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Full Length Research Paper

Markers of inflammation and endothelial activation in black South Africans with HIV and acute coronary syndromes

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HIV infection is associated with a pro-inflammatory and thrombophilic state but little is known about the link between inflammation and thrombosis in treatment-naïve patients with acute coronary syndromes (ACS). Prospective single centre study was conducted in Soweto, South Africa, comparing markers of inflammation and endothelial cell activation in highly active anti-retroviral therapy-naïve HIV positive and negative patients presenting with ACS. Between March 2004 and February 2008, 30 consecutive black South African HIV patients with ACS were compared to 30 black HIV negative patients with ACS. The HIV patients were younger (43 ± 7 vs. 54 ± 13, p = 0.004) and besides smoking (73% vs. 33%, p = 0.002) and lower HDL levels (0.8 ± 0.3 vs. 1.1 ± 0.4, p = 0.001) had fewer risk factors than the control group. At baseline, HIV patients had higher levels of tumour necrosis factor-α [5.8 (1.7 - 15.0) vs. 0.19 (0.19 - 19.8) ng/ml, p = 0.0004] and vascular cell adhesion molecule-1 [263.3 (0.38 - 778.5) vs. 151.3 (80.6 - 416.3) ng/ml, p = 0.007] compared to HIV negative patients as well as higher levels of macrophage chemoattractant protein-1 at six months [70 (30 -130) vs. 50 (30 - 90) ng/L, p = 0.004]. Treatment-naïve black South African patients with HIV and ACS have evidence of a pro-inflammatory state and greater degree of endothelial cell activation compared to HIV negative patients, both of which may play a direct role in the pathogenesis of ACS in this otherwise low risk population. MCP-1 may play an important role in HIV-associated coronary artery disease.

Key words: Human immunodeficiency virus (HIV), acute coronary syndrome (ACS), inflammation, endothelial dysfunction, thrombosis.

INTRODUCTION

Inflammation and endothelial cell activation are key components in the initiation, progression and thrombotic complications of atherosclerotic coronary artery disease (CAD) (Koenig and Khuseyinova, 2007). C reactive protein (CRP) and Interleukin-6 (IL-6), both pro-inflammatory cytokines, as well as having pathogenic roles in atherosclerosis, also have strong and independent prognostic implications in patients with atherosclerotic vascular disease and acute coronary syndromes (ACS) (Koenig and Khuseyinova, 2007). Monocyte chemoattractant protein-1 (MCP-1) is a potent activator of macrophages and monocytes and is actively involved in the initiation and progression of atherosclerosis (de Lemos et al., 2003). A significant association between increasing concentrations of the endothelial activation markers [soluble E-selectin (sE-selectin), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cellular adhesion molecule-1 (sVCAM-1)] and future cardiac events was shown in apparently healthy individuals in the ARIC (atherosclerosis risk in communities) study (Hwang et al., 1997). HIV infection is characterised by a profound inflammatory response with elevated levels of a number of pro-inflammatory

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cytokines including tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6 and CRP (Hsue et al., 2004; Hazenberg et al., 2000; Frostegard et al., 1999) which persist even after the introduction of highly active anti-retroviral therapy (HAART) (Valdez et al., 2002) and contribute to endothelial dysfunction (Gupta et al., 2008), atherogenesis and a prothrombotic state. Among HIV patients with subclinical atherosclerosis by carotid and femoral ultrasound, MCP-1 plasma levels were higher compared to HIV patients without atherosclerosis (Alonso-Villaverde et al., 2004). Endothelial activation markers including sE-selectin, sICAM-1 and sVCAM-1 have all been shown to be elevated in HIV positive patients (de Gaetano et al., 2004) but the link between *in vitro* findings and clinical events in HIV patients is still lacking. HIV-associated coronary artery disease described in the developed world is characterised by accelerated atherosclerosis and is thought to be due to a synergistic effect of viral mediated effects and the atherogenic effects of protease inhibitor (PI) containing HAART (Hsue and Waters, 2005). Little data exists on the nature of HIV-associated CAD in the developing world and specifically in South Africa where risk factors for CAD have traditionally been low (di Bisceglie et al., 1982). Within the above context, we have shown that treatment-naïve HIV positive black South Africans presenting with ACS are younger with fewer traditional risk factors compared to HIV negative patients with less atherosclerotic burden but a higher thrombotic burden on angiography (Becker et al., 2010). In a subsequent study we showed that this group of HIV patients had evidence of thrombophilia as evidenced by lower protein C and higher Factor VIII levels (Becker et al., 2010). We sought to determine whether markers of inflammation and endothelial cell activation differ between treatment-naïve black HIV positive patients with ACS compared to the HIV negative population and in so doing try and determine their importance in the pathogenesis of HIV-associated CAD and ACS. We hypothesized that HIV patients would have a higher inflammatory burden and higher levels of endothelial cell activation markers and that these would be contributory in the pathogenesis of ACS.

METHODS

Study design and patient enrollment

We conducted a prospective single centre study in the Department of Cardiology at Chris Hani Baragwanth Hospital, Soweto, South Africa. The protocol was approved by the ethics committee of the University of the Witwatersrand and adheres to the Declaration of Helsinki. All patients gave informed consent before study entry. Between March 2004 and February 2008, 30 consecutive HIV patients presenting with ACS (ACS+/ HIV+ group) were enrolled. For each HIV patient with ACS, we selected the first presenting non-HIV patient with ACS as a case-control comparator (ACS+/ HIV- group). In addition, a second control group without ACS, consisting of 30 asymptomatic HIV patients matched for age, sex and ethnicity (HIV+ alone group) were recruited from the HIV clinic. Consistent with current guidelines (Van der Werf, 2003; Bertrand et al., 2002), ACS was defined as either ST-elevation myocardial infarction, non ST-elevation myocardial infarction or unstable angina. Patients were categorized as having diabetes, hypertension or dyslipidemia when being treated chronically for these conditions or when diagnosed with the condition on admission. Patients were classified as having “other” coronary risk factors if any of the following conditions were present: (1) Family history of premature CAD (men < 55 years, women < 65 years); (2) chronic kidney disease; (3) post menopausal state and (4) abdominal obesity (abdominal circumference > 102 cm in men and 88 cm in women). Demographic data was recorded for each patient and anthropometric measurements including weight, height, body mass index (BMI) , waist to hip ratio and abdominal circumference (AC) were measured on admission according to guidelines set out in the INTERHEART study (Yusuf, 2004). Infection with HIV was diagnosed with a standard enzyme linked immunosorbent assay and Western blot techniques after obtaining consent and offering pretest counseling. In the HIV group, Plasma HIV RNA level was determined by quantitative polymerase chain reaction. CD4 count was determined by flow cytometry and patients were staged according to the CDC staging system (CDC, 1993).

Laboratory methods

Standardised venipuncture was used to collect blood samples (20 ml in an EDTA tube) in all patients on enrollment and again at 6 months in the two ACS groups only. Plasma was separated by centrifugation at 2500 rpm for 12 min within 15 min of collection. Aliquots were stored at -70°C. All plasma samples used in these studies were thawed only once for analysis. Markers selected for analysis included TNF-α, IL-6, high sensitivity-CRP (hs-CRP) [pro-inflammatory cytokines], MCP-1 [chemokine] and sE-selectin, sICAM-1 and sVCAM-1 [endothelial CAMS (cellular adhesion molecules)]. TNF-α, IL-6, MCP-1, sICAM-1 and sVCAM-1 were measured using a Bio-Plex cytokine assay (Bio-Rad Laboratories, Hercules, CA).hs-CRP was measured by latex immunoassay (CRP Vario, Sentinal Diagnostics, Milano, Italy) and E-selectin with an enzyme-linked immunosorbent assay (Human sE-selectin immunoassay kit, Invitrogen Corporation, Carlsbad, CA).

Stastistical analysis

Statistical analysis was performed using SAS 9.1 software (SAS, Cary, NC, USA). Normally distributed continuous data are presented as the mean (± standard deviation), and variables with non-Gaussian distribution as the median (min - max range). Categorical data are presented as frequencies and percentages. The initial analysis compared variables between the 3 groups using the one way anova test for continuous variables with normal distribution and the Kruskal Wallis test in case of non-normal distribution. For categorical variables the Chi-square test was performed with a Fisher exact test when necessary. Significant differences between variables in the 3 groups was assumed at $p < 0.05$. Subgroup analysis with multiple pair-wise comparisons was then performed applying the Bonferroni correction with a p value < 0.0166 considered significant.

RESULTS

The clinical characteristics of the three study groups are presented in Table 1 and markers of inflammation and endothelial activation in Table 2.

Table 1 Clinical characteristics.

	ACS+ / HIV+ (n = 30)	ACS+ /HIV- (n = 30)	HIV+ alone (n = 30)	p value
Demographic Profile				
Black African n (%)	30 (100)	30 (100)	30 (100)	-
Mean age (years)	43 ± 7	54 ± 13*	41 ± 8	0.0002
Men (%)	20(67)	18(60)	19(63)	N/S
Coronary risk factors n (%)				
Smoking	22(73)	10(33)*	11(37)*	0.004;0.003
Diabetes Mellitus	1(3)	7(23)*	0(0)	0.05
Hypertension	7(23)	23(77)*	2(7)	< 0.001
Total cholesterol (mmol/l)	3.6 ± 1.0	4.6 ± 1.4*	3.7+/-0.8	0.003
LDL cholesterol (mmol/l)	2.2 ± 0.9	3.0 ± 1.2*	2.0 ± 0.5	0.003
HDL cholesterol (mmol/l)	0.8 ± 0.3	1.1 ± 0.4*	1.0 ± 0.5*	< 0.001; 0.011
Triglycerides (mmol/l)	1.4 ± 0.8	1.1+/-0.4	1.4+/-0.8	N/S
BMI (kg/m^2)	25 ± 5	28 ± 5*	21± 4*	0.008;0.003
Other coronary risk factors	2 (7)	16 (53)*	0 (0)	< 0.001
HIV related factors				
CD4 (cells/mm^3) median (range)	230 (30 - 1356)	N/A	125 (6 - 1041)	0.013
Viral load (RNA copies/ml) median (range)	29000 (25 – 7 x 10^5)	N/A	54000 (25 – 11 x 10^5)	N/S
AIDS defining criteria n (%)	11 (37)	N/A	21 (70)	0.01
Current opportunistic infection	0	N/A	1 (3)	N/S
HIV related malignancies	0	N/A	2 (7)	N/S

Data are presented as mean ± standard deviation, percentages or median (range)
Key: BMI = Body mass index; * p < 0.05 vs. ACS+/ HIV+ group.

Patients presenting with an acute coronary syndrome

Patients in the ACS+/ HIV+ group were younger with a similar sex distribution. Besides smoking, (33% vs. 73%, p = 0.004), coronary risk factors were higher in the ACS+/ HIV- group with more hypertension (p = 0.0001), LDL hyperlipidaemia (p = 0.003), diabetes mellitus (p = 0.03) and "other coronary risk factors" (p = 0.0001). Alternatively, this group had lower HDL levels (p = 0.0006) and a lower mean BMI (p = 0.008). The angiographic features of this group have been described previously (Becker et al., 2010).

At baseline, the ACS+/ HIV+ group had higher levels of TNF-α [5.8 (1.7 - 15.0) vs. 0.19 (0.19 - 19.8) ng/ml, p = 0.0004] but there were no differences between the levels of IL-6, MCP-1 or hs-CRP. This group did however have higher levels of VCAM-1 [263.3 (0.38 - 778.5) vs. 151.3 (80.6 - 416.3) ng/ml, p = 0.007] but there was no difference in levels of ICAM-1 or E-selectin. A 6 month comparison was made in this group to correct for the influence of acute thrombosis on inflammatory and endothelial markers. At 6 months, 12/30 (40%) patients in the ACS+/ HIV+ and 3/30 (10%) in the ACS+/ HIV- groups had died, and therefore did not have repeat testing. MCP-1 levels were higher in the ACS+/HIV+ group [70 (30 - 130) vs. 50 (30 - 90) ng/L, p = 0.004]. Alternatively, ICAM-1 levels were significantly higher in the ACS+/HIV- group [273.6 (64.8 - 1128.7) vs. 94.5 (18.8 - 245.3) ng/ml, p < 0.0001] as were levels of E-selectin [31.6 (2.4 - 80.4) vs. 8.8 (2.4 - 54.1) ng/ml, p = 0.004].

HIV+ alone patients

The ACS+/ HIV+ and HIV+ alone groups were well matched with respect to age, sex and viral load. Patients with an ACS were less immune compromised as evidenced by higher CD4 counts (p = 0.013) and less patients with AIDS defining criteria (p = 0.01) which were all based on a CD4 count< 200 cells/ml^3. There were no opportunistic infections or HIV related malignancies in the ACS+/ HIV+ group and 18/30 (60%) patients had early disease being classified as either stage A1 or A2 (CDC, 1993). In the HIV+ alone group, 21/30 (70%) patients had AIDS, 18/30 (60%) due to a CD4 count < 200 cells/ml^3 and 3/30 (10%) patients with either opportunistic infections or AIDS related malignancies. 6/30 (20%) had

Table 2. Markers of Inflammation and endothelial activation.

	ACS+/ HIV+ (n = 30)	ACS+/ HIV- (n = 30)	HIV+ alone (n = 30)	p value
Baseline Inflammatory markers				
TNF-α (ng/ml)	5.8(1.7 - 15.0)	0.19 (0.19 - 19.8)*	3.5(0.38 - 94.1)	0.0004
IL-6 (ng/ml)	26.2(3.3 - 479.0)	23.2(0.92 - 277.4)	6.2(1.5 - 21.7)*	< 0.0001
MCP-1(ng/L)	60(20 - 720)	50(30 - 90)	60(20 - 510)	N/S
hs-CRP (mg/L)	36.1(0.5 - 173.8)	59.9(2.3 - 255.1)	6.1(0.34 - 51.7)*	< 0.0001
Baseline endothelial activation markers				
ICAM-1(ng/ml)	81.3(0.48 - 179.9)	112.3(41.2 - 248.4)	350.4(208.1 - 1659.5)*	< 0.0001
VCAM-1 (ng/ml)	263.3(0.38 - 778.5)	151.3(80.6 - 416.3)*	395.0(29.9 - 1141.9)*	0.007;0.0016
E-selectin (ng/ml)	18.5(2.4 - 65.9)	21.3(2.4 - 58.2)	44.1(2.4 - 148.2)*	< 0.0001
6 month Inflammatory markers				
TNF-α (ng/ml)	3.1(0.19 - 8.2)	4.3(0.19 - 15.3)	N/A	N/S
IL-6 (ng/ml)	5.6(0.92 - 54.1)	5.9(0.92 - 24.2)	N/A	N/S
MCP-1(ng/L)	70(30 - 130)	50(30 - 90)*	N/A	0.004
hs-CRP (mg/L)	4.5(1.4 - 109.8)	4.3 (1.1 - 71.7)	N/A	N/S
6 month endothelial activation markers				
ICAM-1(ng/ml)	94.5(18.8 - 245.3)	273.6(64.8 - 1128.7)*	N/A	< 0.0001
VCAM-1(ng/ml)	296.1(153.0 - 555.5)	251.5(120.6 - 613.4)	N/A	N/S
E-selectin (ng/ml)	8.8(2.4 - 54.1)	31.6(2.4 - 80.4)*	N/A	0.004

Data are presented as median (min - max range)
Key: TNF-α, Tumour necrosis factor- α; IL-6, Interleukin-6; MCP-1, Macrophage chemoattractant protein-1; hs-CRP, high sensitivity C reactive protein; ICAM-1, Intercellular adhesion molecule-1; VCAM-1, Vascular cellular adhesion molecule-1; sE-selectin, soluble Endothelial-selectin; * $p < 0.05$ vs. ACS+/ HIV+ group.

early disease (stage A1 or A2). In terms of coronary risk factors, there were more smokers in the ACS+/HIV+ group ($p = 0.0026$) and the mean HDL levels were lower ($p = 0.011$) compared to the HIV+ alone group. At baseline, markers of inflammation were significantly higher in the HIV+/ACS+ group with higher levels of IL-6 [26.2 (3.3 - 479) vs. 6.2 (1.5 - 21.7) ng/ml, p,0.0001] and hs-CRP [36.1 (0.5 - 173.8) vs. 6.1 (0.34 - 51.7) mg/L, p, 0.0001]. Levels of endothelial activation markers were all higher in the HIV+ alone group: ICAM-1 [350.4 (208.1 - 1659.5) vs. 81.3 (0.48 - 179.9) ng/ml, p, 0.0001], VCAM-1 [395 (29.9 - 1141.9) vs. 263.3 (0.38 - 778.5) ng/ml, $p = 0.0016$] and E-selectin [44.1 (2.4 - 148.2) vs. 18.5 (2.4 - 65.9) ng/ml, $p < 0.0001$].

DISCUSSION

By studying a treatment naïve group of HIV patients with ACS we were able to look at markers of inflammation and endothelial cell activation without having the confounding effects of HAART. Considering the ACS+ group first, the pro-inflammatory cytokine TNF-α was significantly higher, at baseline, in HIV patients (ACS+/HIV+ group) compared to their HIV negative counterparts (ACS+/HIV- group) despite being younger with less traditional risk factors for CAD. There was no evidence of infectious disease in either group at the time of blood collection making it unlikely that the difference in inflammatory markers could be explained by an underlying, confounding infectious process which has been shown previously to be a precipitant in the pathogenesis of ACS (Ross, 1999). Baseline markers of endothelial activation were also different between the two groups with higher levels of VCAM-1 in the HIV group. VCAM-1 is a member of the immunoglobulin super-family and is involved in the firm adhesion and transmigration of leucocytes through endothelial cells (de Gaetano et al., 2004). Increased levels of VCAM-1 have been shown to occur with stimulation of endothelial cells with pro-inflammatory cytokines (Figure 1) and have a strong predictive value of future cardiovascular events (Blankenberg et al., 2003). This pro-inflammatory state is likely related to the well described effects of the HIV virus on CD4 cell and macrophage activation with consequent elaboration of pro-inflammatory cytokines including TNF-α and the interleukins (Frostegard et al., 1999) which in turn may lead to accelerated atherosclerosis and a prothrombotic

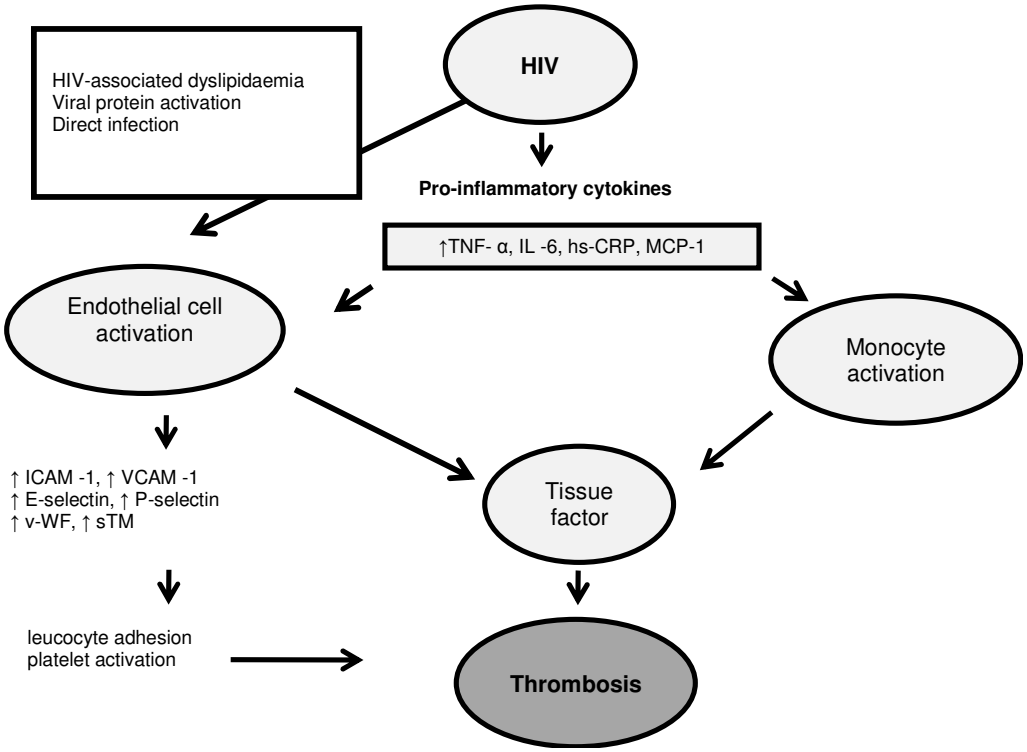

Figure 1. A proposed link between HIV, inflammation and thrombosis.
Key: TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; hs-CRP, high sensitivity CRP; MCP-1, macrophage chemoattractant protein-1; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; E-selectin, endothelial selectin; P-selectin, platelet-selectin; vWF, von Willebrand factor; sTM, soluble thrombomodulin.

state with the elaboration of tissue factor which is acritical and potent factor in the initiation of coagulation in both physiologic and pathologic conditions (Grignani and Maiolo, 2000) (Figure 1). The HIV+/ACS+ group were also found to have greater thrombus burden on angiography in a previous study (Becker et al., 2010) which may, in part, be related to this well documented relationship between inflammation and thrombosis (Frostegard et al., 1999) (Figure 1). Furthermore, we showed that this group of patients also had higher rates of in-stent restenosis (Becker et al., 2010) which is thought to be related to a heightened inflammatory state during percutaneous coronary intervention (PCI) (Hsue et al., 2004). There was no difference in the inflammatory markers at six months but levels of the pro-atherogenic chemokine MCP-1 was significantly higher in HIV+ patients. MCP-1 is a chemokine responsible for the recruitment of monocytes to sites of inflammation where they promote atherosclerotic lesions and plaque vulnerability (de Lemos et al., 2003). Levels of MCP-1 have been shown to correlate with carotid intima-media thickness, a surrogate marker of atherosclerosis in HIV patients (Joven et al., 2006). Furthermore, MCP-1 is thought to play an important role in the pathogenesis of restenosis after PCI (Jianli and Kolattukudy, 2009). An unexpected finding was that ICAM-1 and sE-selectin levels were significantly higher at six months in the ACS+/ HIV- group. This may have been due to selection bias as a greater number of HIV+ patients died prior to the six month follow up compared to those without HIV; thus selecting out the sicker patients who may have had a greater degree of endothelial activation. With respect to the HIV+ group comparison could only be made at baseline as the HIV+ alone group did not have markers performed at 6 months. At baseline, IL-6 and hs-CRP were significantly higher in the ACS+/ HIV+ group but when comparing the baseline levels of inflammatory cytokines of the HIV+ alone group with the 6 month levels of the ACS+/ HIV+ group (that is both free of a thrombotic event), there was no difference. All markers of endothelial activation were significantly higher at baseline in the HIV+ alone group despite having a lower pro-inflammatory burden. This may be explained by the fact that endothelial cell activation in HIV has many triggers with pro-inflammatory cytokines being only one of them. Other known mechanisms include lipid disorders associated with HIV infection (Grinspoon and Carr, 2005), viral protein-related endothelial activation (Ren et al., 2002) and direct HIV infection of the endothelium and vascular smooth muscle cells (Conald et al., 1995). Of note, is that patients in the HIV+ alone group had lower CD4 cell counts with a higher percentage of patients with

AIDS; all factors which favour a greater degree of endothelial cell perturbation (Seigneur, 1997). A proposed link between HIV, inflammation and thrombosis is presented in Figure 1.

Although the study constitutes one of the largest prospective analyses on treatment-naïve patients with ACS, certain limitations need to be acknowledged. Firstly, given the nature of clinical presentations and our planned analyses, we were unable to completely match case-controls according to age, sex and risk parameters. The sample size in each group is relatively small resulting in a lack of power to detect small differences between the groups which may have been significant. In addition, not all patients had repeat testing at 6 months which would have influenced the validity of the 6 month markers of inflammation and endothelial cell activation in the patients who had thrombotic events. Wherever possible, however, we have adhered to the recently published STROBE guidelines in our reporting of study data (von Elm et al., 2007).

Conclusions

Treatment-naïve black South African patients with HIV and ACS have evidence of a heightened pro-inflammatory state and greater degree of endothelial cell activation compared to HIV negative patients, factors which may play a direct or indirect role in the path-genesis of thrombosis and ACS in this otherwise low risk population. The role of MCP-1 as a potential risk factor and marker of HIV-associated CAD and restenosis needs to be further elucidated.

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