, 2.65]	1.87 [1.58, 2.29]	0.002
HDL (mmol/L)	1.47 [1.24, 1.73]	1.36 [1.14, 1.67]	0.078
Triglycerides (mmol/L)	0.91 [0.68, 1.23]	0.59 [0.50, 0.76]	<0.001

Median [Interquartile Range]

Bold values represent $p < 0.05$

BMI: body mass index, HDL: high density lipids, LDL: low density lipids, YLP HIV: youth living with perinatally acquired HIV

Table 3:

Changes in Biomarkers over 24 months within each groups

	YLP HIV Median [IQR]	P	HIV- Median [IQR]	P
sCD163 (ng/mL)	-29.00 [-113.50, 44.50]	0.058	-82.00 [-126.00, 5.00]	0.065
sCD14 (ng/mL)	-84.00 [-323.00, 138.00]	0.011	-86.00 [-253.00, 61.00]	0.107
IL6 (pg/mL)	-0.12 [-0.88, 0.58]	0.062	-0.10 [-0.64, 0.78]	0.871
IFAB-P (pg/mL)	-182.00 [-943.50, 447.00]	0.004	-190.00 [-795.75, 245.25]	0.286
sTNF-RII (pg/mL)	-84.00 [-318.00, 198.00]	0.07	-51.00 [-319.50, 253.75]	0.747
oxLDL (mU/L)	344.50 [-4257.25, 4277.25]	0.712	-138.50 [-2424.00, 3786.25]	0.911
hsCRP (mg/L)	-0.12 [-1.60, 1.27]	0.184	0.07 [-0.35, 0.83]	0.098

Median [Interquartile Range]

Bold values represent p<0.05

high sensitivity C reactive protein, IL6: interleukin 6, hsCRP: high sensitivity C reactive protein, IFAB-P: intestinal fatty acid binding protein, oxLDL: oxidized LDL, sCD14 and 163: soluble CD 14 and 163, sTNFR-II: soluble tumor necrosis factor receptor α II