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HIV infection, Antiretroviral Therapy, and Measures of Endothelial Function, Inflammation, Metabolism, and Oxidative Stress

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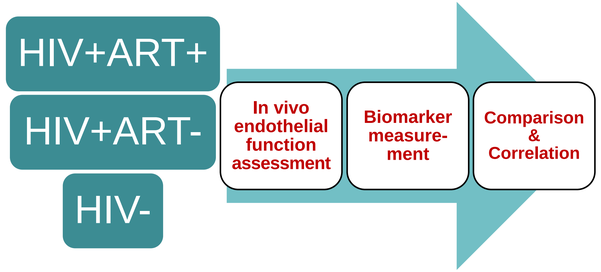
Background

People with HIV infection have an increased risk of cardiovascular disease (CVD). Impaired endothelial function is an early risk factor for CVD in the general population. It is presumed that HIV infection is associated with impaired endothelial function, but results have been inconsistent due to differences in study designs and measurement methodologies.

Objective

To determine the relationships between HIV infection, virological suppression with antiretroviral therapy (ART), in vivo measures of endothelial function, and circulating biomarkers of biologic pathways associated with CVD.

Methods



- 28 were HIV-infected and virologically-suppressed on a regimen of FTC/TDF/EFV (HIV+ART+)
- 44 were HIV-infected but not on ART (HIV+ART-)
- 39 were HIV-uninfected healthy volunteers (HIV-)
- The HIV+ART- and HIV- groups were matched by age, sex, smoking status and height.

Flow mediated dilation (FMD), nitroglycerin-mediated dilation (NTGMD), reactive hyperemia velocity time integral (RHVTI), and shear stress corrected FMD/RHVTI of the brachial artery were measured.

Markers* of oxidative stress, systemic inflammatory, metabolism, cellular immune activation, and endothelial activation were measured.

Images:
https://www.onlinewebfonts.com/icon/266606
https://openclipart.org/detail/205886/syringe
http://www.clipartpanda.com/clipart_images/simple-magnifying-glass-3818942

Results

Comparisons of Endothelial Function Parameters amongst the Three Study Groups

	HIV+ART+ (N=28)	HIV+ART- (N=44)	HIV- (N=39)	p-Value
FMD, %	3.48 (2.54)	3.98 (2.95)	3.24 (2.64)	0.46
NTGMD, %	9.05 (8.34)	9.87 (3.76)	10.94 (4.66)	0.42
RHVTI, cm	64.36 (23.56)	67.55 (20.70)	74.18 (22.22)	0.17
FMD/RHVTI, %/cm	0.06 (0.06)	0.06 (0.05)	0.05 (0.03)	0.22

Note: Data presented as unadjusted mean (standard deviation). No significant differences were found after adjustment for baseline diameter, age, sex, race, HDL-C, LDL-C, triglycerides, HOMA-IR, smoking, and BMI ≥ 25.

Comparisons of Circulating Biomarkers amongst the Three Study Groups

Biomarker	Study Group mean (SD)			Pairwise Comparison P-value			Overall P-value
	HIV+ART+	HIV+ART-	HIV-	HIV+ART+ vs HIV+ART-	HIV+ART- vs HIV-	HIV+ART+ vs HIV-	
sTNFRII, pg/mL	5327.55 (1247.13)	*8550.48 (3388.05)*	5806.56 (1134.79)	<0.05	<0.05	N.S.	<0.0001
sCD14, ng/mL	*2454.49 (336.95)*	1964.40 (561.55)	1883.96 (285.53)	<0.05	N.S.	<0.05	<0.0001
sCD163, ng/mL	579.47 (223.35)	*790.15 (255.39)*	482.75 (152.62)	<0.05	<0.05	N.S.	<0.0001
β2MCG, mcg/mL	1463163.97 (690501.73)	*3751961.36 (1559440.88)*	1942211.72 (549424.29)	<0.05	<0.05	N.S.	<0.0001
sIP-10, pg/mL	207.08 (104.85)	*520.55 (284.60)*	150.54 (89.78)	<0.05	<0.05	N.S.	<0.0001
ADMA µmol/L	*0.48 (0.09)*	0.62 (0.17)	0.60 (0.11)	<0.05	N.S.	<0.05	<0.0001
HDL-C, mg/dL	41.07 (10.77)	37.02 (10.27)	*49.84 (18.68)*	N.S.	<0.05	<0.05	<0.0001
TIMP-1, ng/mL	95.34 (16.05)	*116.87 (33.43)*	82.72 (20.00)	<0.05	<0.05	N.S.	<0.0001
sVCAM-1, ng/mL	603.00 (154.17)	*1101.63 (356.45)*	557.75 (139.95)	<0.05	<0.05	N.S.	<0.0001

Note: Only presenting biomarkers found to have significant differences among the three groups adjusted for multiple comparisons, and where one group was significantly different from the other two in pairwise comparisons. In red are pairwise comparison with significant differences, significantly different groups are also in italics. N.S.: not significant

Correlations between Circulating Biomarkers & Endothelial Function

Group/Biomarker	FMD r (P-value)	FMD/RHVTI r (P-value)
HIV+ART+		
sTNFRII	-0.48 (p<0.01)	-0.48 (p<0.01)
IL-8	0.42 (p=0.03)	N.S.
RANTES	0.48 (p=0.03)	N.S.
HDL-C	0.41 (p=0.03)	0.38 (p<0.05)
HIV-		
RANTES	0.41 (p<0.05)	N.S.
IP-10	N.S.	0.34 (p=0.03)

Note: Only statistically significant correlations between serum biomarkers, FMD, and FMD/RHVTI within the study groups are presented. No other significant correlations were found.

Conclusions

- We did not find any significant differences in endothelial function as measured by FMD, NTGMD, RHVTI, and FMD/RHVTI between the HIV-, HIV+ART-, and HIV+ART+ participants.
- sTNFRII, sCD163, B2MCG, sIP-10, TIMP-1, and sVCAM-1 were significantly elevated in the HIV+ART- group compared to the other study groups, whereas ADMA was significantly lower in the HIV+ART+ group, sCD14 was significantly higher in the HIV+ART+ group, and HDL-C was significantly higher in the HIV- group.
- In the HIV+ART+ group, we found a modest inverse correlation between sTNFRII, and a modest positive correlation between HDL-C, and FMD. We also found unexpected positive correlations between IL-8 and RANTES with FMD in this group.
- Our study was limited by the relatively small sample sizes. Lack of adjustment for multiple testing may have led to false positive findings.
- Further studies are needed to determine the underlying mechanisms for the increased risk of CVD in HIV.

Acknowledgements

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*List of biomarkers measured: F2-isoprostane and malondialdehyde; interleukin-6, high sensitivity C-reactive protein, soluble tumor necrosis factor-α receptors I and II, regulated on activation normal T-cell expressed and secreted, monocyte chemotactic protein-1, interferon-γ- induced protein-10, interleukin-8; homeostasis model assessment –insulin resistance, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides; circulating percentage of activated CD8 cells, β-2 microglubulin, soluble cluster of differentiation-14, soluble cluster of differentiation-163; tissue inhibitor of metalloproteinase-1, soluble vascular cell adhesion molecule-1, plasminogen activator inhibitor-1, asymmetric dimethyl arginine.