THE HISTOLOGICAL CHARACTERIZATION AND ENDOTHELIAL FUNCTION IN HIV POSITIVE PATIENTS PRESENTING WITH ACUTE CORONARY SYNDROMES

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirement for the degree of **Doctor of Philosophy**

Johannesburg 2019

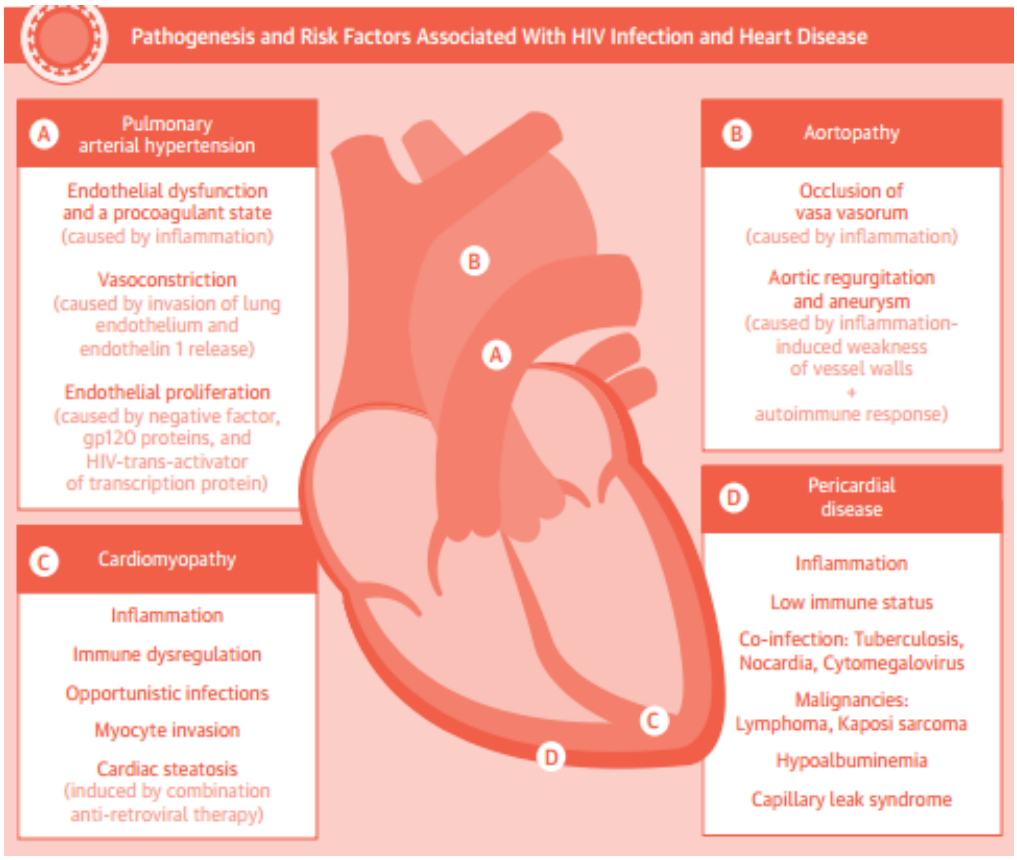


Figure 1.1 : Pathogenesis of HIV and Non-ischaemic Heart Disease (Manga et al., 2017)

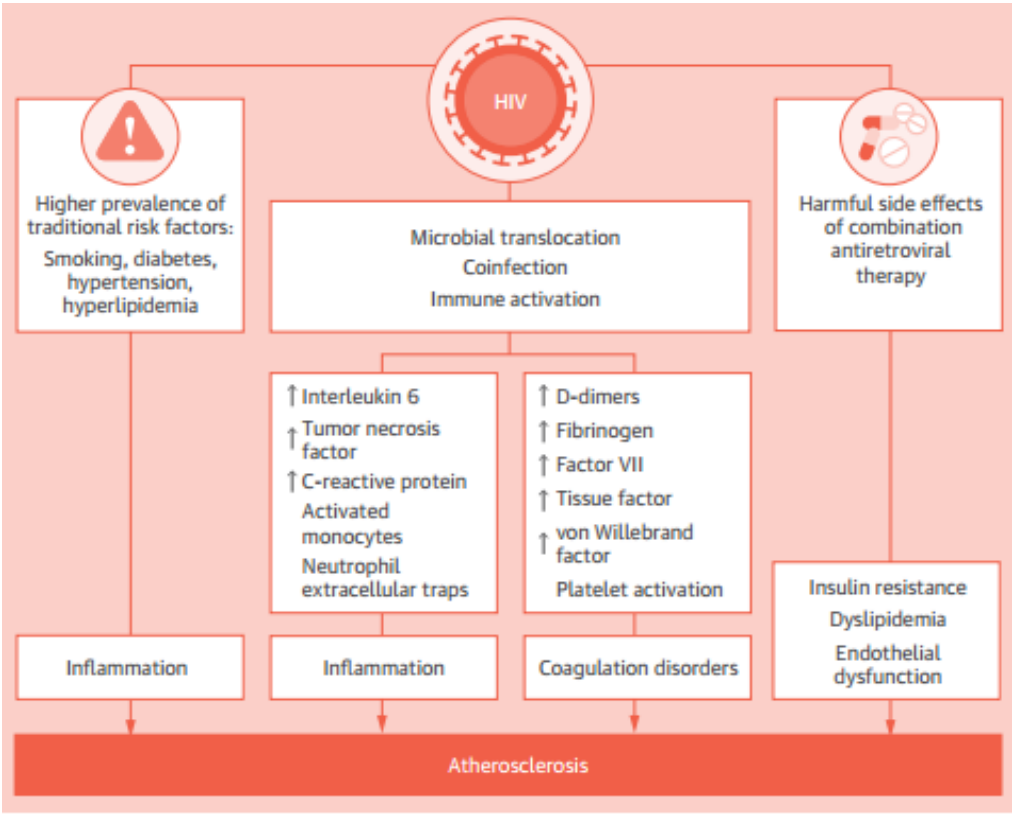


Figure 1.2: Pathogenesis of HIV and coronary artery disease (Vachiat et al., 2017)

Table 1.1: Table of HIV and Ischaemic heart disease (>5000 HIV-positive patients) (Vachiat et al., 2017)

Authors	Year	Population	HIV- positive patients	Age (years)	Effect of HIV infection	Effect of Anti-retroviral therapy
Bozette et al	2003	Veterans Affairs USA	36766 (98,1% male)	35-55 (71,3%)	No significant increase in CAD admissions or mortality	No difference between PI vs no PI
Mary-Krause et al	2003	French Hospital Database	34976 (All male)	37.7 (mean)	No controls	Increased MI in PI > 30 months Standardized morbidity ratio 2.9
Currier et al	2003	California Medicaid	28513 (72,7% male)	25-54 (89,7%)	Increased incidence of CAD in men < 35y and women < 45y	Increased CAD with cART (age 18-33y) RR 2.06 No difference in other age groups
Friis-Moller et al	2003	D.A.D study 188 clinics in 21 countries	23468 (74,9% male)	39 (median)	No controls	Incremental increase in MI with cART RR 1.26 per additional year exposure
Coplan et al	2003	Meta-analysis phase II/III randomized studies	10986 (85,9% male)	37 (mean)	No controls	No significant difference of MI in PI vs NRTI
Iloeje et al	2005	USA (HOPS cohort)	7542 (88% male)	18-49 (88%)	No controls	PI exposure ≥ 60 days associated with greater events: HR 1.71
Lang et al	2010	French Hospital Database	74958 (89% male)	47 (median)	No controls	Increased risk of MI to all PI (except saquinavir) OR 1.53 NRTI not associated with risk of MI
Durand et al	2011	Quebec, Public Health Insurance Database	7053 (91,2% male)	39,5 (mean)	Increased risk of MI in HIV- positive patients IR 2.11	Increased MI with ; abacavir, OR 1.79 efavirenz OR 1.83 lopinavir OR 1.98 ritonavir OR 2.29
Freiberg et al	2013	Veterans Affairs USA	27350 (97,3% male)	48,2 (mean)	Increased risk of MI in HIV- positive patients HR 1.48 copies/ml and CD4 <200cells/mm^3	Recent PI use had borderline significance 50,8% no cART use
Silverberg et al	2014	Kaiser Permanente California	22081 (90,6% male)	30-49 (70,3%)	RR 1.4 Increased risk if CD4 <200 cells/mm^3	cART not associated with MI
Paisible et al	2015	Veterans Aging Cohort Study	26836 (96% male)	45y (mean)	HR 2.0	51% no cART use

Table 1.2: HIV and Ischaemic heart disease (<5000 HIV-positive patients) Adapted from (Ho and Hsue, 2009)

Author	Population	Patients	Years	HIV-positive vs HIV-negative
Rickets et al	Frankfurt HIV cohort	4933	1983-1998	No controls
Klein et al	Kaiser Permanente Northern California	4159	1996-2001	Higher incidence rate of CAD hospitalization: 6.5 vs 3.8 events per 1000 PY, p=0.003 Non-significant increase in incidence of MI: 4.3 vs 2.9 events per 1000 PY, p=0.07
Obel et al	Danish National Hospital Registry	3953	1995-2004	Incidence rate for CAD hospitalization increased after cART initiation
Triant et al	Health-Care based cohort	3851	1996-2004	Increased incidence of MI: 11.13 vs 6.98 events per 1000 PY, p<0.0001, adjusted relative risk 1.75, 95% CI 1.51 to 2.02, p<0.0001
Kaplan et al	Multicentre AIDS cohort Study and Women's Interagency Study	931 men, 1455 women (2386 total)	1984-2003	No controls
Barbaro et al	Italian cohort	1551	1999-2002	No controls
Hsue et al	San Franscisco	68	1993-2003	HIV-positive patients more likely to be more younger males, low HDL, single vessel disease, Higher restenosis rates
Becker et al	South Africa	30	2004-2008	Higher thrombus burden

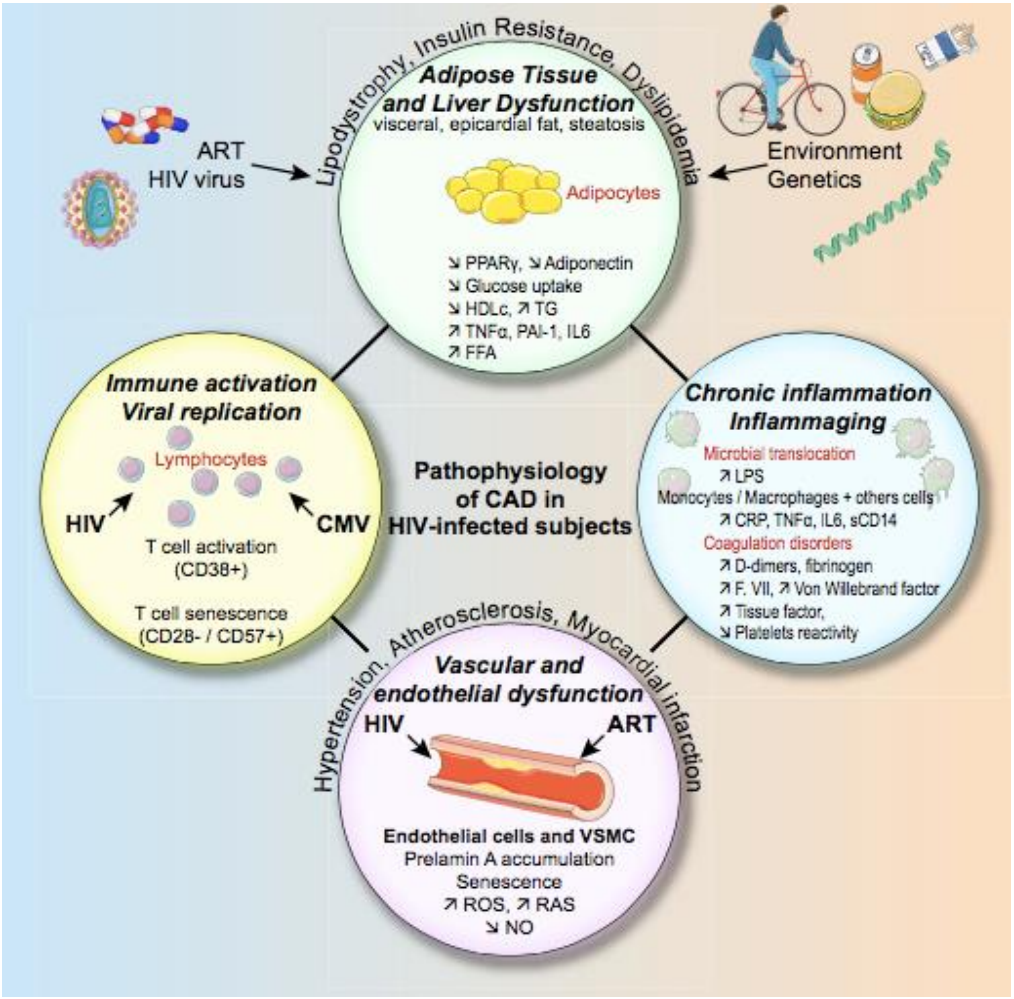


Figure 1.3: Pathophysiology of HIV and Ischaemic heart disease (Boccara 2013)

practitioners must be aware of potential drug interactions (Table 1.3). The majority of protease inhibitors interacts with cytochrome P450 3A4 and thus should be avoided in patients on simvastatin or lovastatin (Fichtenbaum et al., 2002). However, sound dietary intervention may limit pill burden and drug interactions (Stradling et al., 2012). Pravastatin and fluvastatin are the recommended first choice statins in patients on protease inhibitors followed by low-dose rosuvastatin (Cerrato et al., 2012).

Table 1.3: Effect of antiretroviral therapy and dyslipidaemia

(HDL: high-density lipoprotein, LDL: low-density lipoprotein, NNRTI: non-nucleoside reverse transcriptase inhibitors, NRTI: nucleoside reverse transcriptase inhibitors, TC: total cholesterol, TG: triglyceride) (Vachiat et al., 2017)

cART	Effect on Dyslipidemia	Comment
NRTI		
Zidovudine	↑↑	Significant increase in TC/LDL
Stavudine	↑↑	Significant increase in TC/TG
Abacavir	↑	TC/HDL ratio unchanged
Tenofovir	↓	Reduction in LDL/TC
NNRTI		
Nevirapine	↓	Can increase HDL level
Efavirenz	←→/↑	May increase lipid level slightly
Etravirine	←→/↑	No significant changes
Protease Inhibitor		
Lopinovir/ritonavir	←→/↑	Elevation of TC/ TG frequent
Fosamprenavir/ritonovir	↑	Elevation of TC/TG
Atanazavir/ritonavir	←→	PI with best lipid profile
Darunavir/ritonavir	←→	Good lipid profile
Integrase Inhibitor		
Ralegrevir	←→	Low frequency of dyslipidemia
Chemokine Receptor-5 Antagonist		
Maraviroc	←→	No significant changes

Patient selection

1) HIV+/ACS patients

Twenty HIV-positive patients presenting with ACS to CMJAH were prospectively recruited, irrespective of cART status. In these patients an IVUS and virtual histology intravascular ultrasound assessment was performed to characterize the atherosclerotic plaque and to assess the total plaque burden in the coronary arteries. Flow mediated dilatation as well as endothelial biomarkers were measured to assess endothelial function. Carotid intima media thickness assessment, as a surrogate for atherosclerosis, was also measured (Table 3.1).

2) HIV-/ACS patients

Twenty HIV-negative patients presenting with ACS to CMJAH were voluntarily recruited. These patients were age and sex matched to the HIV+/ACS group. They too were evaluated for endothelial function (FMD and biomarkers) and had CIMT measurement.

3) HIV+/no ACS patients

Twenty HIV-positive patients without ACS constituted the third group. These patients were all cART naïve. These patients also underwent endothelial function assessment and CIMT measurements.

Table 3.1: Invasive and non-invasive investigations

	HIV+/ACS n=20	HIV-/ACS n=20	HIV+/no ACS n=20
IVUS and VH	Yes		
CIMT	Yes	Yes	Yes
FMD	Yes	Yes	Yes
Biomarkers	Yes	Yes	Yes

3.2 Intravascular Ultrasound

Intravascular ultrasound has improved the understanding of plaque characteristics and has complemented percutaneous interventions (PCI). The main uses of IVUS are to determine vessel and lumen diameter for accurate measurements, to determine length of lesions and also the types of plaque. Intravascular ultrasound is also beneficial pre- and post-PCI to help guide strategy and optimal stent placement. It is ideal to confirm stent apposition, hence decreasing adverse events such as stent thrombosis. The IVUS catheter is used over a wire and the images are obtained on a portable or built-in unit in the catheterization laboratory. The arterial wall consists from the inside of ; the endothelium, the internal elastic lamina, the media, the external elastic lamina and lastly the adventitia (Figure 3.1). Intravascular ultrasound depicts arterial layers such as the intima, media and the adventitia (Figure 3.2).

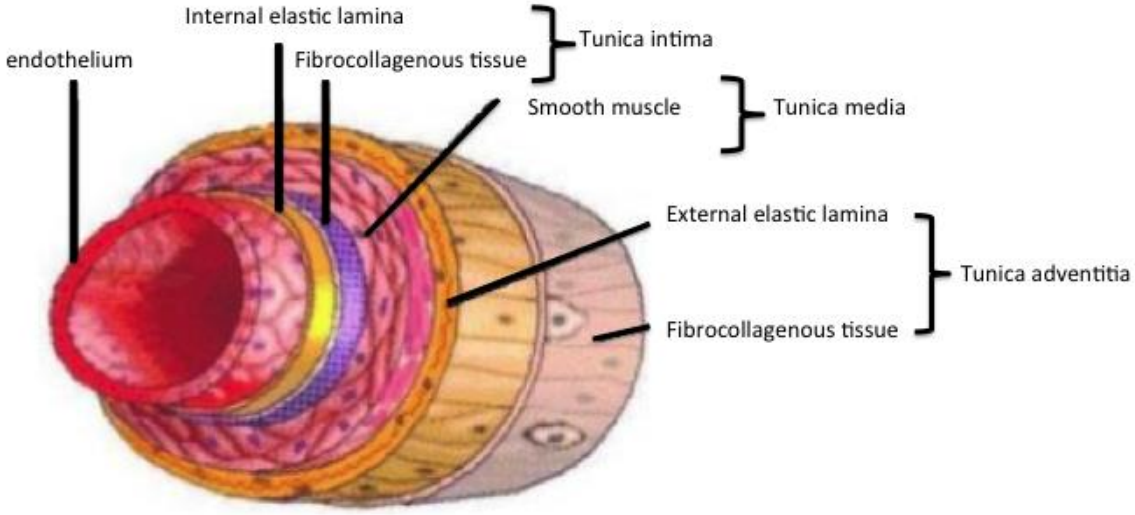


Figure 3.1: Arterial layers

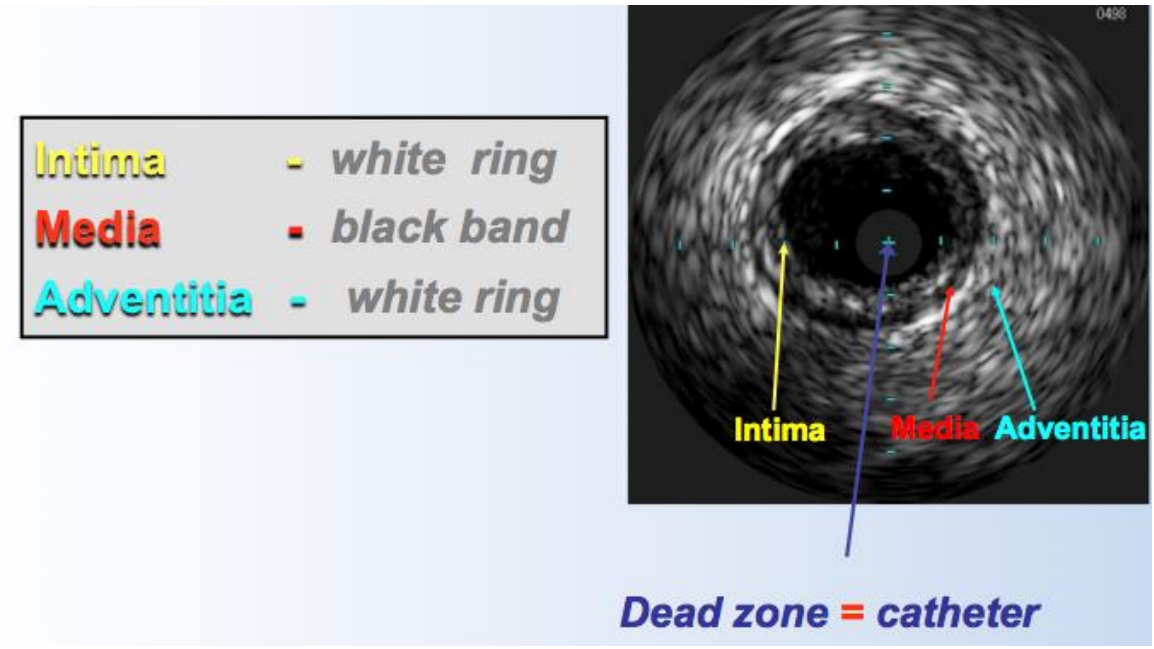


Figure 3.2 : Intravascular ultrasound : arterial layers description

Virtual histology intravascular ultrasound uses ultrasound backscatter signal in order to colour code plaques into four pre-specified subtypes based on their histological composition. There are four spectral parameters red, white, dark green and yellow-green representing the necrotic core, calcium, fibrous and fibro-fatty lesions, respectively (Figure 3.3).

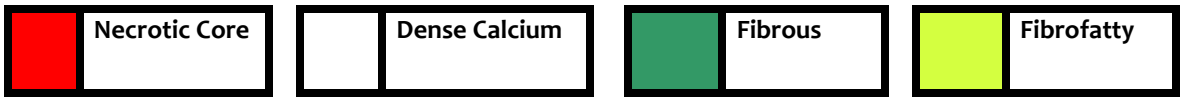


Figure 3.3: Virtual histology plaque colour description

Virtual Histology's clinical utility includes determining which plaques are inert and which ones have an active lipid rich plaque, identifying the vulnerable plaque with a thin cap fibrous atheroma. IVUS derived thin cap fibrous atheroma is defined as a necrotic core ≥ 10% without evidence of overlying fibrous tissue and the percentage of atheroma ≥ 40% (Layland et al., 2011) The virtual plaque has been correlated with histological specimens (Figure 3.4 and 3.5).

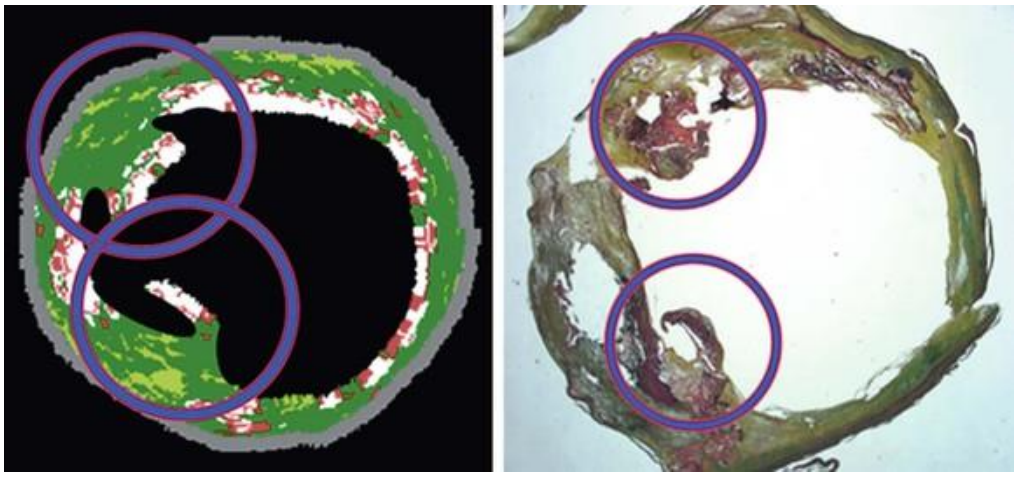


Figure 3.4: Intravascular ultrasound virtual histology and a histological specimen (Diethrich et al., 2007)

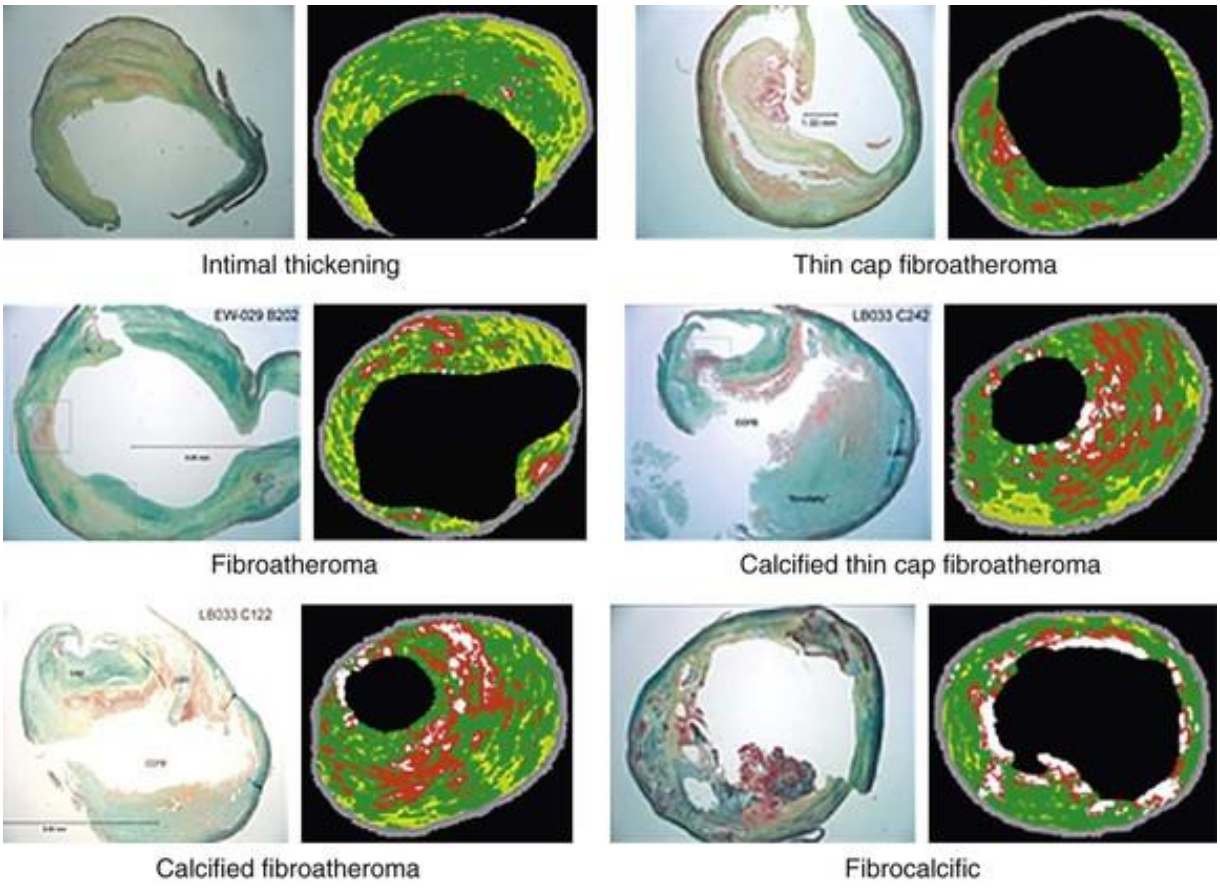


Figure 3.5: Correlation of virtual histology and histological specimens (Diethrich et al., 2007)

The interface with the operator (Figure 3.6) allows either live images to be assessed by the cardiologist or the technician who calculates the vessel and lumen diameters.

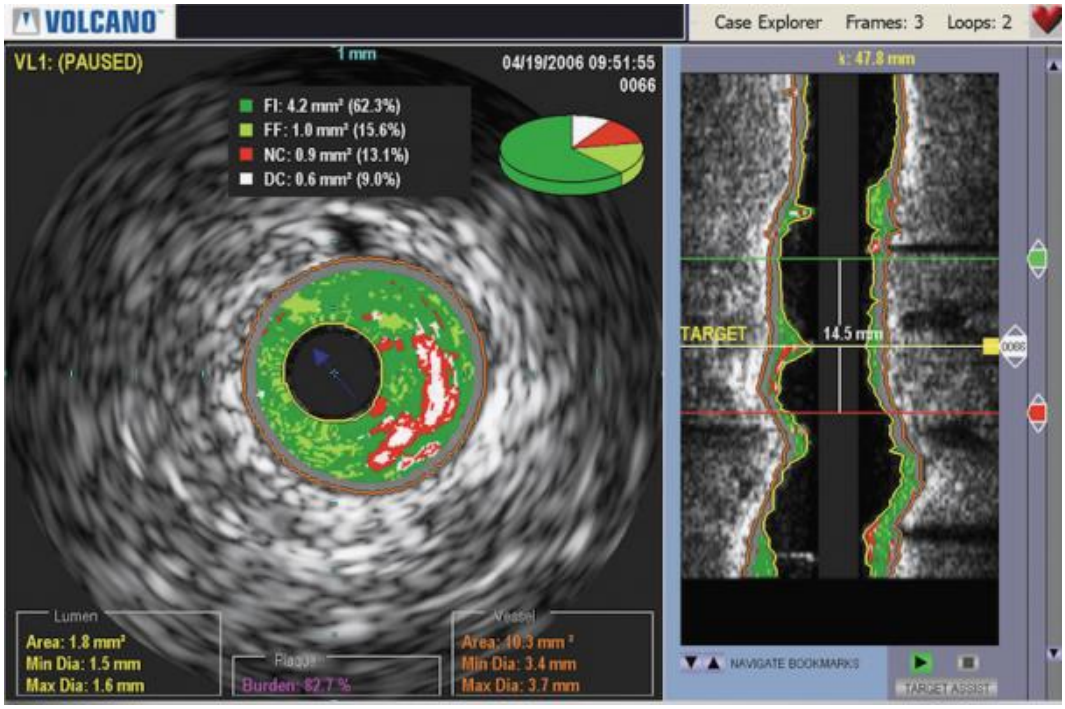


Figure 3.6 : Intravascular ultrasound interface

For optimum length assessment and for research purposes a pullback device (Figure 3.7) is used which automatically pulls the catheter (Figure 3.8) back by either 0.5mm/s or 1mm/s. Images are stored either as frames or as loops which can be later analyzed.

Figure 3.7 : Intravascular ultrasound pullback device

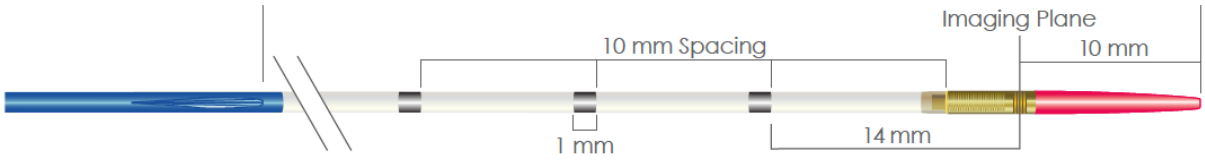


Figure 3.8 : Intravascular ultrasound catheter

Intravascular ultrasound was performed in all HIV-positive patients with ACS. Both the culprit and non-culprit vessels were imaged. A diagnostic wire was positioned into the coronary artery with the aid of a guiding catheter in the coronary artery. The IVUS catheter (Volcano) (Figure 3.8) was passed over the wire. Intravenous heparin was administered in all cases. If imaging of the coronary artery was deemed unsafe i.e. too high thrombus burden, small calibre vessel, complete occlusion, IVUS was not performed.

Each coronary artery was divided into proximal, mid and distal segments and an automatic pullback was performed. Minimal lumen diameter, maximum lumen diameter, minimum vessel diameter and maximum vessel diameter (Figure 3.9 and 3.10) was measured automatically and reviewed independently by an experienced technologist (Ms Jacqui De Sousa). The technologist was completely blinded to all patient data. The Volcano software measured the narrowest lumen area automatically. The vessel area minus the lumen area calculated plaque burden. Virtual histology assessment was performed in all imaged coronary arteries. There are four spectral parameters (red, white, dark green and yellow-green) representing the necrotic core, calcium, fibrous and fibro-fatty lesions, respectively as mentioned above. The frame VH as well as the segment (proximal/mid/distal) VH was measured using the Volcano software.

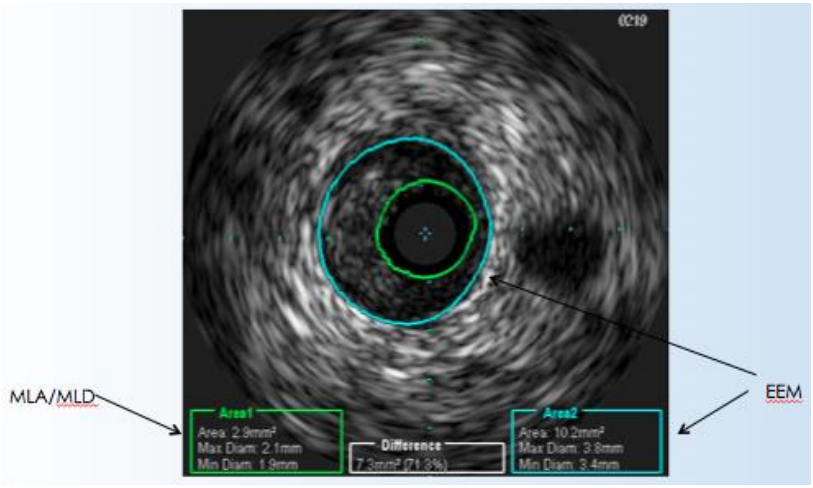


Figure 3.9: Intravascular ultrasound frame :

minimum lumen area (MLA), minimum lumen diameter (MLD), external elastic membrane (EEM)

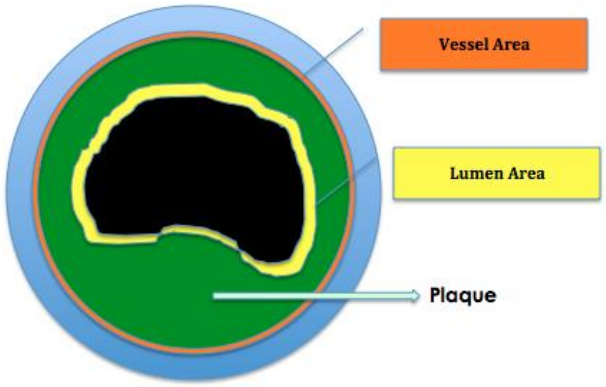


Figure 3.10: Intravasular ultrasound measurements

Coronary endothelial reactivity

In addition to IVUS and virtual histology, coronary endothelial reactivity was also assessed using IVUS by measuring the maximum luminal diameter (MLD) at baseline and after vasodilators, namely adenosine and glyceryl trinitrate (TNT). Adenosine was administered initially as it has a short half-life and the MLD was measured. Thereafter TNT was administered and the MLD was measured at 30 and 60 seconds. This was performed for each segment (proximal/mid/distal) of all the coronary arteries where possible.

3.3 Endothelial function

3.3.1 Brachial flow mediated dilatation

Endothelial function can be tested non-invasively by using brachial FMD. The maximum brachial artery diameter is initially measured at rest. The blood pressure cuff is inflated above the systolic BP (Figure 3.11). In normal patients with no endothelial dysfunction, there is hyperaemia following BP cuff inflation and the maximum diameter of the brachial artery increases. If there is endothelial dysfunction the hyperaemic response is attenuated. Nitrates can also be given which will cause the maximum diameter of the brachial artery to increase.

A high frequency transducer (11 MHz) was used to image the brachial artery in the longitudinal plane. A blood pressure cuff was then inflated to at least 50mm above systolic pressure to occlude arterial inflow for five minutes. There was reactive hyperaemia once the blood pressure cuff was deflated. A pulse doppler in the mid artery was obtained, no longer than 15 seconds after cuff deflation, to assess the hyperaemic response. The maximum dilation of the vessel usually occurs within one to two minutes after cuff release. Nitroglycerin was administered after 10 minutes of reactive hyperaemia to assess endothelium independent vasodilation.

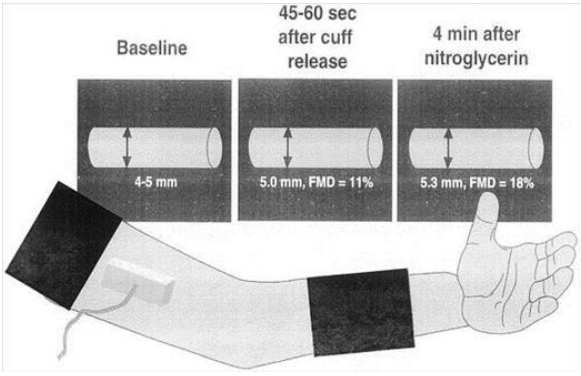


Figure 3.11 : Brachial flow mediated dilatation (Corretti et al., 2002)

3.4 Carotid Intima Media Thickness

Carotid intima media thickness is used as a surrogate for CAD and is widely used as a non-invasive method of assessing atherosclerosis (Figure 3.12). Carotid intima media thickness was measured in all three groups using an 11Mhz transducer (Phillips iE33 Ultrasound machine) with the patient's head tilted 30 degrees to the left for the right carotid artery assessment in the supine position and then 30 degrees to the right for the left carotid artery. The common carotid artery far wall was used to measure the CIMT, 1 cm from the carotid bifurcation over at least 1cm long distance and 35mm deep. The carotid artery bifurcation was visualized and the CIMT was measured automatically using the software.

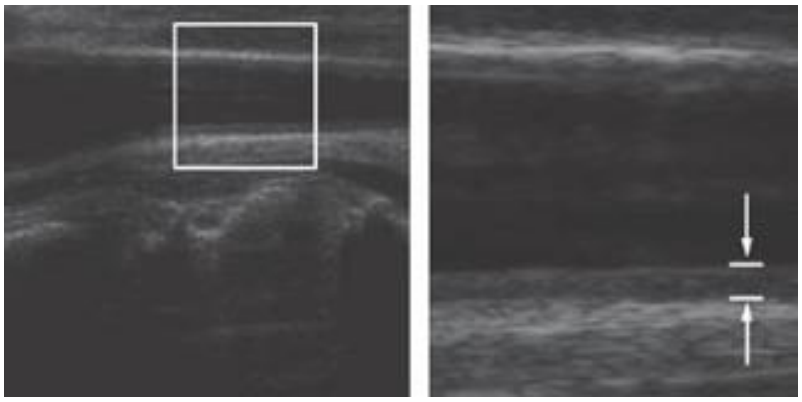


Figure 3.12 : Carotid intima media thickness

3.5 Arterial compliance

Central aortic pressure, measured in the catheterization laboratory is the most accurate method to assess the central BP. Peripheral and central blood pressure measurements can be assessed non-invasively using radial artery applanation tonometry. Hypertension is diagnosed using the brachial BP. There is an increase in pulse pressure, which is systolic blood pressure (SBP) – diastolic blood pressure (DBP) as the SBP, and not the DBP increases from the aorta to the brachial artery. The aortic SBP is augmented by the backward wave (Pb), which is added to the pressure generated by the forward wave (Pf) (Figure 3.13).

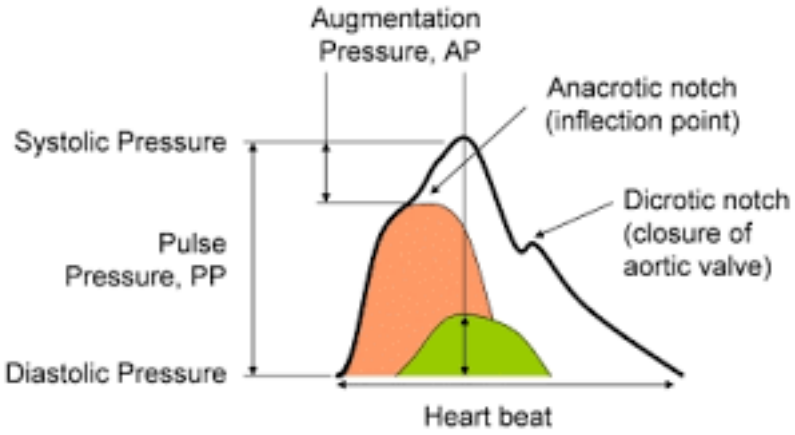


Figure 3.13 : Aortic pressure waveform

The peak brachial BP assesses only the impact of the Pf in young and middle-aged adults and largely ignores the impact of Pb on aortic BP (tidal wave). Due to the increased stiffness of the peripheral arteries compared to the aorta, the aortic BP is lower than brachial BP (Nichols, 2011). Arteries stiffen due to ageing, smoking, diabetes mellitus, hypertension, dyslipidaemia and chronic inflammation (Nichols, 2011) (Figure 3.14).

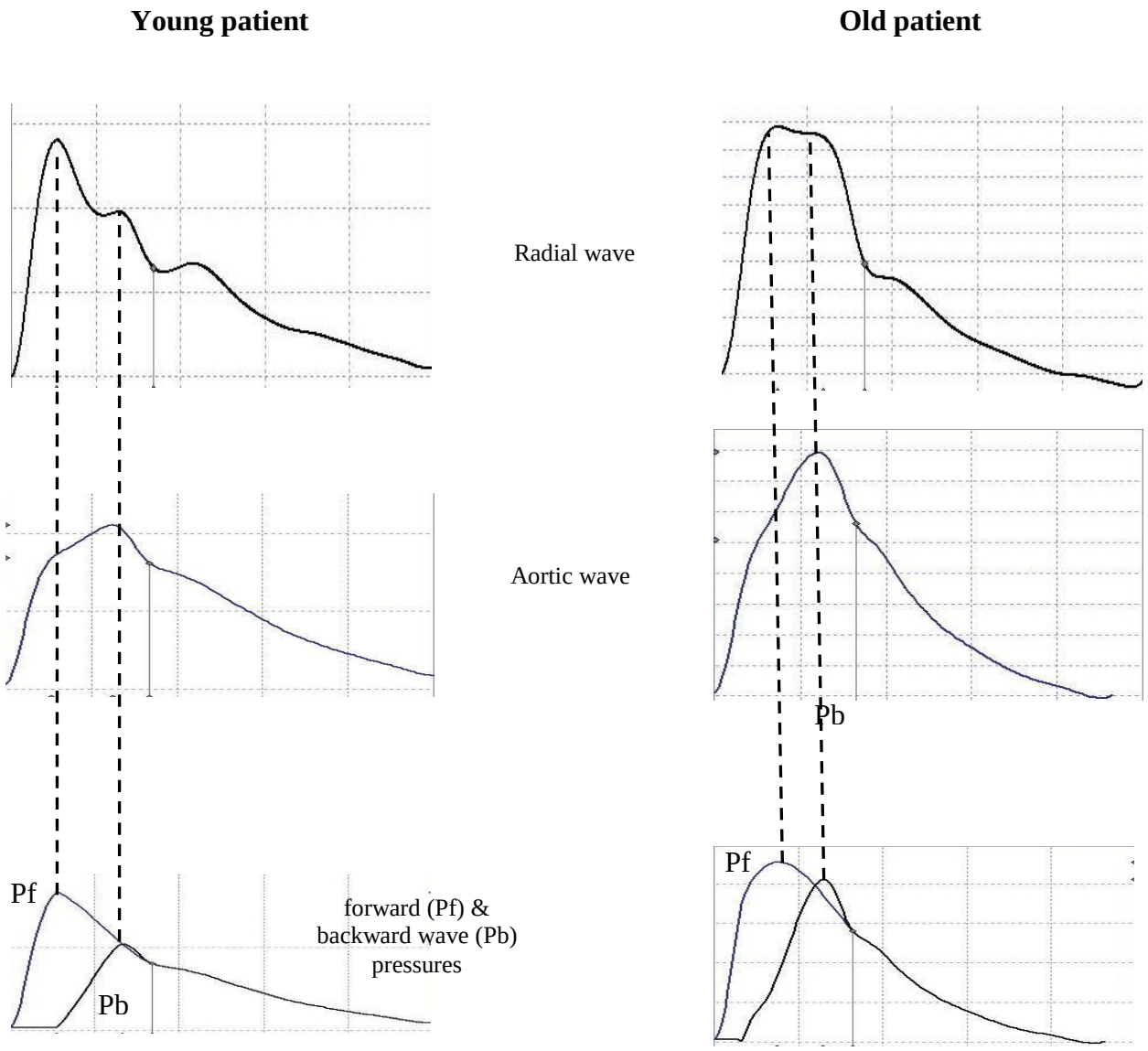


Figure 3.14 : Pressure waveforms in young and old patients

With increased stiffness the aortic BP increases and the BP in peripheral arteries increases less. Brachial BP will then begin to approximate aortic BP (Nichols, 2011, McEniery et al., 2005). The

current ‘gold-standard’ non-invasive assessment of aortic compliance is assessment of aortic stiffness by aortic pulse wave velocity (PWV) (Nichols, 2011). Currently the most reliable and simple technology to assess aortic compliance is radial artery applanation tonometry (Figure 3.15). Applanation tonometry of the radial artery converts the radial pulse wave into an aortic pulse wave. Pulse wave velocity was measured from sequential waveform measurements at the carotid and femoral sites. The distance that the pulse wave travels was determined as the difference between the distance from the femoral sampling site to the suprasternal notch, and the distance from the carotid sampling site to the suprasternal notch (Figure 3.16).

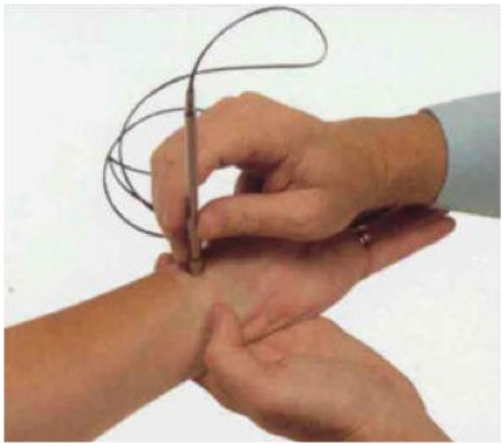


Figure 3.15 : Radial artery applanation tonometry

Current guidelines by the European Society of Hypertension state that a measured PWV larger than 10m/s can be considered an independent marker of end organ damage (Mancia et al., 2013). Hence the higher the PWV, the more arterial stiffness and which would make an individual more prone to developing hypertension. The aortic augmentation index is also a measure of arterial stiffness but this is less well validated.

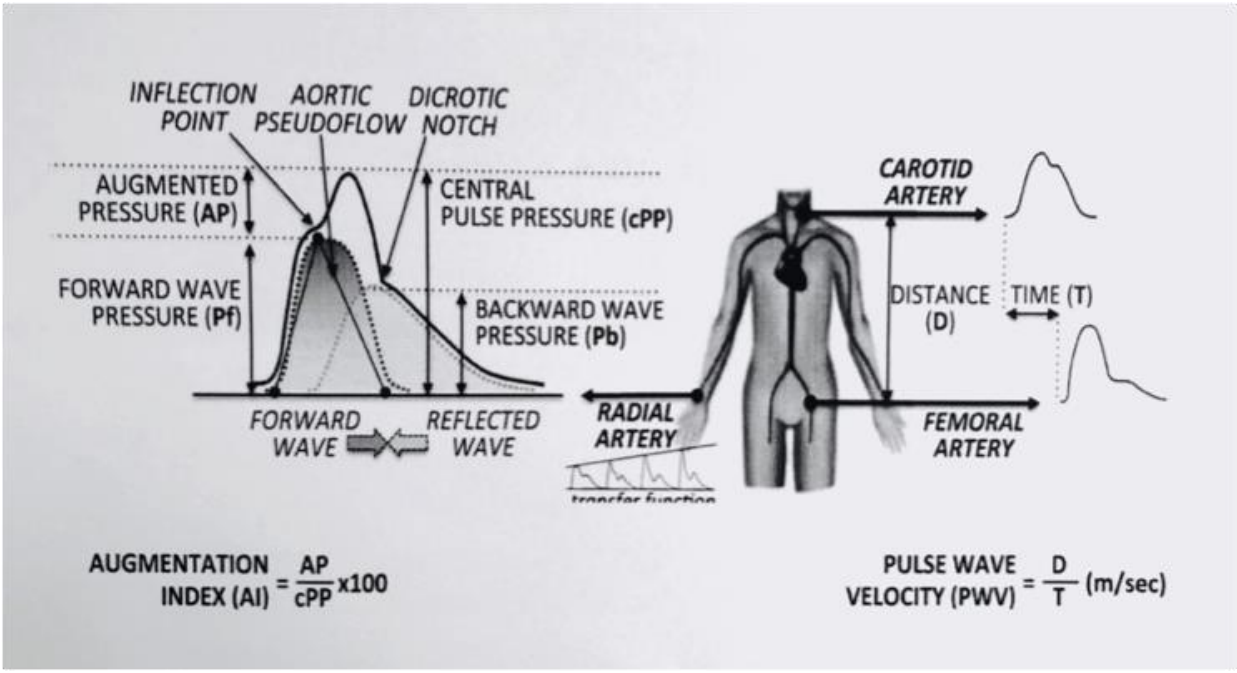


Figure 3.16 : Applanation tonometry. Adapted from (Canepa and AlGhatrif, 2015)

CHAPTER 4 : RESULTS

4.1 Demographic Data

Age

The mean age of the HIV+/no ACS group, 36.0 (sd=6.8) years was significantly lower than both the HIV+/ACS group 51.0 (sd=18.1) years and the HIV-/ACS group 52.3 (sd=9.0) years (one-way ANOVA: $p<0.0001$) (Figure 4.1).

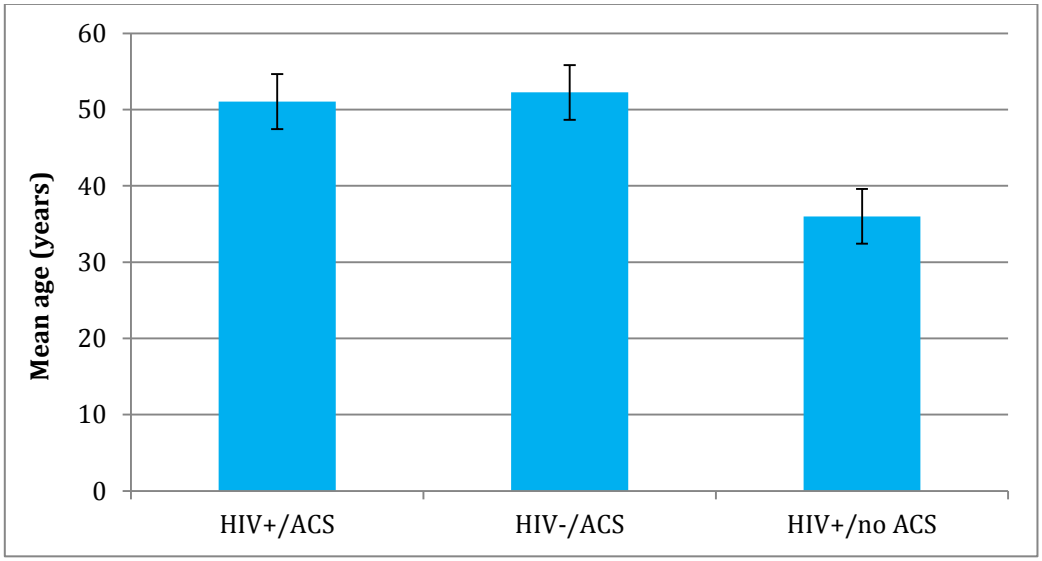


Figure 4.1: Comparison of age

Gender

The proportion of males in each group ranged between 50 and 80%, but the differences were not statistically significant (chi-squared test: $p=0.14$).

Ethnicity

There was a strong association between group and ethnicity (Fisher's exact test: $p<0.0001$; phi coefficient=0.65). The largest differences occurred between the HIV-/ACS and HIV+/no ACS groups (Figure 4.2): the latter group comprised solely black patients, while the former group comprised only 35% black patients, together with 60% white patients.

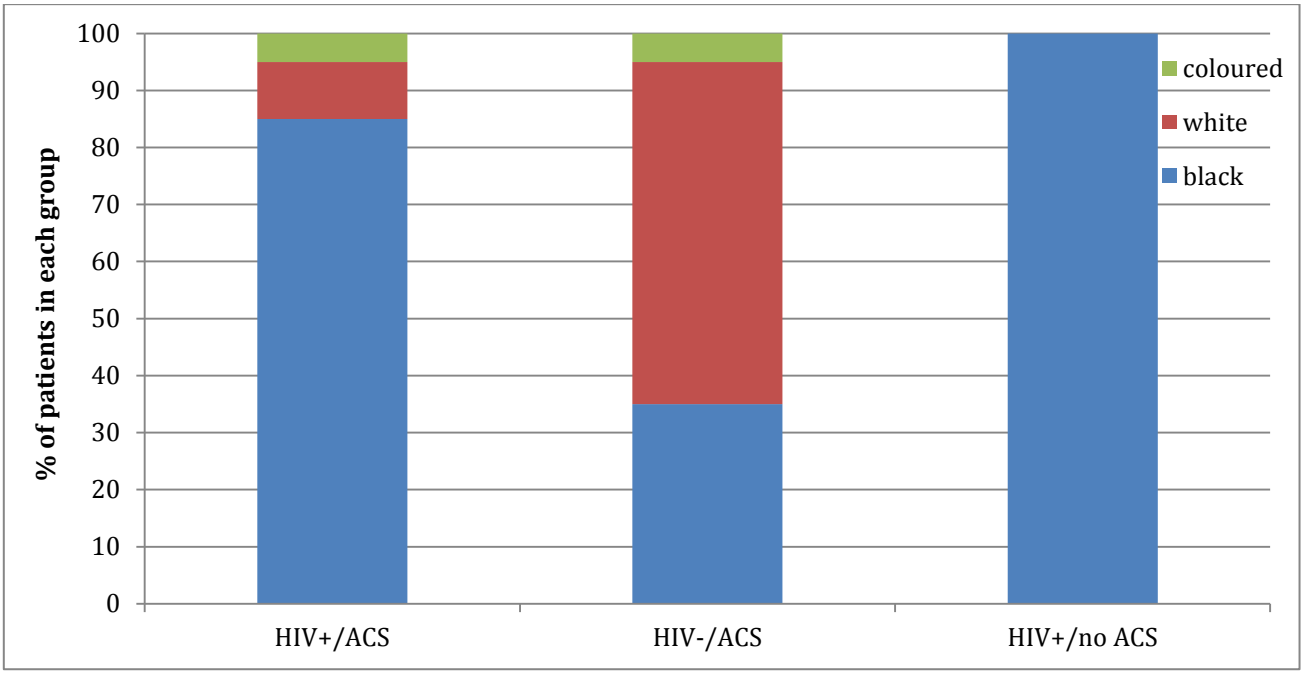


Figure 4.2 : Comparison of race

4.2 Clinical data

In the HIV+/ACS group there were 14 admissions with STEMI (8 anterior, 6 inferior) (70%), followed by 4 NSTEMI admissions (20%) and 2 patients with unstable angina (10%) (Table 4.1). The majority of the cases were elective as most presented late after the reperfusion time window. The typical presentation was a young patient with STEMI involving the left anterior descending artery. Only 4 of the 14 STEMI patients were thrombolysed (29%). There was no history of a previous MI. Risk factors included smoking in 11 (55%), hypertension in 6 (30%), diabetes in 2 (10%), dyslipidaemia in 2 (10%) patients and 1 (5%) patient with a family history of CAD. The average body mass index was 24.4kg/m^2.

Table 4.1 : HIV+/ACS patients presentation and management.

(STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST segment myocardial infarction, UA: unstable angina, PCI: percutaneous intervention, FFR: Fractional flow reserve DES: Drug eluting stents LAD: left coronary artery, RCA: right coronary artery, LCx: left circumflex artery)

	STEMI	NSTEMI	UA	PRIMARY PCI	RESCUE PCI	ELECTIVE	FFR	DES	Management
A1	1	0	0	0	1	0	0	0	Medical therapy
A2	0	0	1	1	0	0	0	1	PCI LCx
A3	1	0	0	0	0	1	0	0	Medical therapy
A4	1	0	0	0	0	1	0	1	PCI RCA
A5	1	0	0	0	1	0	0	0	Medical therapy
A6	1	0	0	0	0	1	0	0	Medical therapy
A7	1	0	0	1	0	0	0	1	PCI LAD
A8	1	0	0	0	0	1	0	0	Medical therapy
A9	1	0	0	1	0	0	0	1	PCI RCA
A10	0	1	0	0	0	1	0	0	Medical therapy
A11	1	0	0	0	0	1	0	0	Medical therapy
A12	0	1	0	0	0	1	0	0	Medical therapy
A13	0	1	0	0	0	1	0	0	Medical therapy
A14	1	0	0	1	0	0	1	0	Medical therapy
A15	1	0	0	0	0	1	1	0	Medical therapy
A16	1	0	0	1	0	1	1	0	Medical therapy
A17	1	0	0	0	0	1	0	0	Medical therapy
A18	0	0	1	0	0	1	0	1	PCI LAD
A19	0	1	0	0	0	1	0	0	Medical therapy
A20	1	0	0	1	0	1	0	1	PCI RCA

The left anterior descending artery (LAD) was the most common artery involved (60%), followed by the right coronary artery (RCA) (35%) and the left circumflex artery (LCx) (20%) (Figure 4.3). Three patients had intermediate proximal LAD lesions and Fractional Flow Reserve was used which demonstrated that these lesions were not significant. Six drug eluting stents (DES) were inserted with an average length of 22mm. Thrombus was present in 8 patients (40%) and one patient was given an intracoronary thrombolytic (Figure 4.4 and 4.5) which resulted in improved perfusion. Four patients had complete occlusions. There were three bifurcation lesions. There were no complications following PCI such as bleeding, perforations, dissections or strokes. No patients were referred for coronary artery bypass grafting. One patient had an in-stent restenosis and another patient died due to sudden cardiac death two weeks after discharge.

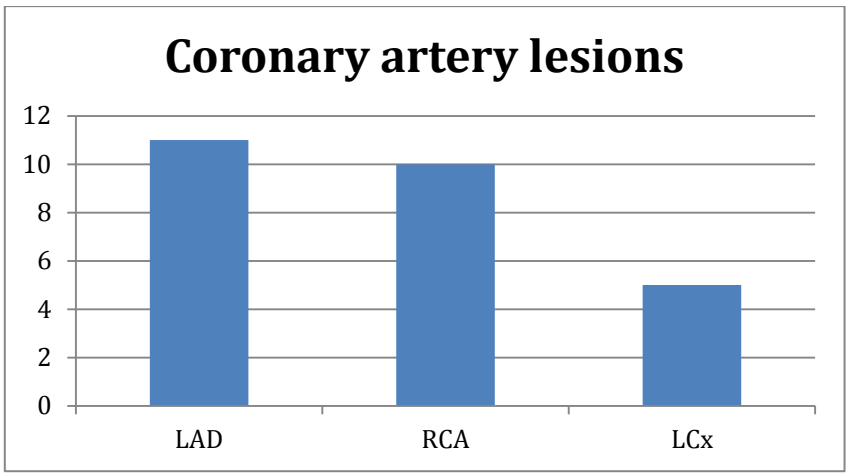


Figure 4.3: Coronary artery lesions

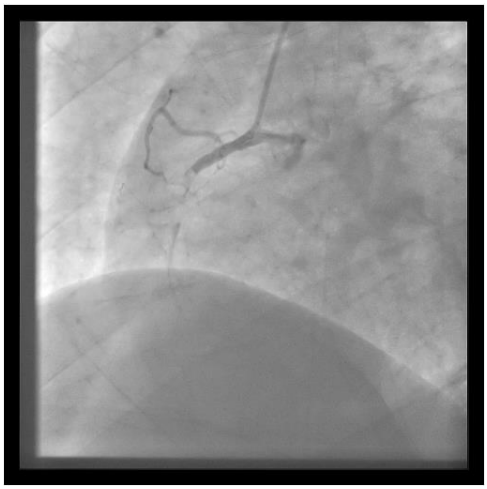


Figure 4.4 : STEMI : complete occlusion of the right coronary artery

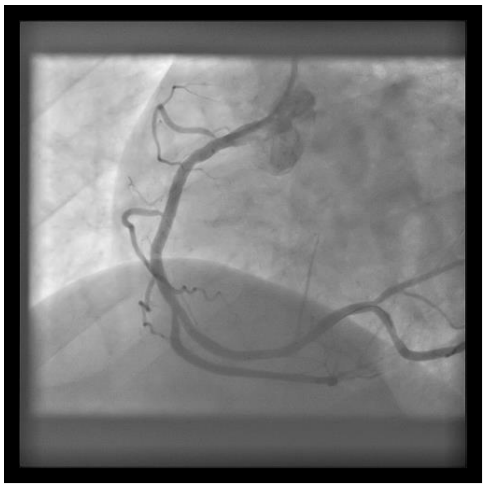


Figure 4.5 : Post intracoronary lytic and stent

HIV+/ACS patients

Seven patients of the 20 HIV+/ACS group (35%) were not aware of their HIV status on admission of ACS.

Ten of the thirteen patients (77%) who knew their HIV status were already on cART.

Combination antiretroviral therapy:

Information was available for only 16 patients (20% missing data). Ten of these 16 patients (63%) were not on cART. The median time for those on cART was 24 months (IQR 5-51). HIV+/ACS patients who were not on cART were started on cART in the HIV clinic.

Waist circumference : The mean waist circumference was 83.0 cm (sd=9.6 cm).

Body mass index: The mean body mass index was 24.4 kg/m^2 (sd=5.5 kg/m^2).

Presentation (ACS groups ONLY)

Each of the ACS groups presented with STEMI (70%), NSTEMI (20%) and UA (10%). There was no significant difference between the groups (chi-square test: p>0.99).

The percentage of patients with CAD risk factors is shown in the graph below (Figure 4.6):

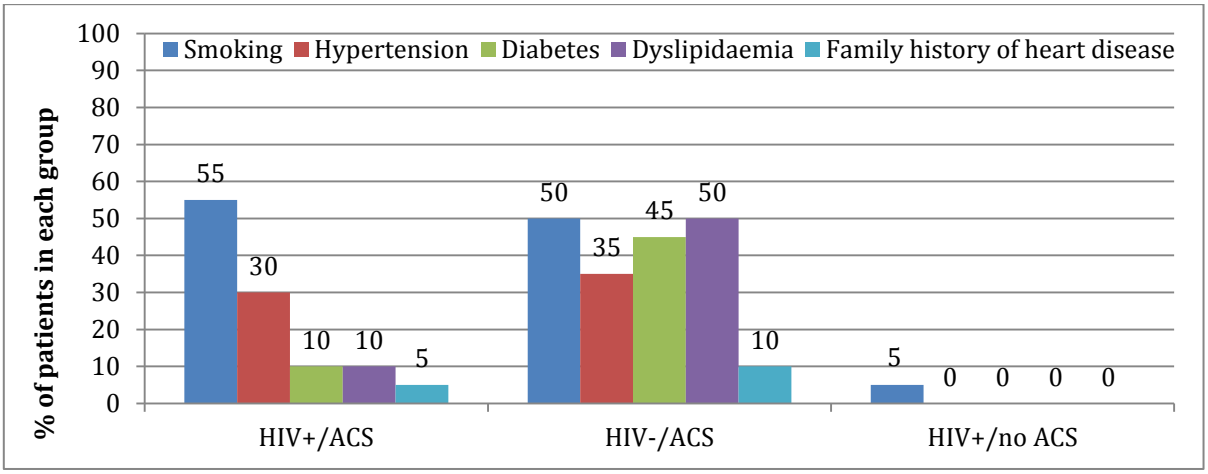


Figure 4.6 : Comparison of traditional risk factors

The prevalence of smoking and hypertension was significantly lower in the HIV+/no ACS group compared to the other two groups (chi-square test: p=0.0012; p=0.0006; respectively).

The prevalence of diabetes and dyslipidaemia was significantly higher in the HIV-/ACS group compared to the other two groups (chi-square test: p=0.0006 and p=0.0002, respectively).

Blood pressure

Mean SBP ranged from 117 to 122 mmHg in all groups and there was no significant difference between the groups (one-way ANOVA: p=0.69).

Similarly mean DBP ranged from 72 to 75 mmHg between groups and there were no significant differences between the groups (one-way ANOVA: p=0.83).

Echocardiogram parameters

The echocardiographic parameters for the different groups are depicted below (Figure 4.7).

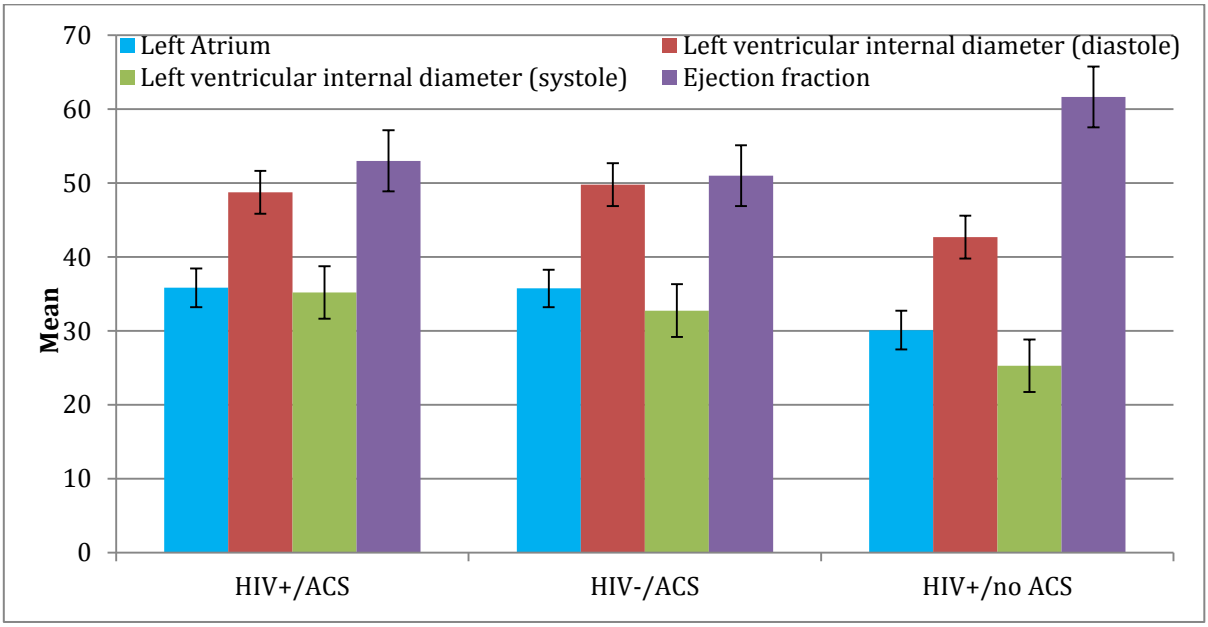


Figure 4.7: Echocardiographic measurements

The ejection fraction was significantly greater in the HIV+/no ACS group 62% (sd=6) as compared to the HIV+/ACS group 52% (sd=12) and the HIV-/ACS group 51% (sd=9) ($p<0.0013$).

4.3 Intravascular Ultrasound

4.3.1 Plaque burden

The plaque burden in each coronary artery was measured only in the HIV+/ACS group (Tables 4.2-4.5) using the difference between the vessel area and the minimum lumen area. Each artery was divided into proximal, mid and distal segments. The automatic pullback device was set at 0.5mm/s. The plaque burden was divided into mild (<40% plaque), moderate (40-70% plaque) and severe (>70%) plaque. If a measurement could not be done, symbols were inserted such as "A": vessel occluded, "B": small calibre vessel, "C": thrombus.

Table 4.2: Plaque burden (right coronary artery)

	PROXIMAL	MID	DISTAL
A1	**A**	**24.6**	**45.8**
A2	**B**	**B**	**B**
A3	**29.9**	**59**	**50**
A4	**67.4**	**61.9**	**C**
A5	**32.9**	**53.3**	**27.5**
A6	**B**	**B**	**B**
A7	**32.9**	**55.5**	**35.2**
A8	**60.5**	**55.4**	**B**
A9	**C**	**78.1**	**76.1**
A10	**B**	**B**	**B**
A11	**52.6**	**44.6**	**38.5**
A12	**91.2**	**44.5**	**62.8**
A13	**43.3**	**75.7**	**56.2**
A14	**39.7**	**28.8**	**32.2**
A15	**59.1**	**56.4**	**31.8**
A16	**15.9**	**24.2**	**40.4**
A17	**48.9**	**53.9**	**59**
A18	**B**	**B**	**B**
A19	**31.6**	**25.3**	**B**
A20	**48.9**	**70**	**36.1**

Table 4.3 : Plaque burden (left circumflex artery)

	PROXIMAL	MID	DISTAL
A1	**49.7**	**31.1**	**23.4**
A2	**62.8**	**61.1**	**62.5**
A3	**43**	**46.5**	**56.9**
A4	**22.2**	**26.7**	**31.9**
A5	**45.3**	**48.8**	**9.2**
A6	**B**	**B**	**B**
A7	**65.4**	**34.1**	**38.2**
A8	**67.9**	**73.6**	**63.4**
A9	**78.6**	**21.5**	**B**
A10	**65.6**	**69.4**	**26.2**
A11	**22.2**	**26.7**	**B**
A12	**79.1**	**56.9**	**28.2**
A13	**B**	**B**	**B**
A14	**61.1**	**51.2**	**32.3**
A15	**59.7**	**56.3**	**27.3**
A16	**53.5**	**39.6**	**13.7**
A17	**53.3**	**12.7**	**B**
A18	**45.9**	**71.3**	**B**
A19	**64.9**	**78.8**	**68.4**
A20	**66.7**	**54.1**	**29.8**

Table 4.4 : Plaque burden (left anterior descending artery)

	PROXIMAL	MID	DISTAL
A1	**46.2**	**41.5**	B
A2	**75.5**	**55.3**	**58.2**
A3	**50**	**29.6**	**25**
A4	**29.4**	**31**	**25.1**
A5	**47.3**	**30.6**	**10.9**
A6	**76.9**	**B**	**B**
A7	**44.3**	**29.3**	**B**
A8	**38.4**	**57.7**	**15.4**
A9	**77**	**38.8**	**30.2**
A10	**59.6**	**37.6**	**27.8**
A11	**22.4**	**26**	**22.1**
A12	**76.1**	**50.3**	**10.1**
A13	**63.6**	**69.8**	**26.2**
A14	**73.5**	**40.1**	**30.1**
A15	**A**	**A**	**A**
A16	**75.8**	**75.3**	**23**
A17	**59.1**	**49.5**	**10.1**
A18	**78.4**	**34.4**	**16.4**
A19	**61.8**	**27.2**	**15.6**
A20	**78.4**	**37.5**	**35.1**

Table 4.5 : Total plaque burden (sum of plaque burden in all coronary arteries)

	PROXIMAL	MID	DISTAL
A1	**48.0**	**32.4**	**34.6**
A2	**69.2**	**58.2**	**60.4**
A3	**41.0**	**45.0**	**44.0**
A4	**39.7**	**39.9**	**28.5**
A5	**41.8**	**44.2**	**15.9**
A6	**25.7**	**B**	**B**
A7	**47.5**	**39.6**	**36.7**
A8	**55.6**	**62.2**	**39.4**
A9	**77.8**	**46.1**	**53.2**
A10	**62.6**	**53.6**	**27**
A11	**32.4**	**32.4**	**26.2**
A12	**82.1**	**50.1**	**33.7**
A13	**53.5**	**72.8**	**41.2**
A14	**58.1**	**40.0**	**31.5**
A15	**59.4**	**56.4**	**29.6**
A16	**64.9**	**46.4**	**25.7**
A17	**51.1**	**38.7**	**34.6**
A18	**62.2**	**52.9**	**16.4**
A19	**52.8**	**43.8**	**49.8**
A20	**64.7**	**53.9**	**33.7**

In 60% of HIV-positive patients the total plaque burden was of moderate degree, while there was mild degree of total plaque in 35% and only in 5% of cases was the total plaque burden severe. There was more severe plaque (30%) in the culprit vessel as opposed to non-culprit vessels (5%) (Figure 4.8).

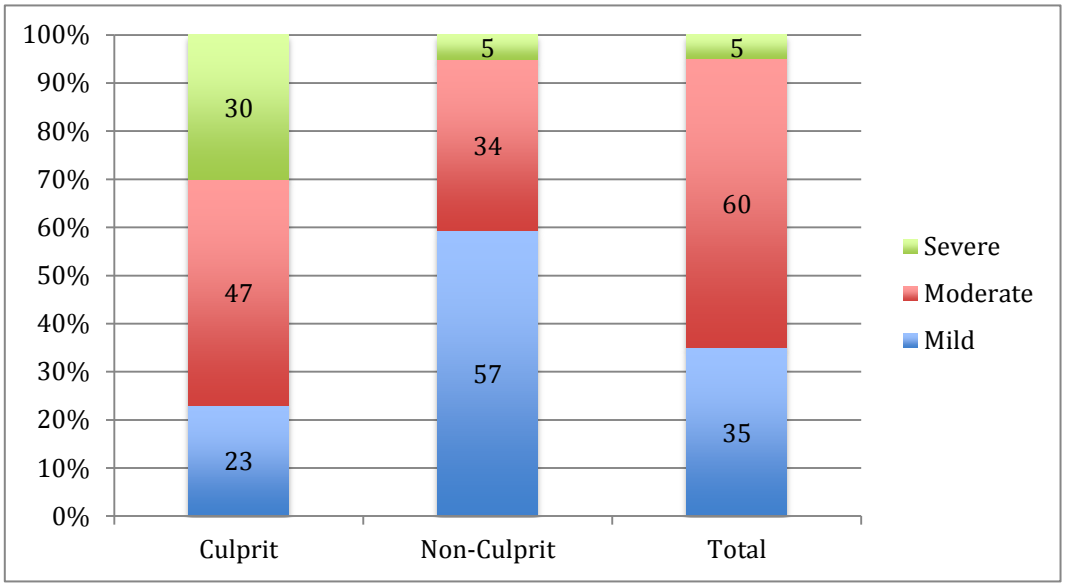


Figure 4.8 : Comparison of plaque burden

Location of Plaque burden

The distribution of the mean total plaque burden in the proximal, middle and distal locations was 54.5%, 47.8% and 34.8%, respectively (Figure 4.9). The total plaque burden was significantly higher in the proximal than in the middle location (paired t-test: p=0.010), and the total plaque burden was significantly higher in the middle as compared to the distal location (paired t-test: p=0.0006) (Figure 4.9-4.13).

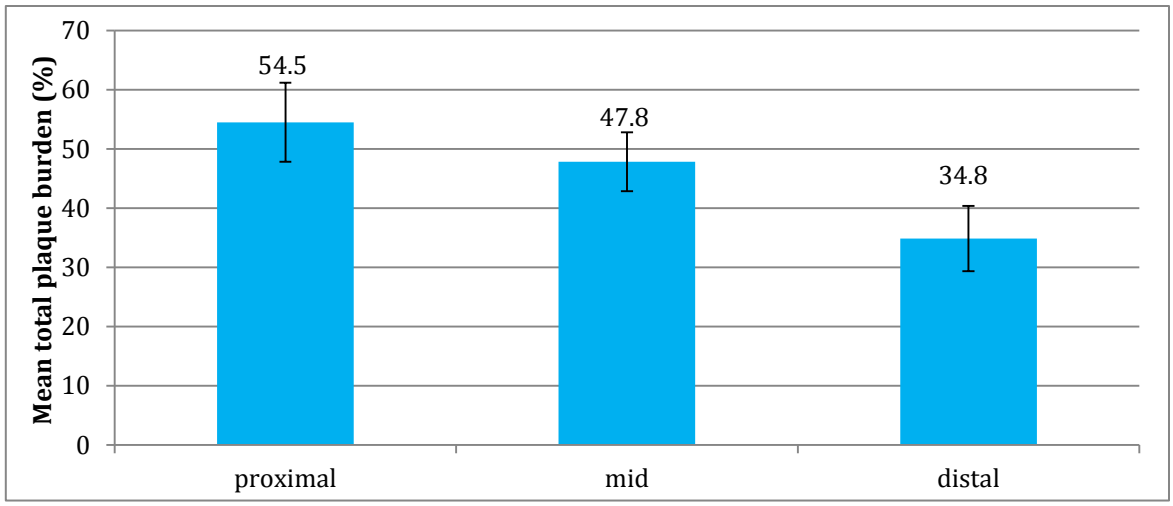


Figure 4.9 : Mean total plaque burden (%)

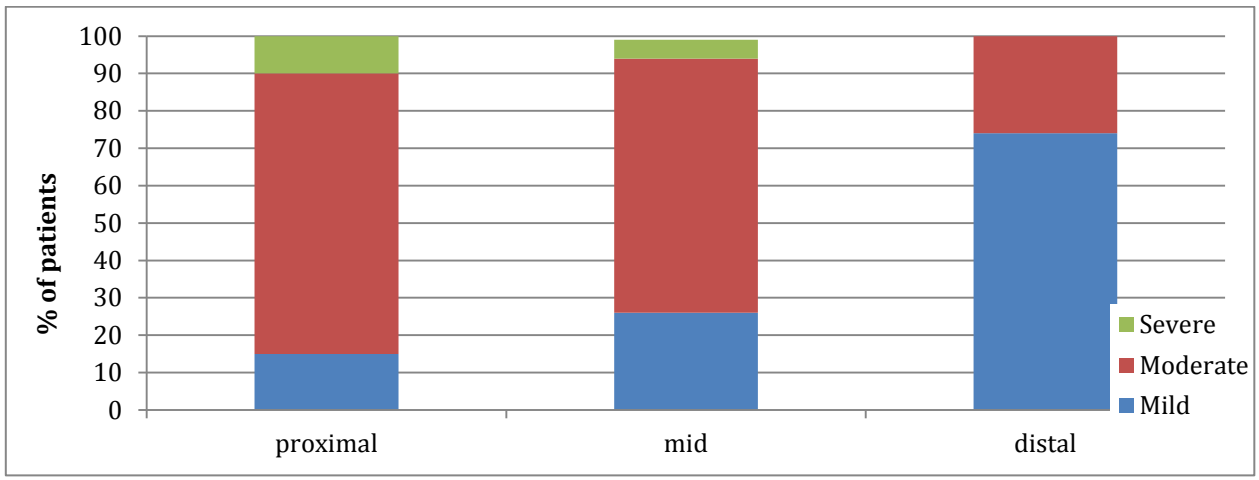


Figure 4.10 : Comparison of plaque burden per segment

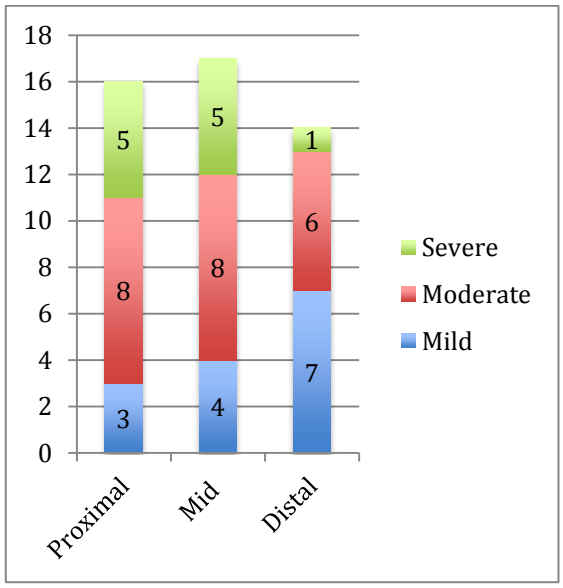


Figure 4.11 : Plaque burden (culprit vessel) per segment

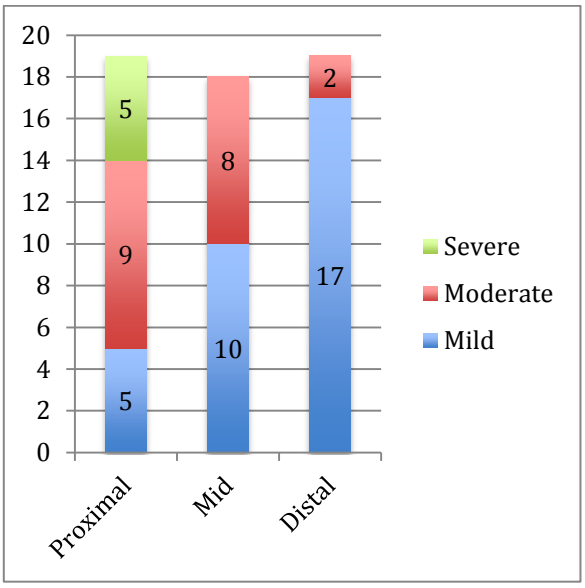


Figure 4.12: Plaque burden (non culprit vessels) per segment

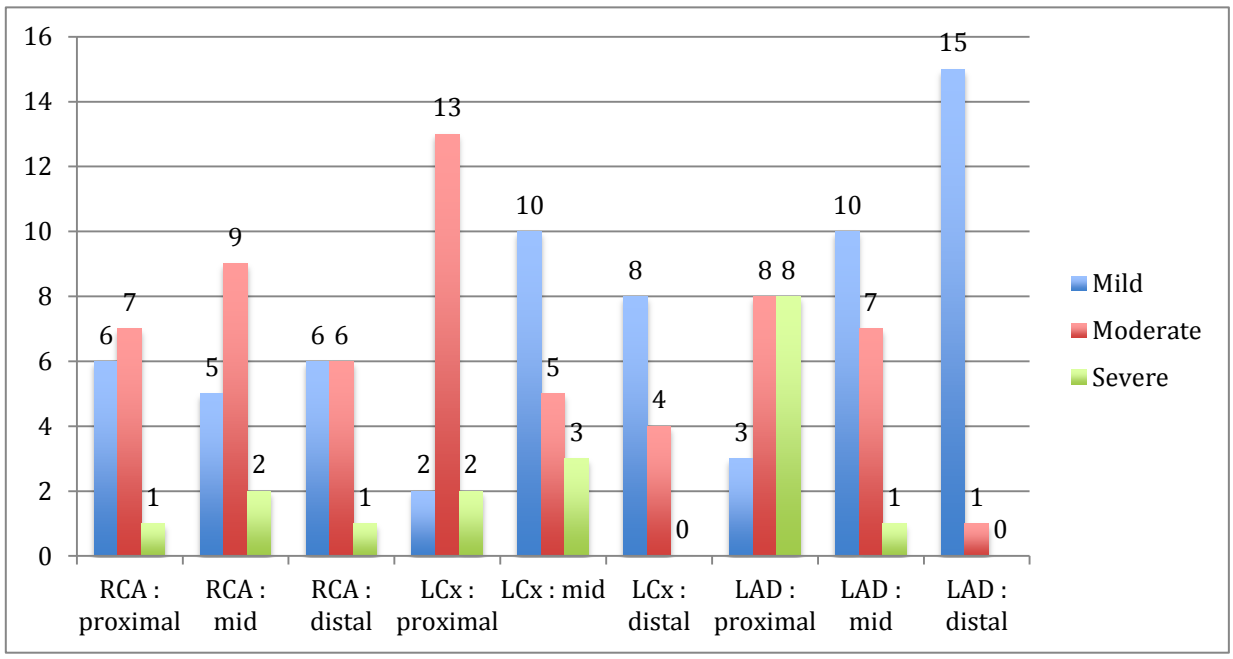


Figure 4.13: Plaque burden (specific coronary artery)

4.3.2 Virtual Histology

Virtual histology was performed in all 20 HIV-positive patients who presented with ACS. The frame (most narrow lumen area was calculated by the Volcano software using the automatic pullback device) and the segment plaque were measured as a percentage (Table 4.6).

Table 4.6: Virtual histology : total plaque characteristics (%)

	Necrotic Core (NC)	Dense Calcium (DC)	Fibrous (FI)	Fibrofatty (FF)
A1	11.3	4.3	62.4	24.0
A2	13.9	6.3	60.6	19.3
A3	12.9	4.9	65.7	21.0
A4	6.2	0.9	65.7	27.3
A5	7.3	0.7	64.0	27.5
A6	21.8	10.6	52.3	15.2
A7	3.9	1.1	50.3	44.7
A8	6.8	1.7	52.6	38.9
A9	18.7	5.5	62.3	13.4
A10	7.6	15.1	33.8	31.8
A11	10.1	3.1	56.5	28.3
A12	5.6	0.7	54.3	39.4
A13	23.4	7.5	57.5	11.7
A14	19.5	10.4	46.5	23.6
A15	8.0	6.5	53.9	31.8
A16	15.8	3.0	57.5	23.7
A17	21.3	12.2	49.8	19.4
A18	8.6	4.3	52.0	35.1
A19	9.2	4.4	49.4	36.9
A20	14.4	4.9	57.0	25.8

The graphs below illustrate and compare the histology results. Note that in these and other graphs, which depict the median values, the error bars denote the IQR.

Segment: culprit and non-culprit vessel:

Segment definition: the coronary artery was divided into three segments

1) proximal to middle

2) middle to distal third

3) distal third to end of the coronary artery

The culprit vessel consisted of the following plaque characteristics; fibrous (56.5%), fibro-fatty plaque (21.2%), necrotic core (14.4%) and dense calcific plaque (3.6%). The plaque characteristics in the non-culprit vessels consisted of fibrous (55.1%), fibro-fatty plaque (29.5%), necrotic core (8.2%) and dense calcific plaque (4.8%) (Figure 4.14).

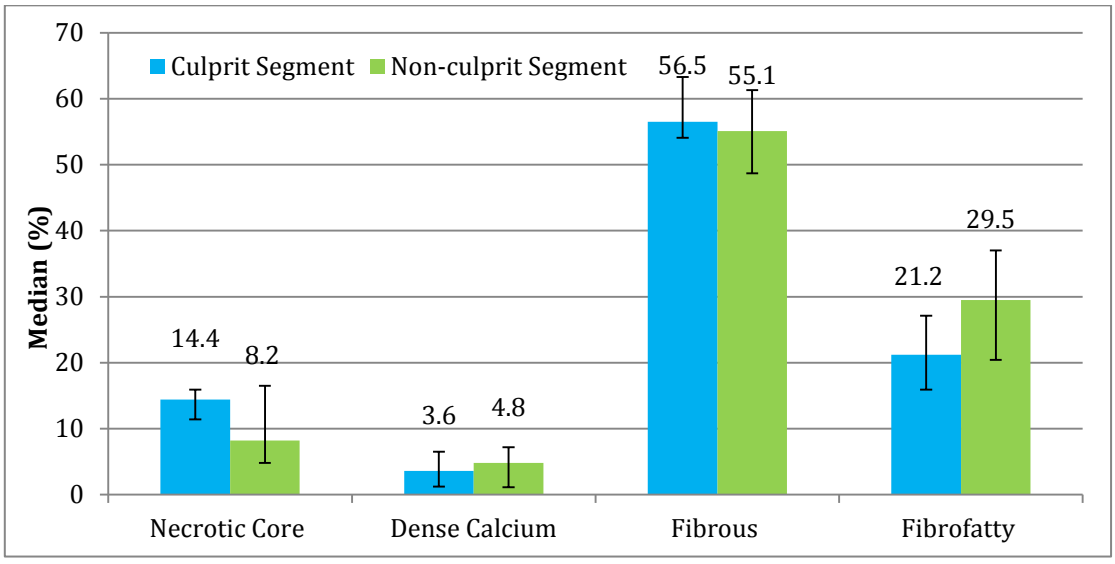


Figure 4.14 : Virtual Histology of the culprit and non-culprit segments

In all cases (with one exception), the median % fibrous plaque was significantly greater than the median % fibrofatty plaque, which in turn was significantly greater than the median % necrotic core plaque, which in turn was significantly greater than the median % dense calcific plaque (all $p<0.05$). The one exception to this was that the median % fibrofatty for culprit segment was not significantly different to the median % necrotic core.

Frame: Culprit and Non-culprit vessel:

Frame definition: The frame of the plaque characteristics where there was the most severe plaque in the culprit and non-culprit vessels (smallest minimum luminal area) is shown below (Figure 4.15).

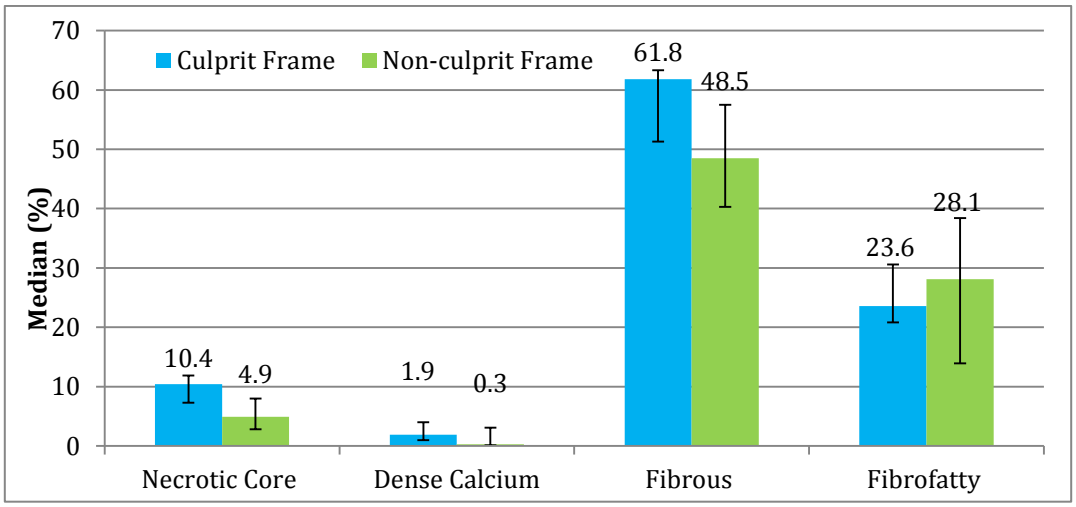


Figure 4.15 : Virtual Histology of the culprit and non-culprit frame

Frame and segment:

The virtual histology plaque characteristics are shown below (Figure 4.16).

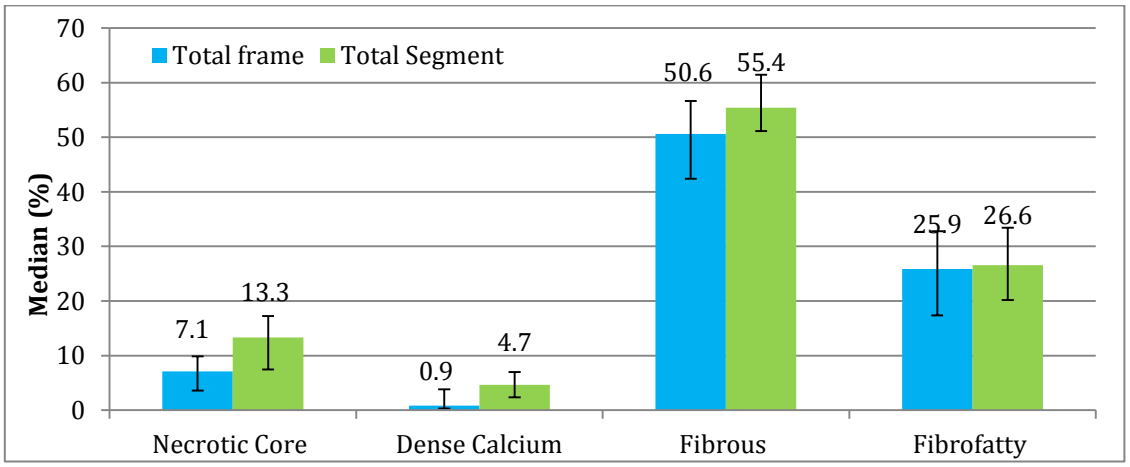


Figure 4.16: Virtual histology of the total frame and segment

Figure 4.17 is the typical IVUS image of an HIV-positive patient with plaque. The plaque consists predominantly of fibrous and fibro-fatty tissue and very little calcium.

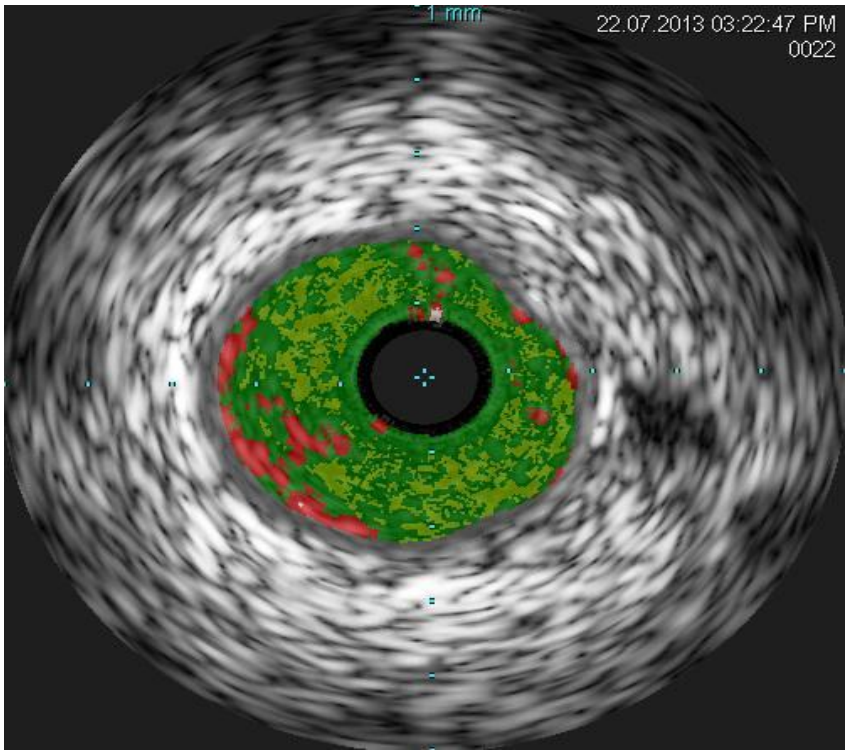


Figure 4.17: Virtual histology (fibrous/fibro-fatty plaque) in an HIV+/ACS patient

Assessment of the entire coronary vasculature by VH in these patients demonstrated that the predominant plaque morphology consisted of fibrous plaque (55.4%). Fibro-fatty plaque was found in 26.6% of patients. Necrotic core was present in 13.3% and dense calcium present in only 4.7% of patients (Figure 4.18). The mean fibrous plaque volume was significantly greater than the mean fibro-fatty plaque volume, which in turn was significantly greater than the mean necrotic core volume, which in turn was significantly greater than the mean dense calcium volume (all $p<0.05$). On assessing plaque morphology in the culprit coronary arteries, the major plaque morphology remained fibrous plaque (56.5%), whilst fibro-fatty tissue (21.2%), necrotic core (14.4%) and dense calcium (3.6%) plaque constituted the remainder (Figure 4.18). In non-culprit arteries, the lesion morphology was similar with fibrous plaque found in 55.1% of patients, fibro-fatty plaque in 29.5%, necrotic core in 8.2% and dense calcium in 4.8% of patients.

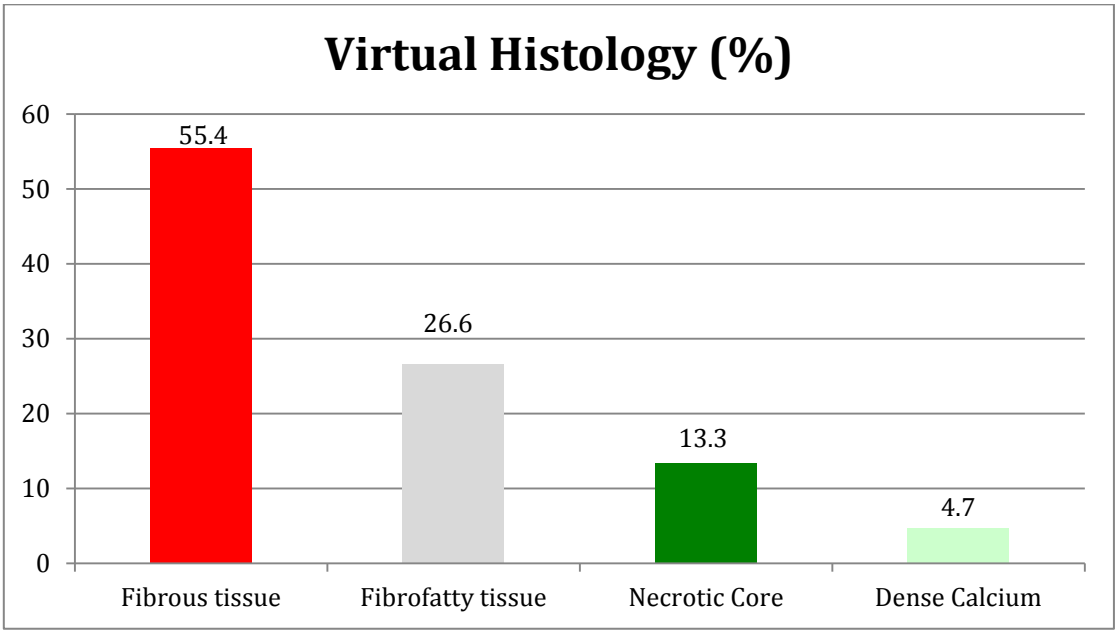


Figure 4.18: Virtual Histology of the atherosclerotic plaque in HIV-positive patients presenting with ACS

4.3.3 Coronary endothelial reactivity

The maximum luminal diameter for each segment of each coronary artery was measured in the HIV+/ACS patients. The maximum lumen diameter (MLD) for each segment of each coronary artery was measured. Post adenosine, the MLD increased by 2% and post TNT, the MLD increased by 6.1% (after 30 seconds) and 8.7% (after 1 minute). (Figure 4.19)

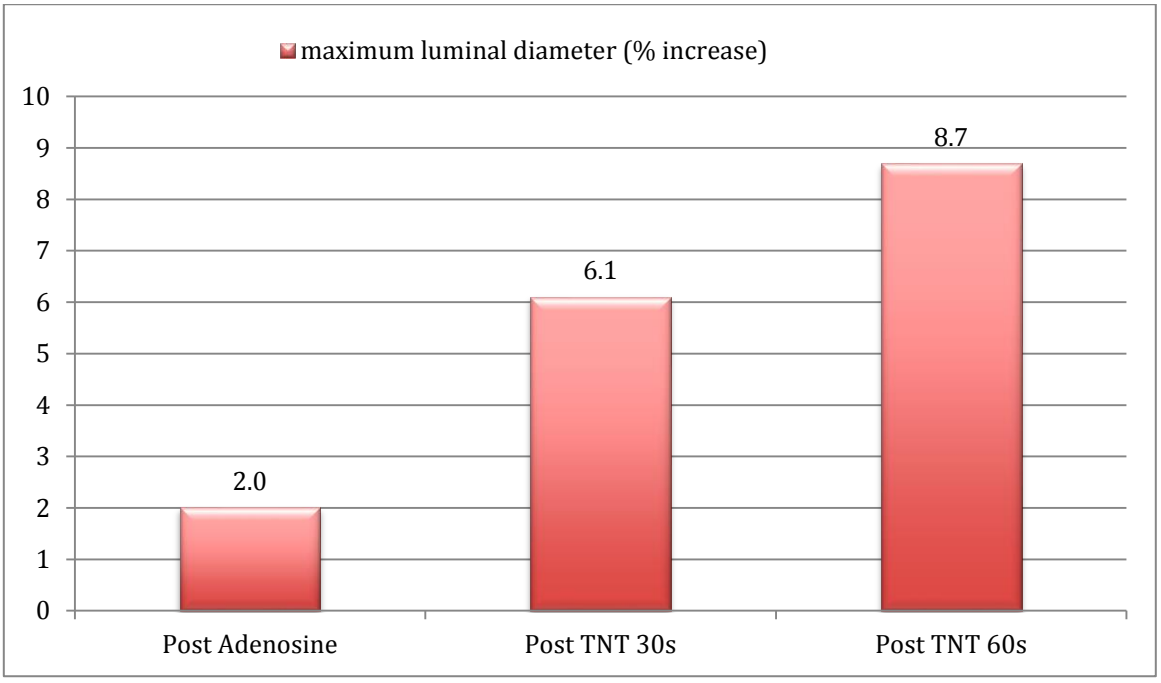


Figure 4.19: Coronary endothelial reactivity in HIV+/ACS group

4.4 Brachial flow mediated dilatation

Endothelial function was measured using FMD in all three groups. The median percentage difference in FMD between baseline and BP cuff inflation was significantly higher for the HIV+/no ACS group (14.3; IQR 6.7-20.6%) compared to the HIV+/ACS group (5.2; IQR 1.4-13.4%) and the HIV-/ACS group (3.7; IQR 2.3-4.4%) (p=0.044 and 0.0016, respectively). (Figure 4.20 and 4.21).

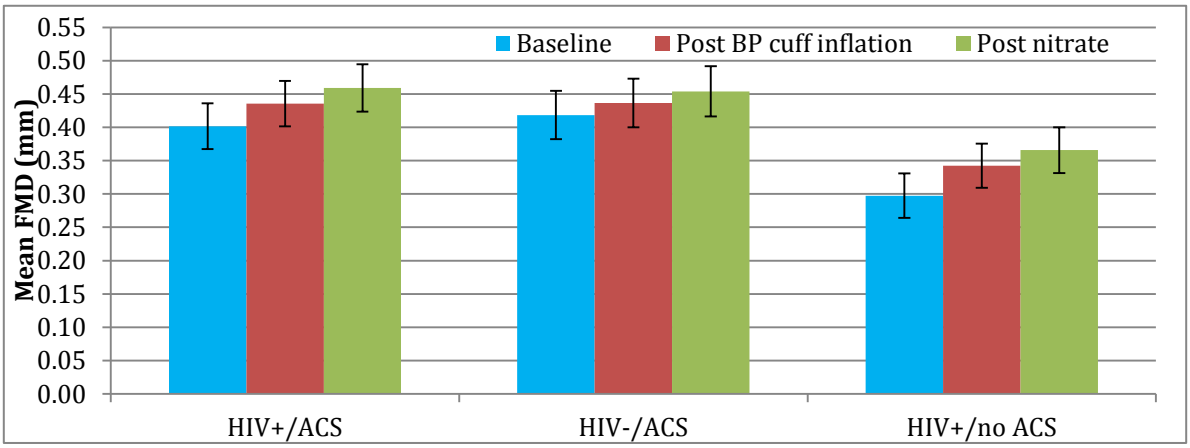


Figure 4.20: Brachial flow mediated dilatation post BP cuff inflation and post TNT

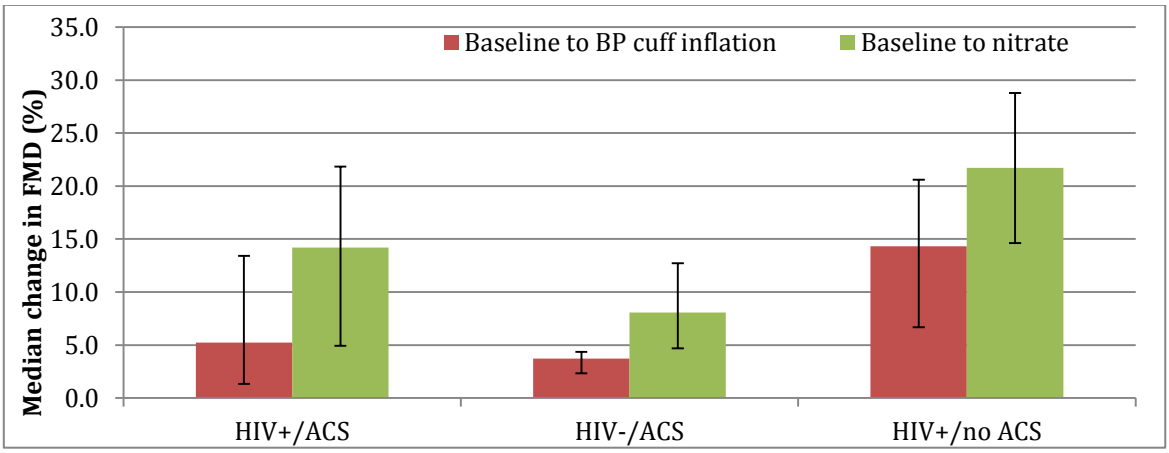


Figure 4.21: Median change in brachial flow mediated dilatation post BP cuff inflation and post TNT

4.5 Endothelial biomarkers

There was no significant difference of the IL1 β, IL1ra, MCP-1, TNFα, P-selectin and PAI-1 levels between all three groups. However, there were significant between-group differences in the following endothelial biomarkers; VCAM-1, ICAM-1, E-selectin, and IL6 (Table 4.7). The median VCAM-1 levels of the HIV+/ACS and the HIV+/no ACS patients were significantly higher than those of the HIV-/ACS cohort. The HIV+/no ACS group had significantly higher median levels of ICAM-1 and E-selectin than the ACS groups. The HIV+/ACS group and the HIV-/ACS had significantly higher median levels of IL6 than the HIV+/no ACS group.

Table 4.7 : Endothelial biomarkers

(VCAM-1=vascular cellular adhesion molecule 1, ICAM-1= intercellular adhesion molecule 1, IL=interleukin, MCP-1= macrophage chemotactic protein 1, TNFα= tumour necrosis factor alpha, PAI-1: plasminogen activator inhibitor 1)

median levels (interquartile ranges)	**HIV+/ACS[1] (n=20)**	**HIV-/ACS[2] (n=20)**	**HIV+/no ACS[3] (n=20)**	***P value for H0: no between-group differences***	***P value for post-hoc group differences***
VCAM-1 *(ng/ml)*	402 (292-609)	287 (257-412)	503 (292-822)	*0.025*	*$p=0.033^{1,2}$ and $0.024^{2,3}$*
ICAM-1 *(ng/ml)*	172 (135-211)	167 (129-193)	225 (199-293)	*0.0009*	*$p=0.0079^{1,3}$ and $0.0010^{2,3}$*
IL-6 *(pg/ml)*	5.9 (3.9-12.4)	10.7 (4.8-50)	3.8 (1.9-5.3)	*0.0053*	*$p=0.033^{1,3}$ and $0.0050^{2,3}$*
E-selectin *(ng/ml)*	24.30 (19.10-30.60)	27.80 (21.50-42.20)	47.10 (31.80-65.80)	*0.0005*	*$p=0.0007^{1,2}$ and $0.012^{2,3}$*
IL-1β *(pg/ml)*	0.36 (0.27-0.48)	0.32 (0.28-0.41)	0.38 (0.30-0.51)	*0.29*	
IL-1ra *(pg/ml)*	224 (173-266)	215 (120-258)	181 (125-258)	*0.75*	
MCP-1 *(pg/ml)*	26.5 (15.0-41.2)	22.4 (18.0-33.3)	22.4 (16.5-27.4)	*0.70*	
TNFα *(pg/ml)*	2.5 (1.4-4.4)	2.0 (1.6-4.4)	2.5 (2.0-4.8)	*0.60*	
P-selectin *(ng/ml)*	25.80 (20.30-32.90)	20.80 (19.30-24.60)	23.50 (19.60-29.70)	*0.12*	
PAI-1 *(ng/ml)*	67.60 (36.70-149.80)	85.60 (34.70-138.40)	66.20 (35.60-91.70)	*0.59*	

VCAM-1

The median VCAM-1 level for the HIV+/ACS group (402.00 *ng/ml*; IQR 292.00-609.00) and the HIV+/no ACS group (503.00 *ng/ml*; IQR 292.00-822.00) were significantly higher than that of the HIV-/ACS group (287.00 *ng/ml*; IQR 257.00-412.00) (Kruskal-Wallis test: p=0.033 and 0.024 respectively) (Figure 4.22).

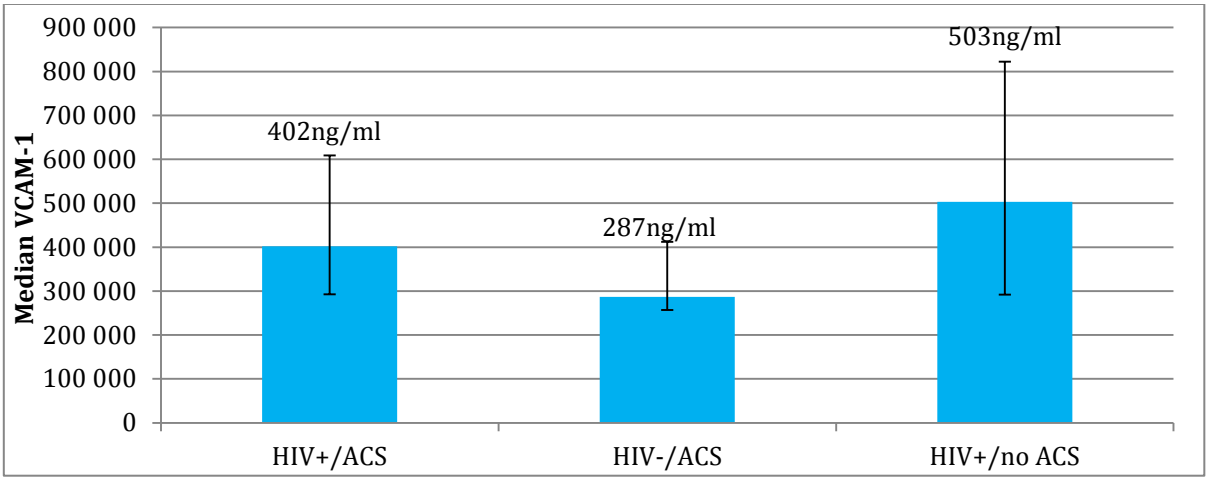


Figure 4.22: VCAM-1(pg/ml): HIV+/ACS and HIV+/no ACS had significantly higher levels than HIV-/ACS patients

ICAM-1

The median ICAM-1 level for the HIV+/ACS group (172.00 *ng/ml*; IQR 135.00-211.00) and the HIV-/ACS group (167.00 *ng/ml*; IQR 129.00-193.00) were significantly lower than that of the HIV+/no ACS group (225.00 *ng/ml*; IQR 199.00-293.00) (Kruskal-Wallis test: p=0.0079 and 0.0010 respectively) (Figure 4.23).

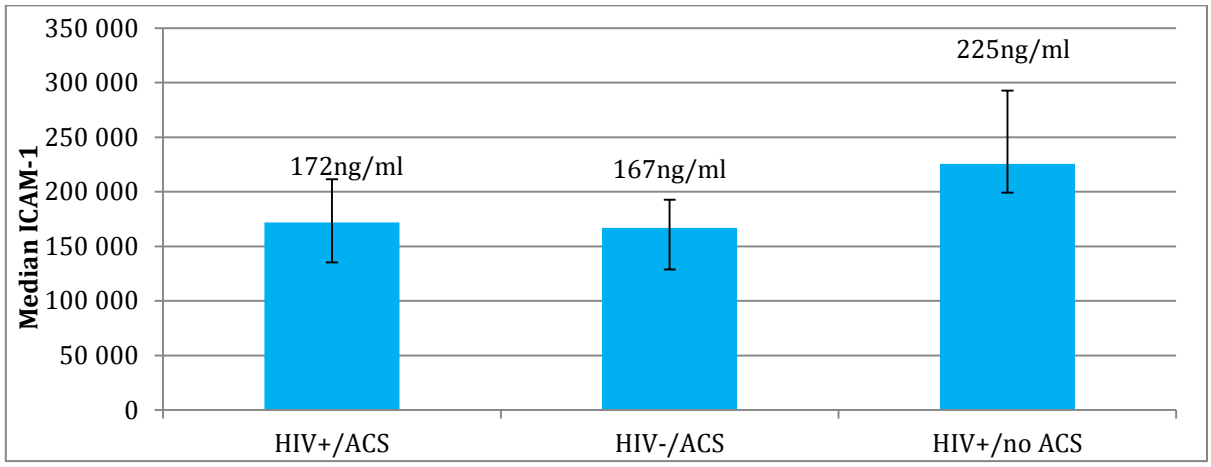


Figure 4.23: ICAM-1 (pg/ml): ACS patients had lower levels compared to the HIV+/no ACS group

IL-6

The median IL-6 level for the HIV+/ACS group (5.9 *pg/ml*; IQR 3.9-12.4) and the HIV-/ACS group (10.7 *pg/ml*; IQR 4.8-50.0) were significantly higher than that of the HIV+/no ACS group (3.8 *pg/ml*; IQR 1.9-5.3) (Kruskal-Wallis test: p=0.033 and 0.0050 respectively) (Figure 4.24).

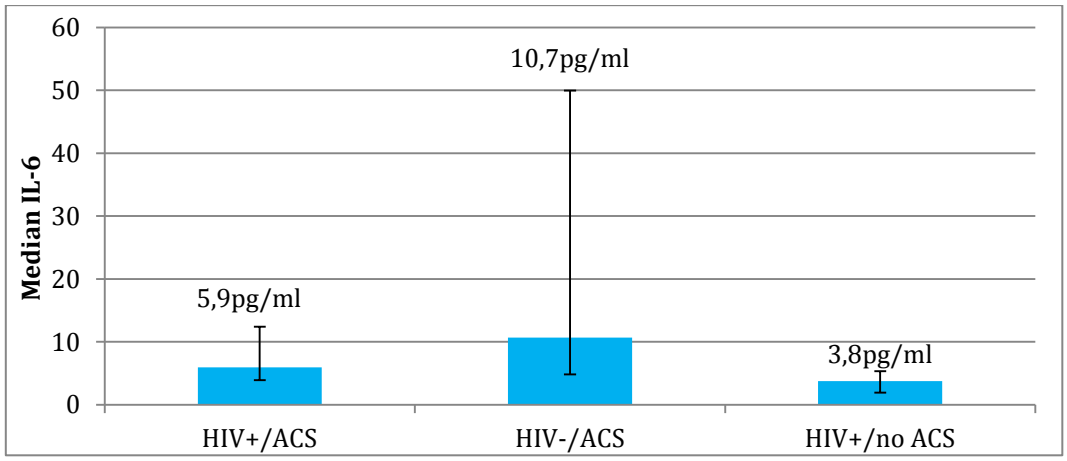


Figure 4.24 : IL-6 (pg/ml): ACS levels were higher than the HIV+/no ACS patients

E-selectin

The median E-selectin level for the HIV+/ACS group (24.30 *ng/ml*; IQR 19.10-30.60) and the HIV-/ACS group (27.80 *ng/ml*; IQR 21.50-42.20) were significantly lower than that of the HIV-/no ACS group (47.10 *ng/ml*; IQR 31.80-65.80) (Kruskal-Wallis test: p=0.0007 and 0.012 respectively) (Figure 4.25).

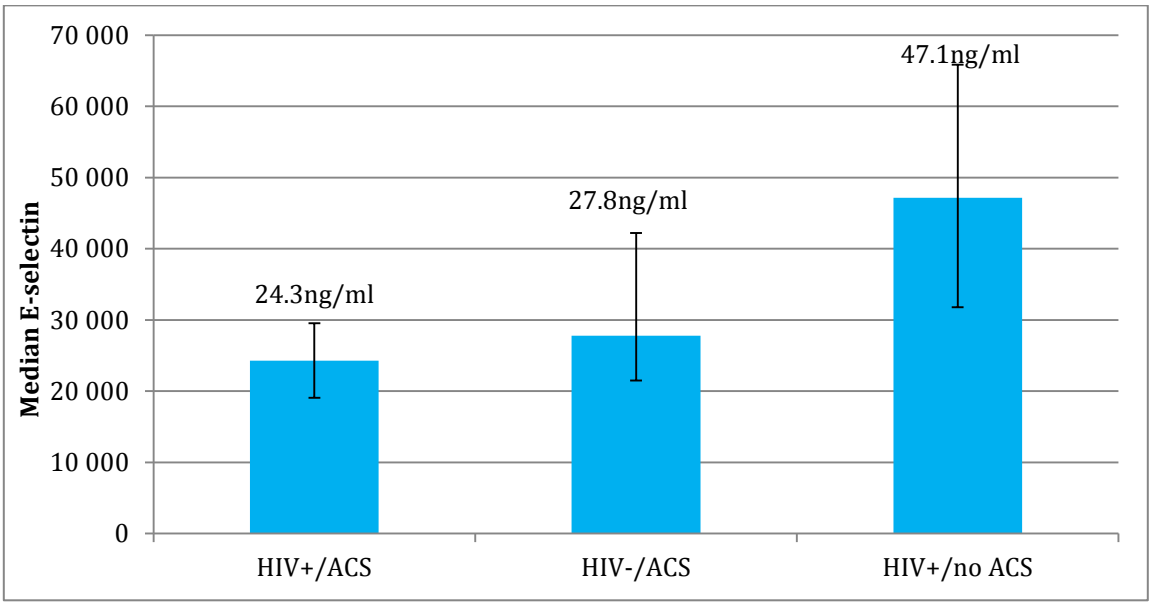


Figure 4.25 : E-selectin (pg/ml): ACS patients levels were lower than the HIV+/no ACS patients

IL-1B

Group medians ranged from 0.32 to 0.38 *pg/ml* (no significant difference; Kruskal-Wallis test: p=0.29) (Figure 4.26).

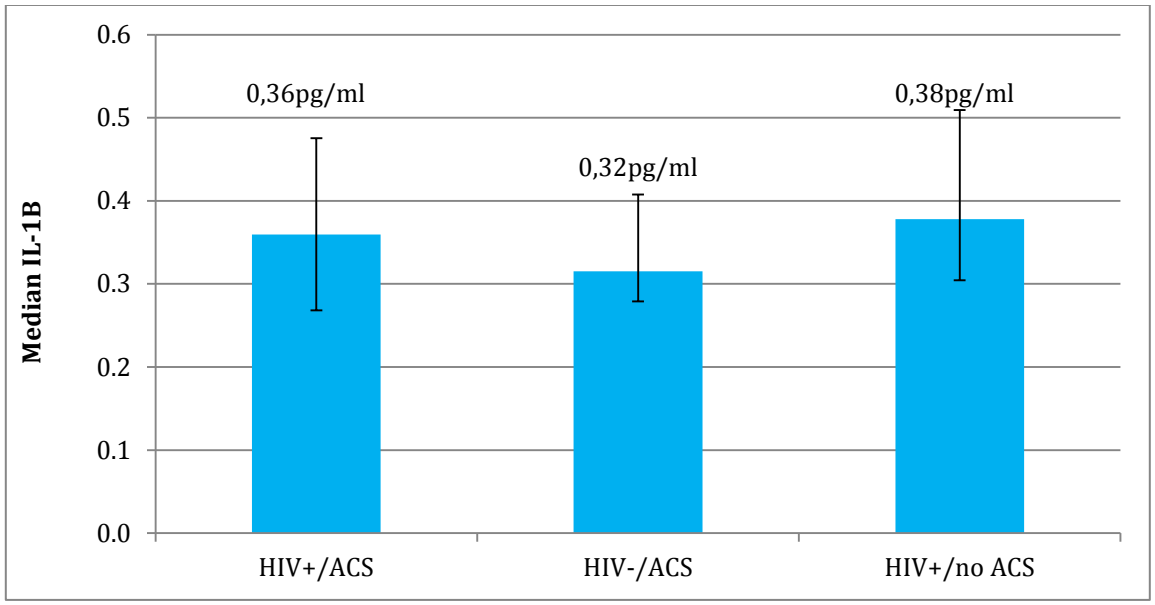


Figure 4.26: IL-1B (pg/ml) : There were no significant differences between the three groups

IL-1ra

Group medians ranged from 181 to 224 *pg/ml* (no significant difference; Kruskal-Wallis test: p=0.70) (Figure 4.27).

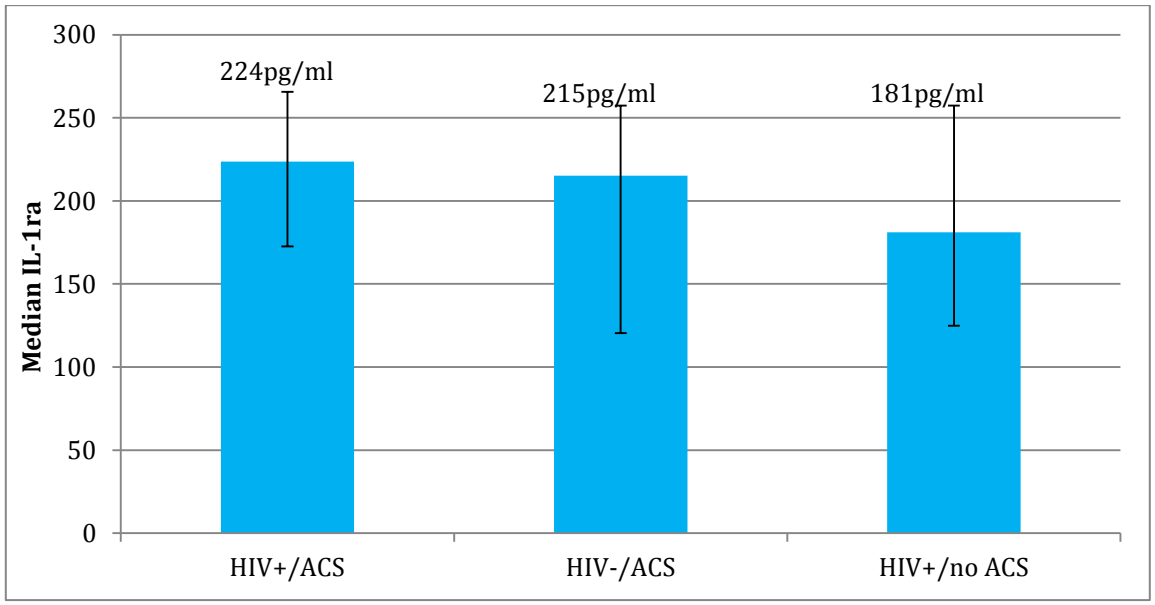


Figure 4.27: IL-ra (pg/ml) : There were no significant differences between the three groups

MCP-1

Group medians ranged from 22.4 to 26.5 *pg/ml* (no significant difference; Kruskal-Wallis test: p=0.70) (Figure 4.28).

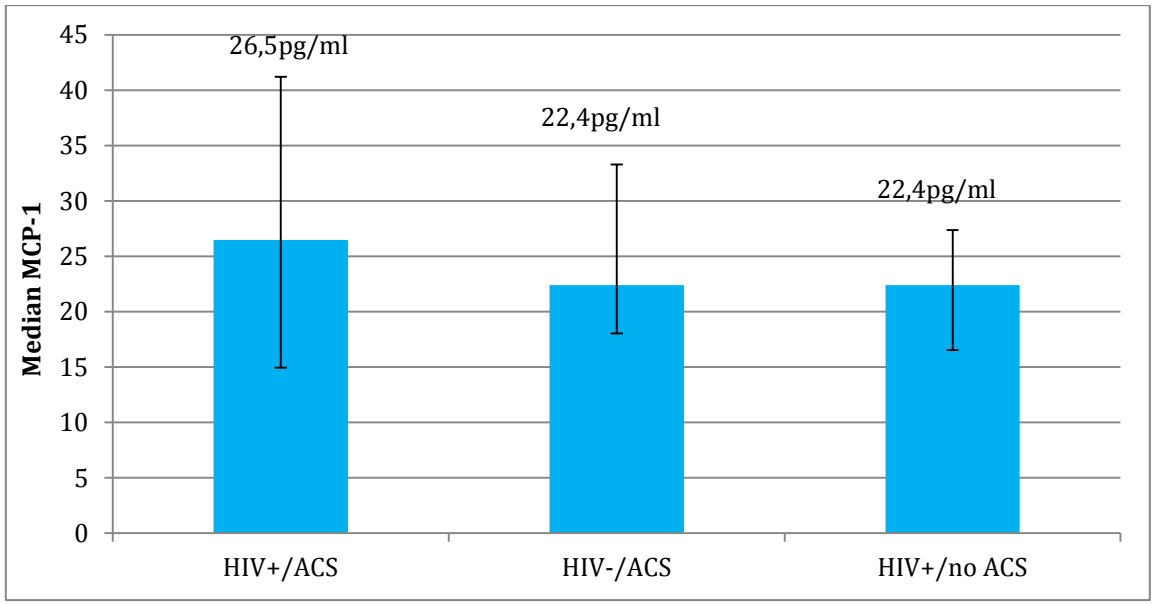


Figure 4.28: MCP-1 (pg/ml) : There were no significant differences between the three groups

TNFα

Group medians ranged from 2.0 to 2.5 *pg/ml* (no significant difference; Kruskal-Wallis test: p=0.60) (Figure 4.29).

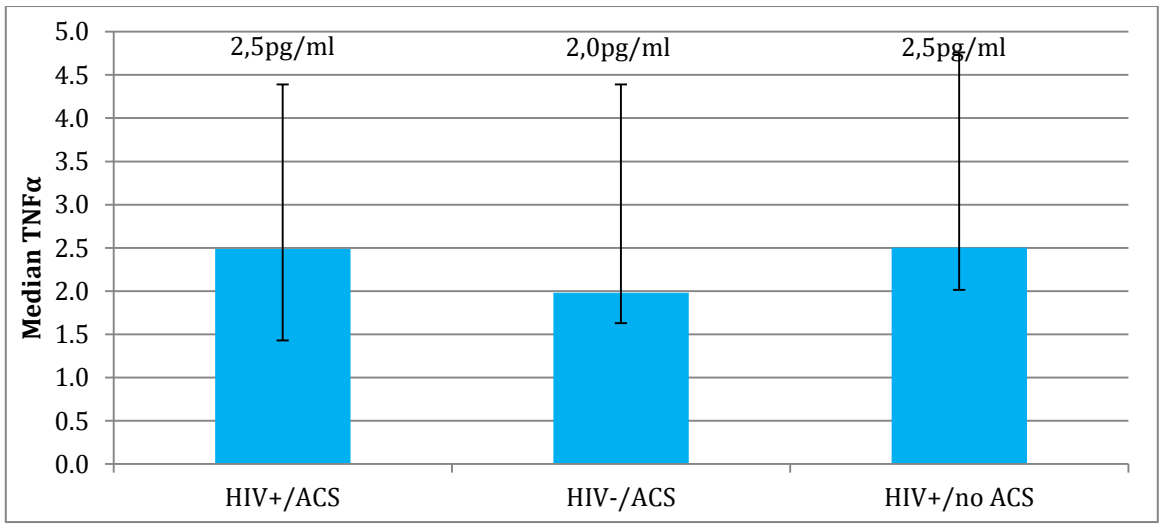


Figure 4.29: TNFα (pg/ml) : There were no significant differences between the three groups

P-selectin

Group medians ranged from 20.80 to 25.80 *ng/ml* (no significant difference; Kruskal-Wallis test: p=0.12) (Figure 4.30).

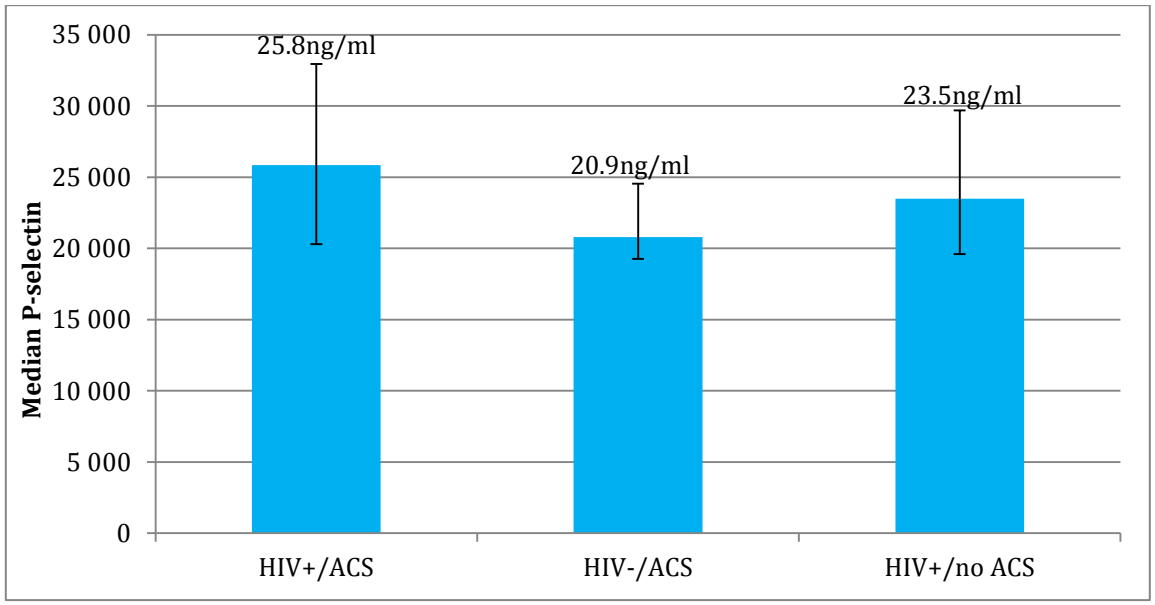


Figure 4.30 : P-selectin (pg/ml) : There were no significant differences between the three groups

PAI-1

Group medians ranged from 66.20 to 85.60 *ng/ml* (no significant difference; Kruskal-Wallis test: p=0.59) (Figure 4.31).

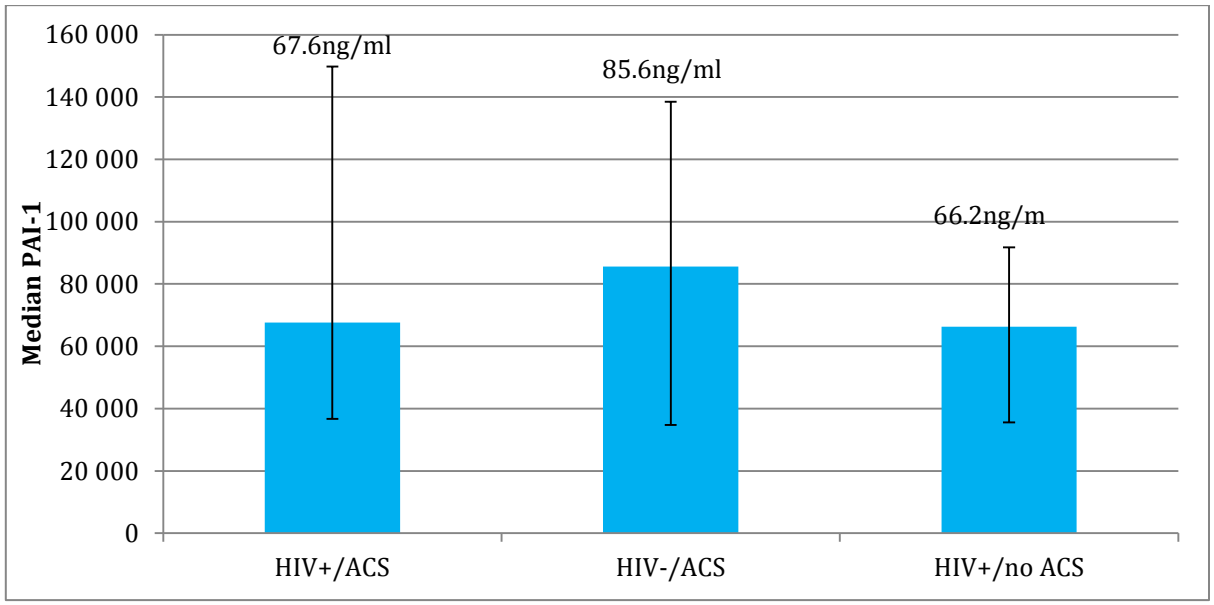


Figure 4.31 : PAI-1(ng/ml) : There were no significant differences between the three groups

4.6 Carotid Intima Media Thickness

Carotid intima media thickness was measured in all three groups. The mean CIMT of the HIV+/no ACS group (0.50; sd=0.08 mm) was significantly lower than that of both the HIV+/ACS (0.66; sd=0.16 mm) and HIV-/ACS groups (0.70; sd=0.06 mm) ($p=0.0005$ and $p<0.0001$, respectively) (Figure 4.32).

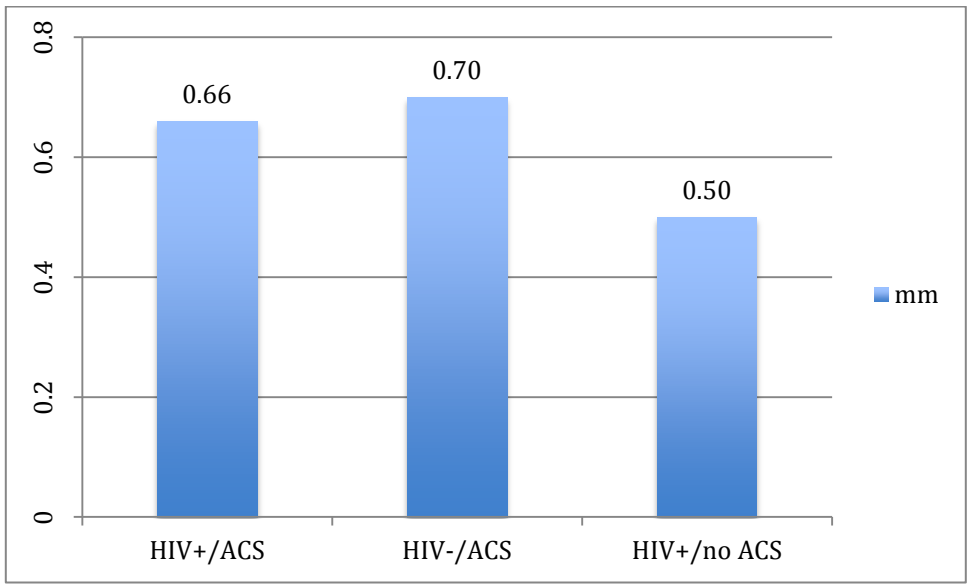


Figure 4.32: Carotid intima media thickness

In the HIV+/ACS group, the left carotid artery average CIMT was 0.65 mm and the right carotid artery average CIMT was 0.66 mm. In the HIV-/ACS group, the left carotid artery average CIMT was 0.73 mm and the right carotid artery average CIMT was 0.68 mm. In the HIV+/ no ACS group, the left carotid artery average CIMT was 0.51 mm and the right carotid artery average CIMT was 0.48 mm (Figure 4.33).

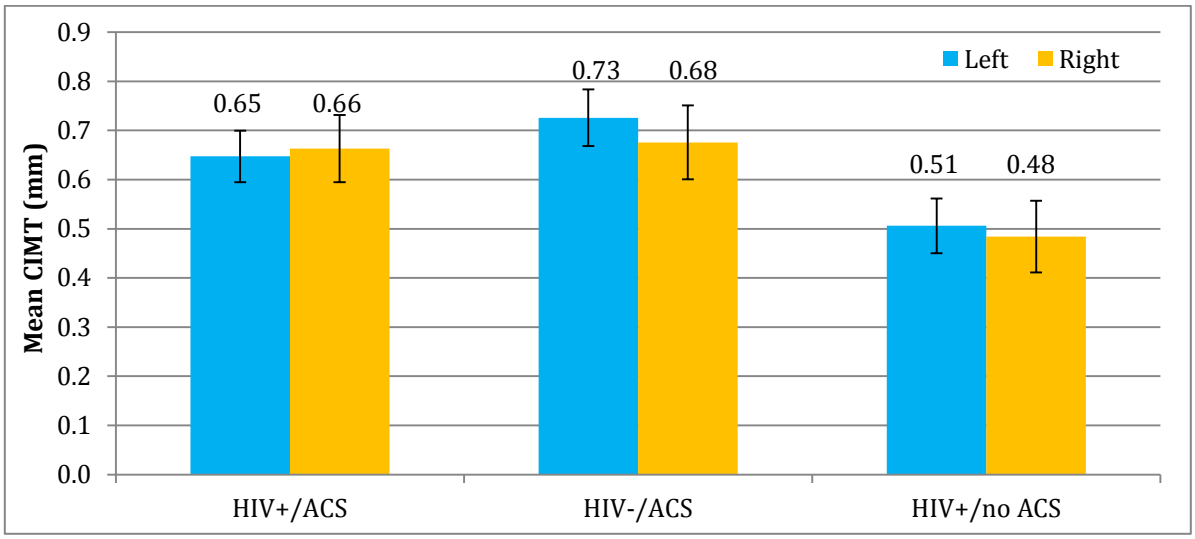


Figure 4.33 : Comparison of left and right carotid artery intima media thickness

The mean CIMT-left of the HIV+/no ACS group (0.51; sd=0.06 mm) was significantly lower than that of both the HIV+/ACS (0.65; sd=0.13 mm) and HIV-/ACS groups (0.73; sd=0.11 mm) (one-way ANOVA; p=0.0016 and p<0.0001 respectively). The mean CIMT-right of the HIV+/no ACS group (0.48; sd=0.07 mm) was significantly lower than that of both the HIV+/ACS (0.66; sd=0.22 mm) and HIV-/ACS groups (0.68; sd=0.05 mm) (one-way ANOVA; p=0.0022 and p=0.0018 respectively).

4.7 Arterial compliance

Conventional arm manual blood pressure measurements were compared with central measurements inferred by applanation tonometry of the radial artery. The systolic BP, diastolic BP, mean BP and pulse pressure were measured for all three groups (Table 4.8).

Table 4.8: Blood pressure measurements

(SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, PP; pulse pressure)

	SBP	SBP (peripheral)	SBP (aortic)	DBP	DBP (peripheral)	DBP (aortic)	MBP (peripheral)	PP (peripheral)	PP (aortic)
HIV+/ACS	117	115	105	73	75	76	89	40	30
HIV-/ACS	121	116	105	72	70	71	85	46	35
HIV+/no ACS	122	121	109	75	73	77	93	48	32

All BP variables

The mean BP measurements for the HIV+/ACS group are illustrated below (Figure 4.34).

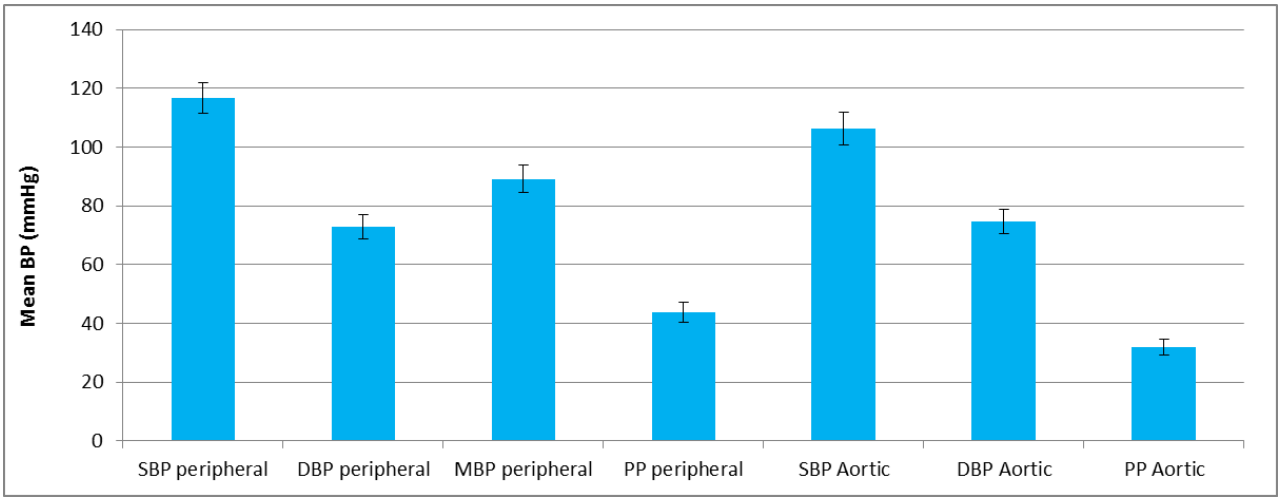


Figure 4.34 : BP measurements (HIV+/ACS patients)

Pulse Wave Velocity

The mean PWV in the HIV+/ACS group was 4.1 (sd=1.1) m/s, 4.6 (sd=1.1) m/s in the HIV-/ACS group and 3.9 (sd=1.1) m/s in the HIV+/no ACS group. These values were all low (p=0.12) (Figure 4.35). Group means ranged from 3.9 to 4.6 m/s (no significant difference; one-way ANOVA: p=0.12).

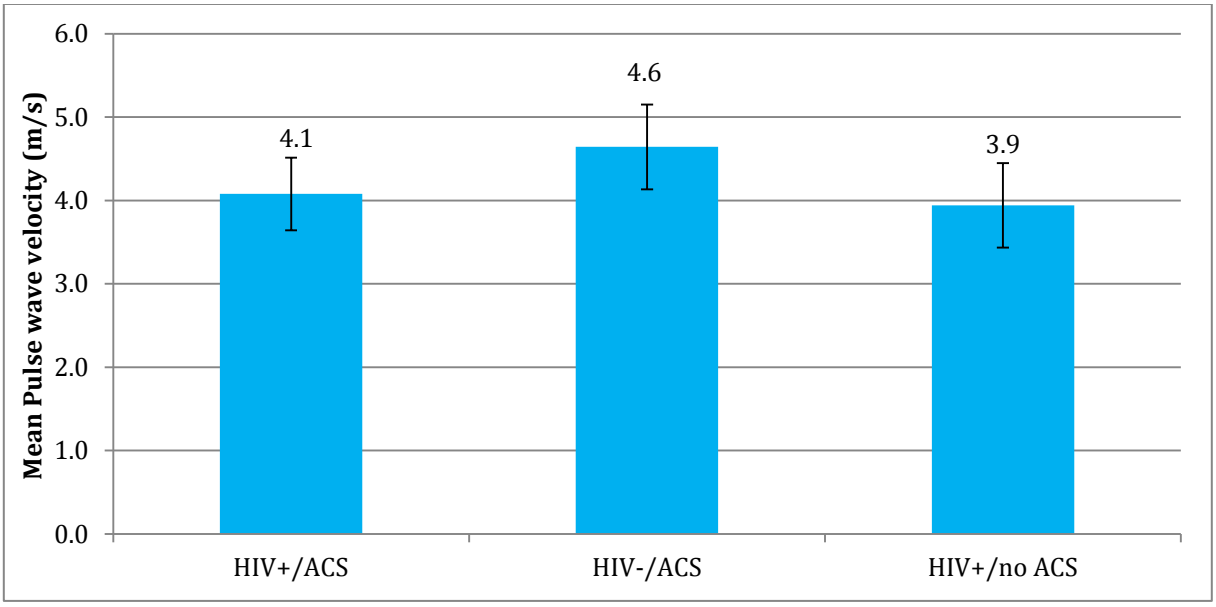


Figure 4.35: Pulse wave velocity

The radial waveform and aortic waveform from an HIV+/ACS patient are shown below (Figure 4.36 and 4.37) together with the forward and backward reflected pressures (Figure 4.38).

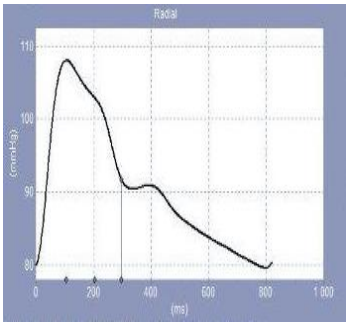


Figure 4.36: Radial waveform

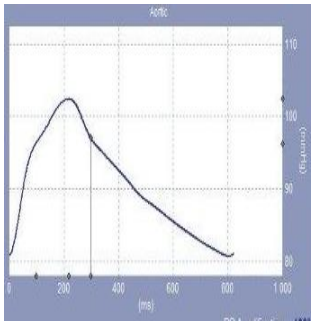


Figure 4.37: Aortic waveform

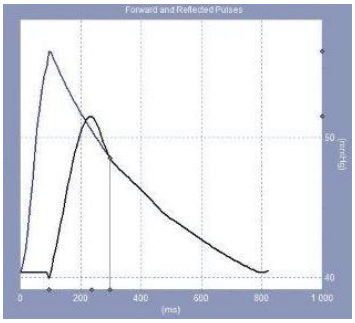


Figure 4.38: Forward and Backward pressures

4.8 Laboratory tests

Laboratory results for all three groups included basic blood tests (Table 4.9).

Table 4.9: Laboratory results

	Normal values	**HIV+/ACS**	**HIV-/ACS**	**HIV+/no ACS**	
Haemoglobin[#] (g/dl)	*(14.3-18.3g/dl)*	12.9 (2.6)	15.0 (1.7)	11.4 (2.1)	p=0.0086[1,2], p<0.0001[2,3]
Na[#] (mmol/l)	*(136-145mmol/l)*	139 (2.2)	140 (4.1)	137 (3.1)	p=0.013
K[#] (mmol/l)	*(3.5-5.1mmol/l)*	4.4 (0.6)	4.2 (0.5)	4.3 (0.5)	p=0.33
Urea[*] (mmol/l)	*(2.1-7.1mmol/l)*	4.6 (3.8-7.3)	6.2 (4.8-7.1)	3.8 (2.8-4.5)	p=0.003
Creatinine[*] (µmol/l)	*(64-104umol/l)*	74 (65-90)	86 (75-99)	63 (48-71)	p=0.017[1,2], p=0.0003[1,3]
Total cholesterol[#](mmol/l)	*(<4.5mmol/l)*	4.0 (0.9)	5.2 (1.2)	3.1 (0.8)	p=0.019[1,3], p=0.0011[2,3]
Triglycerides[*](mmol/l)	*(<1.7mmol/l)*	1.2 (0.95-1.45)	1.3 (0.95-1.95)	1.2 (0.90-1.40)	p=0.27
HDL[#](mmol/l)	*(>1.0mmol/l male >1.3mmol/l female)*	1.05 (0.29)	1.03 (0.24)	0.94 (0.27)	p=0.44
LDL[#] (mmol/l)	*(<2.5mmol/l)*	2.3 (0.7)	3.5 (1.0)	1.6 (0.6)	p=0.028[1,3], p<0.0001[2,3]
CD4[*] (cells/mm^3)	*(cells/mm^3)*	301 (205-417)	N/A	122 (19-198)	p=0.0020
CRP[*] (mg/l)	*(0-10mg/l)*	15 (10-71)	30 (13-97)	24 (10-33)	p=0.44

Key: [#]mean (sd), [*]median (IQR)

Haemoglobin

The mean haemoglobin level of the HIV-/ACS group (15.0; sd=1.7 g/dl) was significantly raised relative to that of both the HIV+/ACS (12.9; sd=2.6 g/dl) and HIV+/no ACS groups (11.4; sd=2.1 g/dl) (one-way ANOVA; p=0.0086 and p<0.0001, respectively) (Figure 4.39).

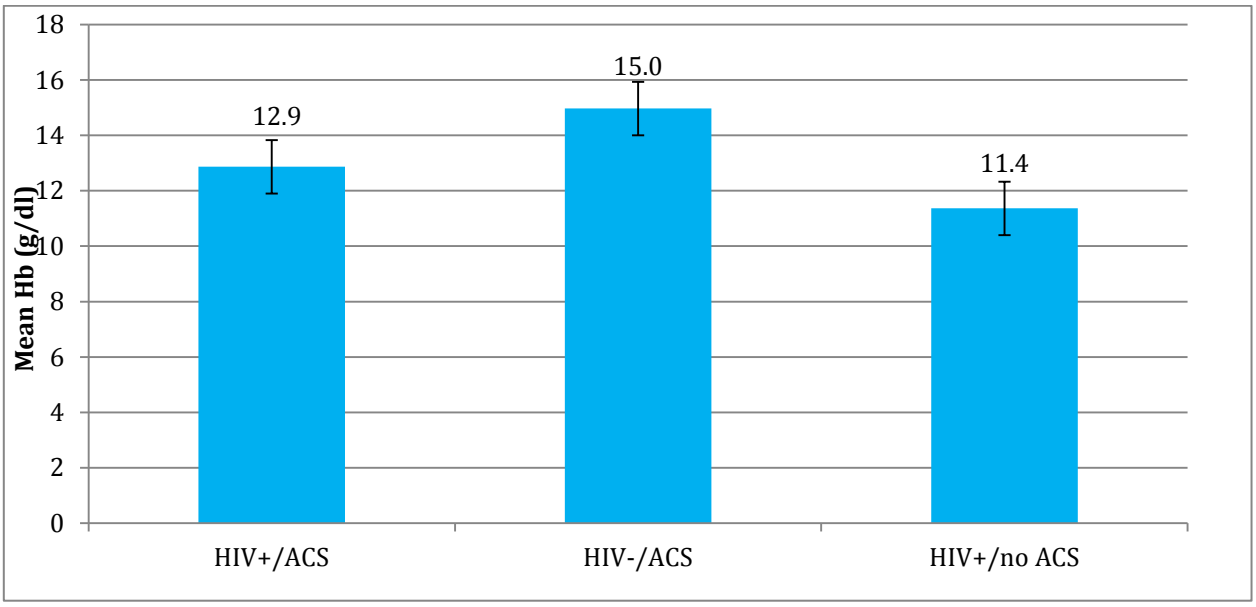


Figure 4.39 : Haemoglobin levels

Sodium

The mean sodium level of the HIV-/ACS group (140.2; sd=4.1 mmol/l) was significantly raised than that of the HIV+/no ACS group (137.2; sd=3.1 mmol/l) (one-way ANOVA; p=0.013).

Potassium

The potassium level mean ranged from 4.2 to 4.4 mmol/l. There were no significant between-group differences (one-way ANOVA: p=0.33).

Urea

The median urea level for the HIV-/ACS group (6.2; IQR 4.8-7.1 mmol/l) was significantly raised than that of the HIV+/no ACS group (3.8; IQR 32.8-4.5 mmol/l) (Kruskal-Wallis test: p=0.003).

Creatinine

The median creatinine level for the HIV+/ACS group (74; IQR 65-90 µmol/l) and the HIV-/ACS group (86; IQR 75-99 µmol/l) were significantly higher than that of the HIV+/no ACS group (63; IQR 48-71 µmol/l) (Kruskal-Wallis test: p=0.017 and 0.0003, respectively) (Figure 4.40).

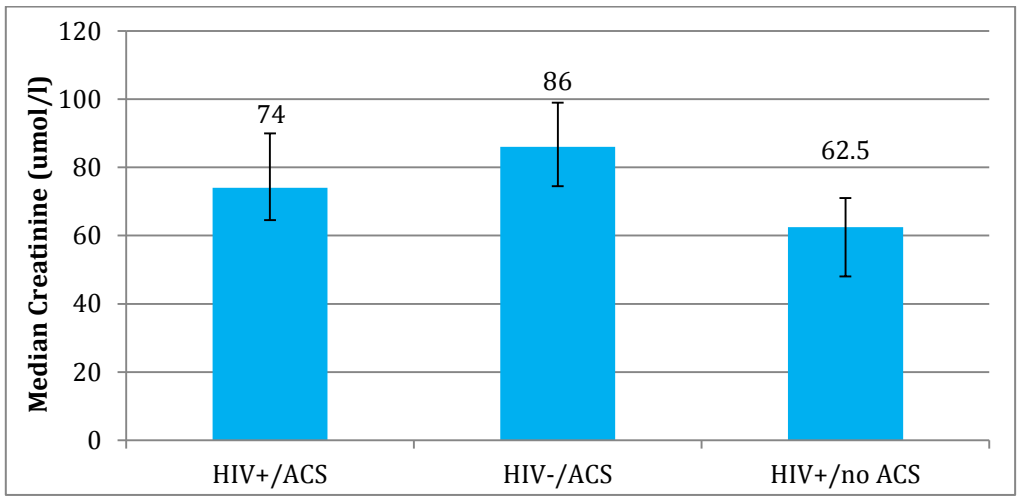


Figure 4.40 : Creatinine levels

Lipogram

The total cholesterol levels were higher in the HIV-/ACS group followed by the HIV+/ACS and lastly the HIV+/no ACS patients. All groups had similar HDL levels. Interestingly, the HIV+/no ACS group pre-cART, had very low LDL levels and a favourable lipid profile (Figure 4.41).

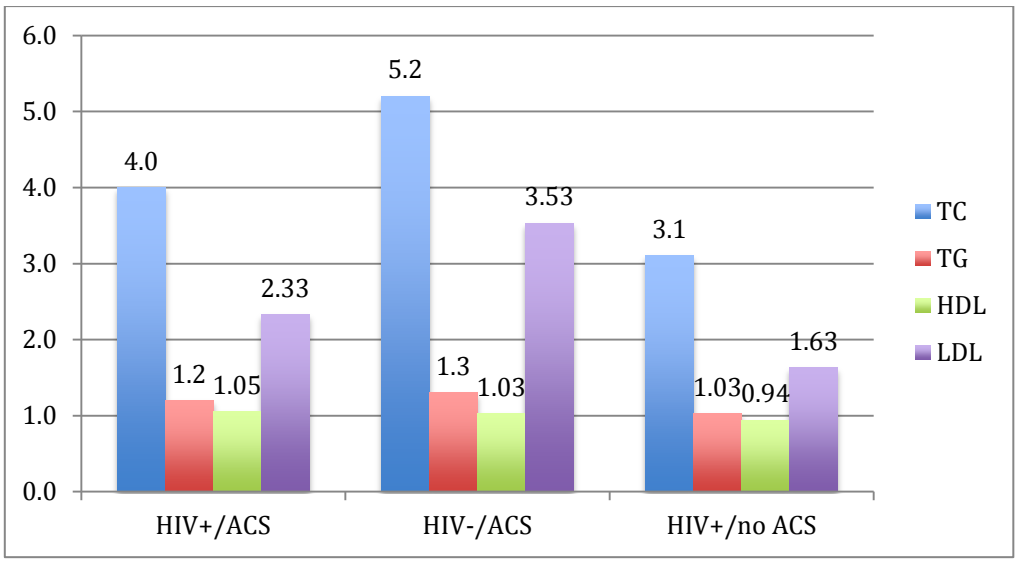


Figure 4.41 : Lipid profile

Total cholesterol

The mean total cholesterol of the groups increased in the order: HIV+/no ACS (3.1; sd=0.8 mmol/l) < HIV+/ACS (4.0; sd=0.9 mmol/l) < HIV-/ACS (5.2; sd=1.2 mmol/l) (one-way ANOVA: p=0.019 and 0.0011 respectively) (Figure 4.42).

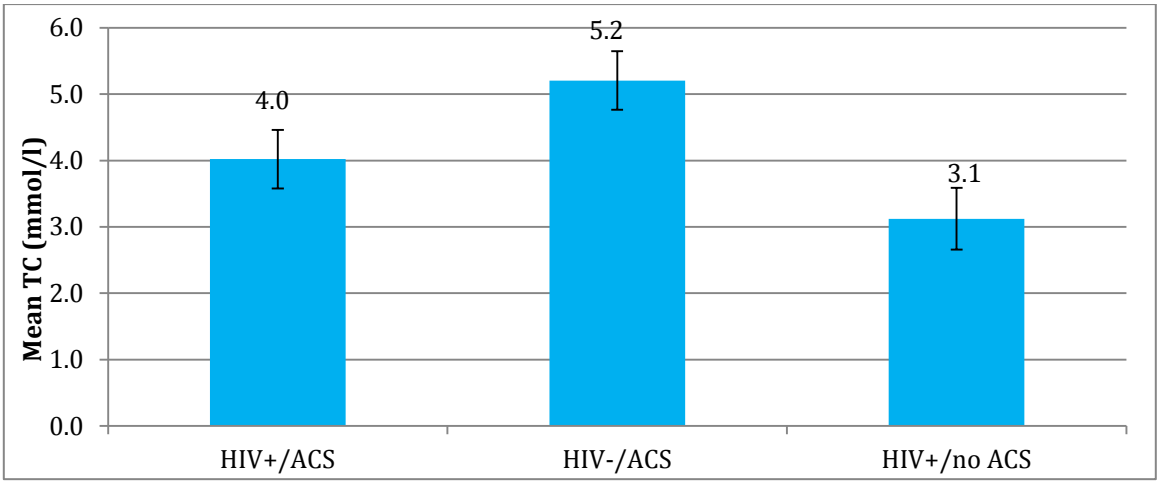


Figure 4.42 : Total cholesterol levels

Triglycerides

The three groups had median Triglycerides in the range 1.15-1.30 mmol/l (no significant difference; Kruskal-Wallis test: p=0.27).

HDL

The three groups had mean HDLs in the range 0.94-1.05 mmol/l (no significant difference; one-way ANOVA: p=0.44).

LDL

HIV-positive patients had much lower LDL levels than HIV-negative patients. The mean LDL of the groups increased in the order: HIV+/no ACS (1.64; sd=0.6 mmol/l) < HIV+/ACS (2.33; sd=0.7 mmol/l) < HIV-/ACS group (3.53; sd=1.0 mmol/l) (one-way ANOVA: p=0.028 and <0.0001 respectively). The HIV-negative group pre-cART, had very low LDL levels and a favourable lipid profile (see Figure 4.43).

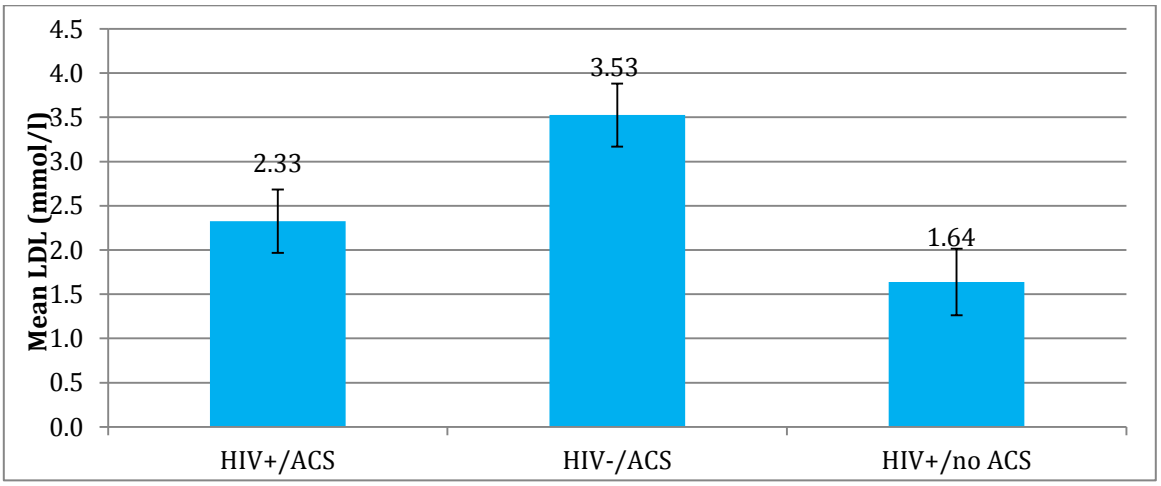


Figure 4.43 : LDL levels

CD4 count (HIV+ groups only)

The median CD4 count of the HIV+/ACS group 301cells/mm^3 (IQR 205-417) was significantly higher than that of the HIV+/no ACS group 122 cells/mm^3 (IQR 19-198) (Wilcoxon rank sum test: p=0.0020).

CRP

The HIV+/no ACS group had missing data in excess of 30% and was not considered in the analysis. The other two groups had median CRPs in the range 15-30 (no significant difference; Wilcoxon rank sum test: p=0.44).

late presentation or non significant lesions. In the current study, significantly more patients presented with proximal LAD lesions as compared to the PHD registry. Furthermore, none of our patient cohort had chronic total occlusion at coronary angiography at the time of presentation. No patients in our cohort were referred for CABG.

Table 5.1: HIV-positive patients with ACS International Registry (D'Ascenzo et al., 2014)

PCI: percutaneous intervention, CABG: coronary artery bypass graft, LAD: left anterior descending artery, CTO: chronic total occlusion

	PHD Registry (206 HIV+/ACS patients)	Our study (20 HIV+/ACS patients)
Primary PCI	75 (36%)	6 (30%)
Management : PTCA	154 (76%)	6 (30%)
CABG	11 (5.4%)	0
Medical therapy	28 (14%)	14 (70%)
Proximal LAD	78 (38.2%)	12 (60%)
CTO	20 (10)	0

ABBREVIATIONS AND ACRONYMS

cART = combination antiretroviral therapy

CCTA = coronary computed tomography angiography

CHD = coronary heart disease

CIMT = carotid intima-media thickness

CVD = cardiovascular disease

MI = myocardial infarction

PI = protease inhibitor

with a concurrent rise in the incidence of noncommunicable diseases, particularly CHD (10).

Large observational studies in the United States and Europe have investigated the epidemiology of CHD in HIV-infected populations (**Table 1**) (5,11–20). These and other studies suggest that HIV infection increases the overall risk for developing CHD by 1.5- to 2.0-fold. Interestingly, an analysis of cohorts over different timeframes suggests that the prevalence rates are falling, presumably due to early recognition of risk factors and use of newer antiretroviral agents (21). Unfortunately, there are scant data on the effect of HIV infection on CHD prevalence in resource-poor countries. Some data suggest that CHD risk factors are prevalent in resource-limited countries, but CVD outcomes data are lacking (22).

With regard to CVD outcomes, HIV-positive patients also have a greater risk of developing cardiovascular complications (4). Data from the Nationwide Inpatient Sample in the United States demonstrated that HIV-positive patients with myocardial infarction (MI) have lower MI-related intervention rates and higher death rates compared with their seronegative counterparts (23). They also have a 4.5-fold increased rate of sudden cardiac death, which has been associated with a history of previous MI, cardiomyopathy, heart failure, arrhythmia, hypertension, and dyslipidemia (24).

RISK FACTORS

TRADITIONAL RISK FACTORS. A number of studies indicate a high prevalence of traditional CHD risk factors in the HIV-positive populations (4,5). However, prevalence estimates vary widely, due to differences in risk cutoffs, genetic background, geographic location, and access to cART. In resource-rich countries, smoking rates are reported to be almost 2-fold higher in HIV-positive individuals (14,25). The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study group reported that in HIV-infected persons, there was almost a 3-fold increased risk of MI in current smokers as compared with HIV-infected nonsmokers (26). The same study group also found that diabetes and dyslipidemia were associated with an increased risk of MI (26). Patients with HIV also have a stepwise increase in their risk of MI, with a hazard ratio of 2.0 for those with 1 major CVD risk factor, increasing to 3.6 for those with 3 or more risk factors (20). Even low pre-hypertension (120 to 129/80 to 84 mm Hg) and high pre-hypertension (130 to 139/85 to 89 mm Hg) were associated with an increased risk of MI of 1.6 and 1.8, respectively (27). Many of the traditional risk factors, such as smoking, dyslipidemia, hypertension and central obesity, are likely related to the socioeconomic factors associated with HIV infection.

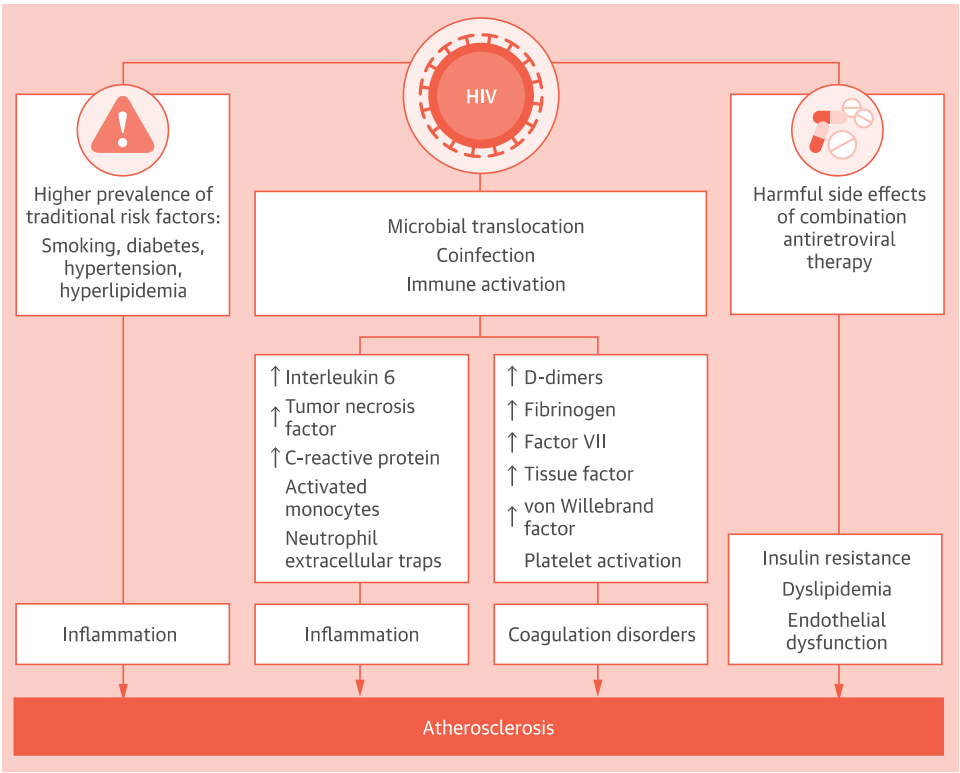
INFLAMMATION AND IMMUNE ACTIVATION. HIV infection, through attendant inflammation and immune dysfunction, is an independent predictor of CVD. Two recent large cohort studies found a strong and consistent association of HIV with a 44% to 48% increased risk of MI, independent of traditional risk factors, such as age, race, socioeconomic status, and substance abuse (5,19). The findings of the SMART (Strategies for Management of Antiretroviral Therapy) trial also suggest that HIV and attendant inflammation are important in conferring CHD risk (8). This is further supported by a recent study, which found that new cycles of HIV replication may also play a role in ongoing inflammation in patients with modest cART nonadherence (28). In HIV-infected patients, studies suggest that immunodeficiency (CD4+ cell counts <200 cells/mm^3) is significantly associated with a higher risk of MI (5,19).

EFFECT OF SEX. HIV has a distinct effect on women with respect to CHD risk. Although the majority of observational data included predominantly male patients, there is a significant difference in the relative risk of CHD for HIV-infected women, who have double the risk compared with HIV-infected men (4,17). This higher risk in women may relate to higher levels of immune activation (17).

ANTIRETROVIRAL THERAPY. Dyslipidemia (elevated total cholesterol and triglyceride levels), as well as endothelial dysfunction, may be caused by cART, particularly protease inhibitors (PIs) (6,7). These agents may also predispose to hypertension through hyperactivation of the renin-angiotensin-aldosterone system (29). In contrast, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, and CCR5 antagonists have thus far been shown to have neutral lipid effects, with no increased risk of CHD (30) (**Table 2**). Endothelial dysfunction secondary to cART has been attributed to reduced nitric oxide production, increased reactive oxygen species production, impaired cholesterol efflux, and accelerated foam cell formation (6).

PATHOGENESIS OF HIV-ASSOCIATED CAD. CAD in HIV-infected patients is the result of a number of interactions causing inflammation, endothelial

CENTRAL ILLUSTRATION **HIV and Ischemic Heart Disease: Etiopathogenesis of HIV-Associated Coronary Artery Disease**



Vachiat, A. et al. J Am Coll Cardiol. 2017;69(1):73–82.

The etiopathogenesis of HIV-associated coronary artery disease is multifactorial. Inflammation is the hallmark of HIV infection. There is interplay between the direct effects of HIV infection, attendant inflammation, traditional risk factors prevalent in HIV infection, and side effects of some antiretroviral therapy regimens. These occur in a milieu of variable environmental and as yet unknown genetic factors. HIV = human immunodeficiency virus.

dysfunction, and coagulation disorders, ultimately leading to atherosclerosis.

ATHEROSCLEROSIS. Recent research focus has shifted to the detection of subclinical atherosclerosis as a surrogate for clinical events. The typical plaque in HIV-infected patients is a noncalcified atherosclerotic plaque, but calcium oxalate crystal deposits (*atherosclerotic oxalosis*) within the plaques have been described in HIV-infected patients on cART (31). Direct HIV infection of the coronary vascular wall appears to stimulate proliferation of vascular smooth muscle cells, and thereby promotes atherosclerosis. Detection of the HIV protein p24 by fluorescence microscopy in smooth muscle cells from tissue sections of human atherosclerotic plaques obtained from HIV-infected individuals supports this hypothesis (32).

Noninvasive imaging, such as carotid intima-media thickness (CIMT) and coronary computed tomography angiography (CCTA), indicates an increased prevalence of subclinical atherosclerosis in HIV-positive patients compared with HIV-negative patients (33–35). A meta-analysis of 13 observational studies suggests a trend toward more increased CIMT in HIV-infected patients compared with HIV-negative patients (33). As early as childhood, HIV-infected

TABLE 1 HIV and CAD Studies*

First Author (Ref. #)	Year	Population	HIV-Positive Patients	Age (yrs)	Effect of HIV Infection	Effect of Antiretroviral Therapy
Bozzette et al. (11)	2003	U.S. Veterans Affairs	36,766 (98.1% male)	35–55 (71.3%)	No significant increase in CHD admissions or mortality	No difference between PI vs. no PI
Mary-Krause et al. (12)	2003	French Hospital Database	34,976 (all male)	37.7 (mean)	No control subjects	Increased MI in PI >30 months Standardized morbidity ratio: 2.9
Currier et al. (13)	2003	California Medicaid	28,513 (72.7% male)	25–54 (89.7%)	Increased incidence of CHD in men <35 yrs of age and women <45 yrs of age	Increased CHD with cART (18–33 yrs of age), RR: 2.06 No difference in other age groups
D:A:D Study Group (14)	2003	D:A:D study 188 clinics in 21 countries	23,468 (74.9% male)	39 (median)	No control subjects	Incremental increase in MI with cART RR: 1.26 per additional year exposure
Coplan et al. (15)	2003	Meta-analysis of phase II/III randomized studies	10,986 (85.9% male)	37 (mean)	No control subjects	No significant difference of MI in PI vs. NRTI
Iloeje et al. (16)	2005	U.S. HOPS cohort	7,542 (88% male)	18–49 (88%)	No control subjects	PI exposure ≥60 days associated with more events, HR: 1.71
Lang et al. (17)	2010	French Hospital Database	74,958 (89% male)	47 (median)	No control subjects	Increased risk of MI to all PI (except saquinavir), OR: 1.53 NRTI not associated with risk of MI
Durand et al. (18)	2011	Quebec Public Health Insurance Database	7,053 (91.2% male)	39.5 (mean)	Increased risk of MI in HIV positive patients (IR: 2.11)	Increased MI with: abacavir (OR: 1.79), efavirenz (OR: 1.83), lopinavir (OR: 1.98), ritonavir (OR: 2.29)
Freiberg et al. (5)	2013	U.S. Veterans Affairs	27,350 (97.3% male)	48.2 (mean)	Increased risk of MI in HIV-positive patients (HR: 1.48) Increased risk if VL >500 copies/ml and CD4 <200 cells/mm^3	Recent PI use had borderline significance 50.8% no cART use
Silverberg et al. (19)	2014	Kaiser Permanente California health plan database	22,081 (90.6% male)	30–49 (70.3%)	RR: 1.4 Increased risk if CD4 <200 cells/mm^3	cART not associated with MI
Paisible et al. (20)	2015	Veterans Aging Cohort Study	26,836 (96% male)	45 (mean)	HR: 2.0	51% no cART use

*Studies with more than 5,000 HIV-positive patients.

CAD = coronary artery disease; cART = combined antiretroviral therapy; CHD = coronary heart disease; HIV = human immunodeficiency virus; HR = hazard ratio; IR = incidence ratio; MI = myocardial infarction; NRTI = nucleoside reverse transcriptase inhibitors; OR = odds ratio; PI = protease inhibitors; RR = relative risk; VL = viral load.

children receiving cART have increased CIMT, suggesting that CHD risk may already be heightened in HIV-infected patients at a young age (36). A recent meta-analysis of 1,229 asymptomatic HIV-positive patients on cART demonstrated a 3-fold higher prevalence of noncalcific coronary artery plaques (vulnerable plaques) at CCTA, compared with HIV-negative control subjects (34). In addition, patients with low CD4+ cell counts had evidence of more vulnerable plaques, further supporting the finding that disease severity may contribute to increased CVD risk (34).

INFLAMMATION. The immune system has a critical role in the development and progression of atherosclerosis in HIV-positive patients. Higher levels of inflammatory markers, such as C-reactive protein, interleukin-6, and tumor necrosis factor (TNF), have been found in HIV-positive patients compared with HIV-negative patients (37–39). The risk for MI is increased more than 4-fold in patients with HIV infection and elevated C-reactive protein levels compared with HIV-negative patients (38). A number of immune activation markers, including soluble CD163, CXCL10, CD14+, and CD16+ monocytes, are increased in HIV-infected individuals and have been found to be independent predictors of the presence of noncalcific coronary plaque (40). Higher levels of interleukin-6, soluble TNF receptor I and soluble TNF II, the kynurenine to tryptophan ratio, and levels of D-dimer at 1 year post-cART have been associated with the occurrence of MI and stroke (39). HIV infection has been postulated to alter the balance of immune cell subsets, such as intermediate monocytes and CD4+ T-helper cells, in a proinflammatory and proatherosclerotic manner (41). Even those who are compliant on cART with complete virological suppression still have a residual risk for CHD, because the inflammation and immune activation are not fully suppressed (3). Hepatitis C virus coinfection, which results in increased immune activation, is also associated with an increased risk of CVD (42). Neutrophil

extracellular traps, which are chromatin structures ejected from neutrophils, have been identified as important in clearing pathogens from the circulation (43). However, neutrophil extracellular traps have also recently been shown to induce numerous proatherogenic and prothrombotic effects, and may play a role in promoting atherogenesis (43).

ENDOTHELIAL DYSFUNCTION. Endothelial dysfunction, which is well known to be associated with atherosclerosis, has been described in many HIV-positive patients (44). There is an intricate interplay between endothelial function and inflammation; for example, markers of endothelial activation, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, both of which are up-regulated by inflammatory cytokines, are elevated in patients early after HIV infection (45). A significant improvement in brachial flow-mediated dilation has been demonstrated in patients in the first 24 weeks after initiation of antiretroviral therapy, suggesting that suppression of HIV viremia leads to improved endothelial function (46).

COAGULOPATHY. Coagulation abnormalities are common in HIV infection. These include elevated levels of D-dimers, fibrinogen, factor VII, von Willebrand factor, soluble thrombomodulin, and tissue factor (47-49). Higher D-dimer levels have been independently associated with the risk for CVD deaths in the SMART study (37). Another mechanism through which HIV infection may alter coagulation pathways is tissue factor activation. Tissue factor levels measured 4 months before a CVD event were elevated compared with tissue factor levels in HIV-infected patients who did not have a subsequent CVD event (48). Thrombophilia is more common in HIV-positive patients with lower protein C levels and higher factor VII levels, as well as in those with higher anticardiolipin and antiprothrombin antibodies (50). Also, HIV leads to chronic platelet activation, which may promote atherogenesis and increase the risk of thrombosis (51). A pilot study has shown that giving aspirin to HIV-positive patients decreases T-cell (CD38 and HLA-DR) and monocyte activation (sCD14), thereby attenuating platelet activation (52).

PRESENTATION

CHD in HIV patients most commonly manifests as an acute episode of acute coronary syndrome (ACS), with the most common mode of presentation being ST-segment elevation MI (49). However, there are distinct characteristics of ACS presentation in HIV-positive patients. Common to most studies is that the mean age at presentation of ACS in HIV-infected patients is a decade younger than in the general population, with a mean age of 50 years (53-55). They are also more likely to be male, be current smokers, and have single-vessel CAD (53-55).

There are limited data from developing nations on HIV-positive patients presenting with ACS. The cause of ST-segment elevation MI in HIV-positive patients from developing nations is often reported as related to a large thrombus burden in the infarct-related artery, with angiographically normal underlying coronary arteries (55). The reasons for this are not clear. It is possible that the HIV virus subtype infection may play a role, as the HIV virus subtype infection differs in various regions. The major subtype infection in Africa is HIV-1 subtype C, whereas in developed countries, the infection is with HIV-1 subtype B. Population genetic factors may also be important (56).

TABLE 2 Effect of Antiretroviral Agents on Lipid Parameters

cART	Effect on Dyslipidemia	Comment
NRTI		
Zidovudine	↑↑	Significant increase in TC/LDL
Stavudine	↑↑	Significant increase in TC/TG
Abacavir	←→/↑	TC/HDL ratio unchanged
Tenofovir	↓	Reduction in LDL/TC
NNRTI		
Nevirapine	↓	Can increase HDL level
Efavirenz	←→/↑	May increase lipid level slightly
Etravirine	←→/↑	No significant changes
Protease inhibitor		
Lopinavir/ritonavir	←→/↑	Elevation of TC/TG frequent
Fosamprenavir/ritonavir	↑	Elevation of TC/TG
Atazanavir/ritonavir	←→	PI with best lipid profile
Darunavir/ritonavir	←→	Good lipid profile
Integrase inhibitor		
Raltegravir	←→	Low frequency of dyslipidemia
Chemokine receptor-5 antagonist		
Maraviroc	←→	No significant changes

HDL = high-density lipoprotein; LDL = low density lipoprotein; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; TC = total cholesterol; TG = triglyceride.

MANAGEMENT

RISK ASSESSMENT. Determining the risk of CHD in HIV patients is challenging because traditional risk calculators, such as the Framingham Risk Score, may underestimate their risk (57,58). Data from the D:A:D study have been used to generate a CVD risk model

TABLE 3 Statin Interactions With Antiretroviral Agents

Drug	Metabolism	PI	NNRTI
Lovastatin	CYP3A4	Contraindicated with PIs	Decreases lovostatin's AUC; thus, a higher lovastatin starting dose may be needed
Simvastatin	CYP3A4	Contraindicated with PIs	Acceptable with appropriate dosing Efavirenz and etravirine decrease simvastatin's AUC
Pravastatin	Partial hepatic (OATP1B1); partial urinary/ biliary excretion	Acceptable with appropriate dosing and monitoring; darunavir increases pravastatin's AUC	Acceptable with appropriate dosing and monitoring
Fluvastatin	CYP2C9, CYP3A4	Acceptable with appropriate dosing and monitoring; not recommended with nelfinavir	Acceptable with appropriate dosing and monitoring Etravirine may increase fluvastatin's AUC
Atorvastatin	CYP3A4	Use with caution. Do not coadminister with tipranavir/ritonavir	Acceptable with appropriate dosing and monitoring Efavirenz and etravirine decrease atorvostatin's AUC
Rosuvastatin	CYP2C9	Acceptable with appropriate dosing and monitoring; lopinavir/ritonavir and tipranavir/ritonavir increases rosuvastatin's AUC	Acceptable with appropriate dosing and monitoring
Pitavastatin	CYP2Cp; glucuronidation	No significant interaction; mild decrease in pitavastatin's AUC with darunavir	No data on NNRTI

Adapted from Aberg et al. (66).

AUC = area under the curve; CYP = cytochrome; NNRTI = non-nucleoside reverse transcriptase inhibitors; OATP1B1 = Organic Anion Transporting Polypeptide 1B1/SLCO1B1.

for HIV patients (59). This model, using traditional risks for CVD in addition to HIV-specific risks, such as CD4+ count, abacavir use, and exposure to PIs and nucleoside reverse transcriptase inhibitors, was able to better predict CVD events than the Framingham risk score. However, this and other HIV-specific risk calculators have not been widely validated or adopted.

Noninvasive imaging, including stress echocardiography, CCTA, and CIMT, has been used to identify HIV patients who are at increased risk of CHD events (35). HIV-positive patients have an increased incidence of high-risk coronary plaque on CCTA and CIMT, which has been shown to improve with statin therapy (60,61). This suggests that there may be a role for noninvasive risk stratification among intermediate-risk HIV patients (62).

RISK REDUCTION. There are no data from large-scale clinical trials to guide specific primary prevention for CHD in HIV-positive patients. However, recent interest has focused on the management of traditional CVD risk factors, reduction of persistent immune activation, and use of newer antiretroviral agents, which have fewer adverse CVD effects and drug interactions.

Smoking cessation should be strongly advocated, as the life expectancy of HIV-infected smokers has been found to be, on average, 8 years less than that of HIV-infected nonsmokers (63). In the D:A:D study cohort, smoking cessation was associated with a fall in the incidence rate ratios for CHD from 2.32 within the first year of stopping smoking to 1.49 after 3 years compared with those who never smoked (64). Other traditional risk factors, such as obesity and sedentary lifestyle, should also be addressed.

Statin therapy should be considered for those who do not reach goal lipid levels. Statins are important in risk reduction in patients with HIV because they directly reduce low-density lipoprotein (LDL) and indirectly reduce immune activation (65). Interactions between cART and statins do exist, and one should be mindful when prescribing these drugs (**Table 3**) (66). Most PIs inhibit the metabolism of statins and can significantly increase statin levels, thus increasing the risk of toxicity. The addition of ezetimibe to statins has been shown to decrease LDL levels without concerns of drug interactions with cART, as it does not interact with cytochrome P450 3A4 (CYP3A4) (67). With regard to fibrates, fenofibrate is preferred over gemfibrozil due to fewer drug interactions (68).

REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) is the largest ongoing trial focusing on HIV-related CVD to date (n = 6,500), with a 6-year follow-up (69). HIV-infected participants who do not meet current national guidelines for statin therapy are being randomized to either placebo or a daily dose of pitavastatin, which has minimal interactions with HIV drugs, while continuing with cART (70).

Other direct anti-inflammatory drugs may have a role to play in reducing inflammatory-mediated CHD. Methotrexate, for example, is currently under investigation in 200 HIV-infected patients (NCT01949116), and several small trials are looking at the effect of aspirin on vascular surrogates, such as flow-mediated dilation (NCT02081638, NCT02401269, and NCT02155985). A drug that lowers phosphate, sevelamer, has been shown to reduce factors related to CVD, such as soluble tissue factor, oxidized LDL cholesterol, and LDL cholesterol, which may have cardiovascular benefits (71).

ANTIRETROVIRAL THERAPY. The START (Strategies for Management of Antiretroviral Therapy) study demonstrated that initiation of cART in patients with CD4+ counts >500 cells/mm^3 significantly reduced

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TABLE 4 Antiplatelet Interactions With Commonly Used Antiretroviral Agents

Antiretroviral Agent	Mechanism of Interaction	PI	NRTI	NNRTI	Integrase Inhibitors
Clopidogrel	CYP3A4, CYP2C19, CYP2C9	Unlikely to be clinically relevant	No interaction	Etravirine and efavirenz decrease effect of clopidogrel	Unlikely to be clinically relevant
Prasugrel	CYP3A4	Ritonavir decreases clinical effect	No interaction	Unlikely to be clinically relevant	Cobicistat decreases clinical effect
Ticagrelor	CYP3A4, Pgp	Increased risk of bleeding	No interaction	Unlikely to be clinically relevant	Increased risk of bleeding with cobicistat

Pgp = P-glycoprotein; other abbreviations as in Tables 1 and 2.

serious AIDS-related events and death at a mean follow-up of 3 years (72). Of note is that in September 2015, the World Health Organization released its revised treatment guideline recommending the initiation of cART in all HIV-infected patients, regardless of CD4+ cell count (73). Which cART regimen to use is not clearly established, but antiretroviral agents with more favorable lipid profiles and fewer drug interactions are suggested (Table 2).

ACUTE CORONARY SYNDROMES. HIV-positive patients with ACS should be treated according to current guidelines, but the treating physician should be cognizant of potential drug-drug interactions. Antiplatelet agents are commonly used in CHD patients. Agents such as the thienopyridines are metabolized by several cytochrome P450 liver enzymes, which predisposes to interactions with antiviral agents, such as efavirenz, and agents used to treat opportunistic infections, including azole antifungals, rifampicin, and isoniazid (74). Because clopidogrel is significantly metabolized by CYP2C19 and CYP2C9, there are a number of potential drug interactions (Table 4) (75). Prasugrel is a reasonable alternative, but should not be combined with ritonavir because this will decrease prasugrel's activity (76). Ticagrelor, which is predominantly metabolized by the CYP3A4/5 isoenzyme, should also not be used in patients who are receiving PI therapy (77).

REVASCULARIZATION. Drug-eluting stents appear to be similarly safe and efficacious in patients with and without HIV (78). Recent studies show that there is no significant difference in target vessel revascularization rates post-stent implantation between HIV-positive and HIV-negative patients (54,79). With respect to stent thrombosis, there are scant data, but some studies suggest a higher rate of stent thrombosis in HIV-positive patients than in individuals without HIV infection (80). Coronary artery bypass grafts are feasible, and perioperative complications are no different from those in HIV-negative patients, even when CD4+ counts are <500 cells/mm^3 (81).

ISCHEMIC CARDIOMYOPATHY. Because of the increased risk of ACS in patients with HIV, there is a concomitant increased risk of ischemic cardiomyopathy in these patients (82). Management of such patients should be the same as for those who are HIV negative, and should follow the recommended heart failure guidelines. Heart transplantation can be considered in selected HIV-positive patients with ischemic cardiomyopathy (83). However, it would be preferable for transplant candidates to have CD4+ counts >200 cells/mm^3, be virally suppressed, and have no evidence of opportunistic infection before transplantation.

PROGNOSIS

As HIV infection becomes a chronic disease, death due to AIDS is declining; however, death from CVD has increased among HIV-infected adults (10). In-hospital mortality from ACS is similar to that of HIV-negative patients (84). Long-term outcomes are also similar (82,84), but important risk factors for death include the presence of chronic kidney disease, nucleoside reverse transcriptase inhibitor-sparing therapy, low ejection fraction, and CD4+ counts <200 cells/mm^3 (80).

Recurrent MI post-ACS has been found to be higher in HIV-positive patients than in HIV-negative patients (80,84). Hospitalization for episodes of heart failure has been reported to be twice as likely in HIV-infected patients as in non-HIV-infected patients (82). This may be due to subclinical systolic and diastolic dysfunction in the broader HIV population, which only manifests after a first episode of ACS (85).

CONCLUSIONS

Both HIV and CHD are global health issues, and as the HIV population ages, the increase in cardiovascular risk will pose future challenges to clinicians and health authorities. The challenge will be greater in developing nations due to an increased burden of disease, as well as having limited health resources

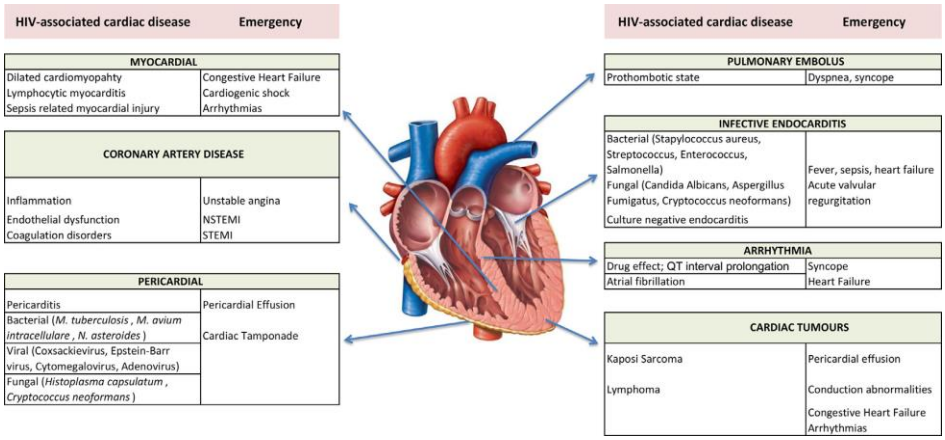

Fig. 1. Cardiac emergencies in HIV. NSTEMI, non-STEMI.

HIV-positive patients.[7,8] Thus, smoking cessation should be strongly advocated, as the life expectancy of HIV-infected smokers has been found to be on average 8 years less than that of HIV-infected nonsmokers.[9]

Clinical Presentation and Management

As compared with the general population, HIV-positive patients presenting with acute coronary syndrome (ACS) are younger (mean 50 years), predominantly male, and usually have single-vessel CAD on coronary angiography.[10–12] Most commonly, HIV-positive patients present with ST elevation MI (STEMI).[11] It is important to consider the type of MI among HIV-positive individuals to guide prevention and treatment strategies. A recent study from 6 US centers found that half (50.4%) of all HIV-positive patients presenting with ACS had Type 2 MI, which occurs in the setting of supply and demand mismatch.[13] The etiology of these MIs was attributed to sepsis, bacteremia, and recent use of cocaine or other illicit drug use.[13]

Patients presenting with ACS should be managed similar to HIV-negative patients according to standard guidelines.[14,15] There are no data to guide which is the most appropriate thrombolytic agent to administer in HIV-positive patients presenting with MI; however, tenecteplase would be the agent of choice, as it can be administered quickly as a bolus dose.

Antiplatelet agents should be standard of care in all patients with ACS. Aspirin 300 to 325 mg together with P2Y12 inhibitors (clopidogrel, ticagrelor, prasugrel) should be administered at the time of presentation. Thienopyridines are metabolized by several cytochrome P450 liver enzymes and may interact with antiviral agents such as efavirenz as well as certain drugs used to treat opportunistic infections, such as antifungals, rifampicin, and isoniazid (**Table 1**).[16,17] Prasugrel should not be combined with ritonavir because this may decrease prasugrel's efficacy. Ticagrelor, which is predominantly metabolized by the CYP3A4/5 isoenzyme, also should be used with caution in patients on protease inhibitor (PI) therapy, as there may be an increased risk of bleeding.[16,17]

Statins should be prescribed for all patients with ACS. Statins not only reduce low-density lipoprotein levels but there is evidence that they may also indirectly reduce immune activation.[18] There are several interactions between cART and statins and one should be mindful when prescribing these drugs.[19] PIs can significantly increase statin levels, thus increasing the risk of toxicity. With regard to fibrate therapy, fenofibrate is preferred over gemfibrozil due to fewer drug interactions.[20]

Combination antiretroviral therapy, particularly PIs, have been implicated in inducing dyslipidemia (elevated total cholesterol and triglyceride levels), as well as endothelial dysfunction.[21,22] On the other hand, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, and CCR5 antagonists have thus far shown to have neutral lipid effects with no increased risk of CAD.[23] The START study found that initiation of cART in all HIV-infected patients with CD4 counts greater than 500 cells/mm^3 significantly reduced serious AIDS-related events and death at a mean follow-up of 3 years.[24] As a result, the World Health Organization now recommends cART to all HIV-infected patients regardless of CD4 count.[25]

Malignant effusions often need chemotherapeutic interventions. Steroids should not be administered to HIV-positive patients with pericardial effusions, as a recent study failed to show improvement in mortality and steroid use was associated with a threefold increased risk of malignancy.[54]

INFECTIVE ENDOCARDITIS

Previous studies have shown higher rates of infective endocarditis (IE) in HIV-infected patients as compared to the HIV-negative counterparts with rates similar to that of intravenous drug users.[56,57] A number of risk factors predispose HIV-positive patients to the development of IE, including intravenous drug use, female sex, prosthetic valves, structural heart disease, and prior history of IE.[56,58] There is a strong correlation with immune status, as a CD4 count of less than 50 cells/mm^3 is associated with a fourfold increased risk of developing IE.[57] Thus, in regions in which there is widespread use of cART, the prevalence of IE has declined.[57]

Clinical Presentation in the Emergency Department

The clinical manifestations of IE, such as pyrexia, heart failure, audible murmurs, or features of embolic phenomena in HIV-positive patients are similar to that of HIV-negative patients. The most common valve involved is the tricuspid valve (**Fig. 3**) and the most common causative organism is *Staphylococcus aureus*.[57,59] The possibility of methicillin-resistant *S aureus* should be ruled out due to higher than normal prevalence in HIV-positive populations.[60,61]

At least 3 blood cultures should be obtained from different venipuncture sites with the first and second separated by at least 1 hour.[62] There is no rationale to delay in blood sampling or waiting for temperature spikes, as patients with IE usually have a constant bacteremia and blood cultures obtained before antibiotic therapy are usually positive.[63] Some studies have reported that culture-negative IE may be as high as 54% and this is partly explained by the concomitant use of cotrimoxazole and other forms of antibiotic prophylaxis.[64] The possibility of fungal endocarditis should be considered in patients who are intravenous drug users and in those with large vegetations on echocardiography. Transthoracic echocardiography imaging should be the initial imaging modality of choice, but when there is doubt or in patients with suspected prosthetic valve endocarditis, transesophageal echocardiography should be the modality of choice.

Prognosis and Therapy

Antibiotics should be commenced immediately after obtaining blood cultures. Depending on geographic sensitivity to S. aureus a suggested protocol for empiric treatment is intravenous Penicillin G 12 to 18million U/day (in 4–6 divided doses) with Gentamycin 3 mg/kg/d (1 dose) and Cloxacillin 12 g/d (4–6 divided doses) or Vancomycin 30 to 60 mg/kg/d (2–3 divided doses).[63] This should be tapered to goal directed therapy once culture sensitivity results are available.

The prognosis of HIV-positive patients with IE is similar to that of HIV-negative counterparts.[61] However, symptomatic HIV-positive patients with low CD4 counts have shown to have a higher mortality.[65] HIV status should not preclude them from undergoing cardiac surgery as data suggests that it is not an independent risk factor for perioperative complications.[66,67]

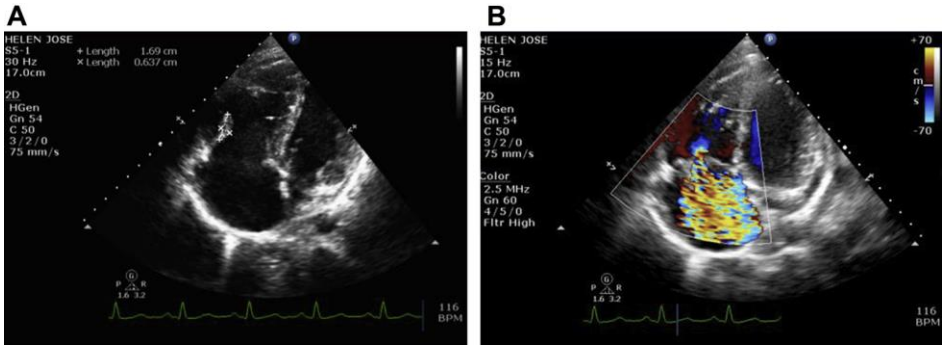

Fig. 3. (*A, B*) Echocardiographic image: HIV-positive, cART-naïve, intravenous drug user showing a large vegetation on tricuspid valve (*A*) caused by *Staphylococcus aureus*, complicated by severe tricuspid insufficiency (*B*).

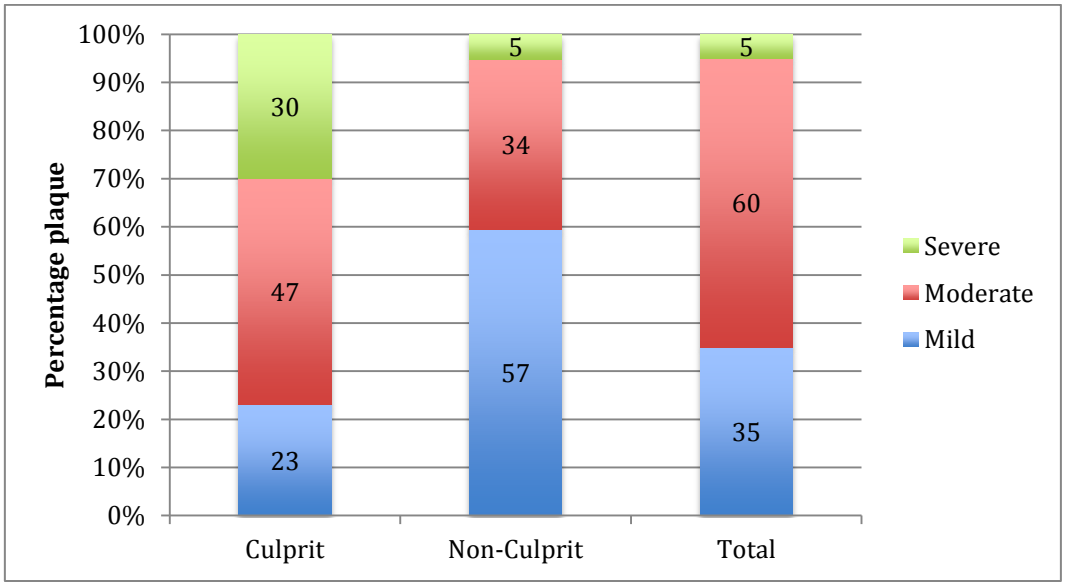

Fig. 1 : Plaque burden in HIV-positive patients with acute coronary syndromes

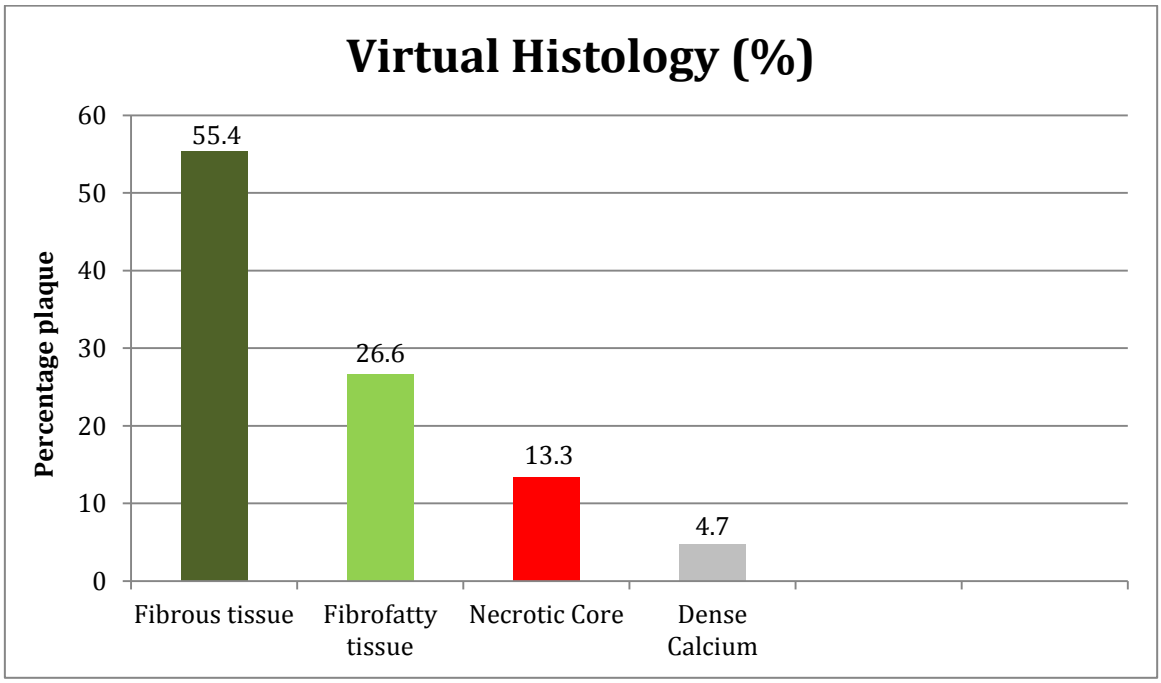

Fig. 2 : Virtual histology in HIV-positive patients with acute coronary syndromes. The mean fibrous plaque volume was significantly greater than the mean fibro-fatty plaque volume, which in turn was significantly greater than the mean necrotic core volume, which in turn was significantly greater than the mean dense calcium volume (all $p<0.05$)

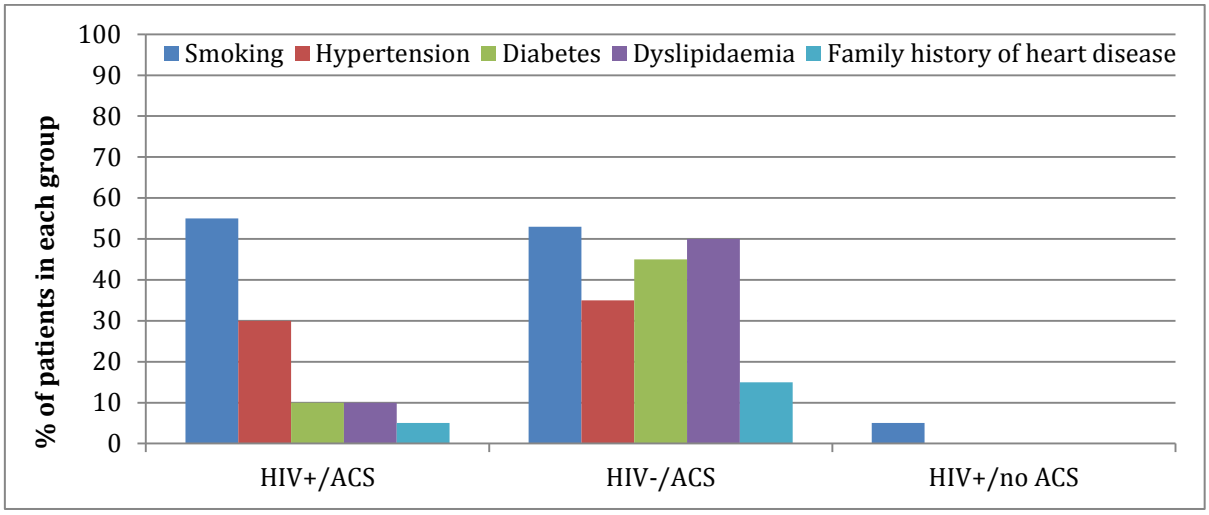

Figure 5 Risk factor profile

There were more smokers but there were less traditional risk factors (hypertension, diabetes, dyslipidaemia and family history of ischaemic heart disease)in the HIV+/ACS cohort compared to the HIV-/ACS and HIV+/no ACS cohorts.

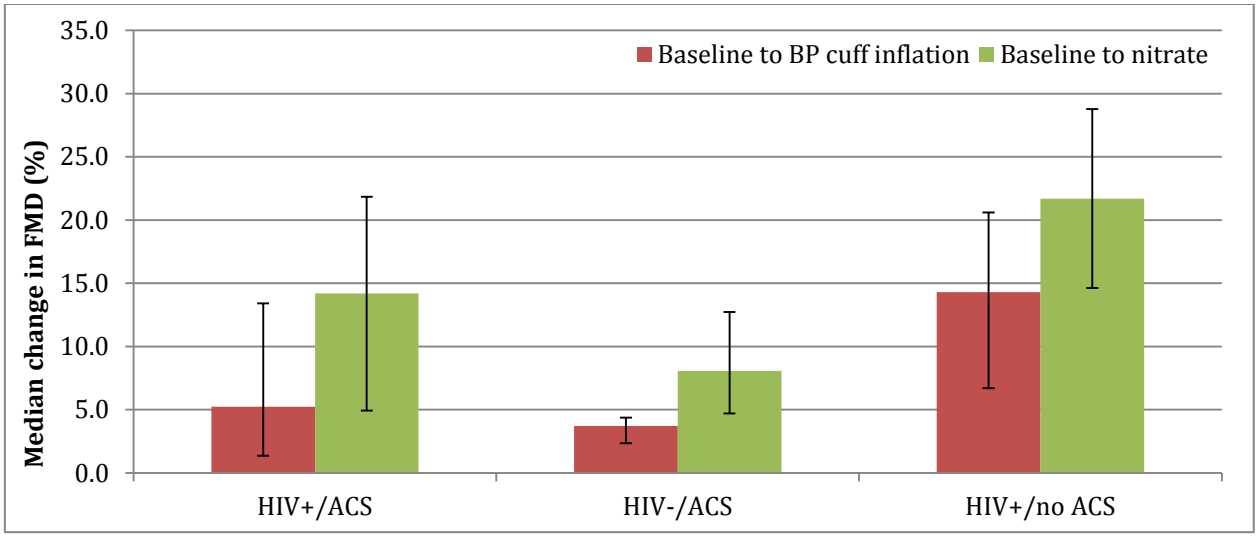

Figure 2: Mean change in FMD post BP cuff inflation. HIV+/ACS patients had similar change from baseline of brachial flow mediated dilatation compared to the HIV-/ACS patients (p=0.78). The HIV+/no ACS group had the most vasoreactivity but they were significantly younger (p=0.0001)

Table 2: Patient demographics, risk factors and clinical investigations

		HIV+/ACS[1]	HIV-/ACS[2]	HIV+/no ACS[3]	p-value
n		20	20	20	
Age (years)[#]		51.1 (8.1)	52.3 (9)	36 (6.8)	<0.0001
Race (black) n (%)		17 (75)	7 (35)	20 (100)	<0.0001
Male n (%)		13 (65)	16 (80)	10 (50)	0.14
Risk Factors n (%)					
Smoking		11 (55)	10 (50)	1 (5)	0.0012
Hypertension		6 (30)	7 (35)	0	0.0006
Diabetes		2 (10)	9 (45)	0	0.0006
Dyslipidemia		2 (10)	10 (50)	0	0.0002
Family history		1 (5)	2 (10)	0	0.31
CIMT[#] (mm)		0.66 (0.16)	0.70 (0.06)	0.50 (0.00)	p=0.0005[1,3] and p=0.0001[2,3]
PWV[#] (m/s)		4.1 (1.1)	4.6 (1.0)	3.6 (0.6)	0.12
Laboratory	***Normal values***				
Haemoglobin[#] (g/dl)	*(14.3-18.3g/dl)*	12.9 (2.6)	15.0 (1.7)	11.4 (2.1)	p=0.0086[1,2] and p<0.0001[2,3]
Creatinine[*] (µmol/l)	*(64-104umol/l)*	74 (65-90)	86 (75-99)	63 (48-71)	p=0.017[1,2] and 0.0003[1,3]
Total cholesterol[#] mean (mmol/l)	*(<4.5mmol/l)*	4.0 (0.9)	5.2 (1.2)	3.1 (0.8)	p=0.019[1,3] and 0.0011[2,3]
Triglycerides[*] (mmol/l)	*(<1.7mmol/l)*	1.2 (0.95-1.45)	1.3 (0.95-1.95)	1.2 (0.90-1.40)	p=0.27
HDL[#] (mmol/l)	*(>1.0mmol/l male >1.3mmol/l female)*	1.05 (0.29)	1.03 (0.24)	0.94 (0.27)	p=0.44
LDL[#] (mmol/l)	*(<2.5mmol/l)*	2.3 (0.7)	3.5 (1.0)	1.6 (0.6)	p=0.028[1,3] and <0.0001[2,3]
CD4[*] (cells/mm^3)	*(cells/mm^3)*	301 (205-417)	N/A	143 (19-198)	p=0.0020

Key: [#]mean ± SD , *median (IQR)

(CIMT= carotid intima media thickness, PWV= pulse wave velocity, LDL= low density lipoprotein, HDL= high density lipoprotein, CD4= cluster of differentiation, ns= not significant)

Table 3: Endothelial biomarkers

There were significant differences in the following endothelial biomarkers; VCAM-1, ICAM-1 IL6 and E-selectin. The median VCAM-1 levels in HIV positive patients with and without ACS were significantly higher than the HIV-/ACS cohort. However, median ICAM-1 levels were significantly higher in HIV positive patients without ACS than the HIV+/ACS and the HIV-/ACS cohorts. The HIV+/no ACS group had significantly lower median levels of IL6 than the both the HIV+/ACS and the HIV-/ACS groups. The median E-Selectin levels in HIV+/ACS patients and the HIV-/ACS patients were significantly lower than that of the HIV+/no ACS group. There was no significant difference in median IL1 β, IL1ra, MCP-1, TNFα, P-selectin and PAI-1 levels between the groups.

(VCAM-1=vascular cellular adhesion molecule 1, ICAM-1= intercellular adhesion molecule 1, IL=interleukin, MCP-1= monocyte chemotactic protein 1, TNFα= tumour necrosis factor alpha, PAI-1: plasminogen activator inhibitor 1)

median levels (interquartile ranges)	**HIV+/ACS[1]**	**HIV-/ACS[2]**	**HIV+/no ACS[3]**	***P value for H0: no between-group differences***	***P value for post-hoc group differences***
VCAM-1 *(ng/ml)*	402 (292-609)	287 (257-412)	503 (292-822)	*0.025*	*$p=0.033^{1,2}$ and $0.024^{2,3}$*
ICAM-1 *(ng/ml)*	172 (135-211)	167 (129-193)	225 (199-293)	*0.0009*	*$p=0.0079^{1,3}$ and $0.0010^{2,3}$*
IL6 *(pg/ml)*	5.9 (3.9-12.4)	10.7 (4.8-50)	3.8 (1.9-5.3)	*0.0053*	*$p=0.033^{1,3}$ and $0.0050^{2,3}$*
E-selectin *(ng/ml)*	24.3 (19.1-30.6)	27.8 (21.5-42.2)	47.1 (31.8-65.8)	*0.0005*	*$p=0.0007^{1,2}$ and $0.012^{2,3}$*
IL1β *(pg/ml)*	0.36 (0.27-0.48)	0.32 (0.28-0.41)	0.38 (0.30-0.51)	*0.29*	
IL1ra *(pg/ml)*	224 (173-266)	215 (120-258)	181 (125-258)	*0.75*	
MCP-1 *(pg/ml)*	26.5 (15.0-41.2)	22.4 (18.0-33.3)	22.4 (16.5-27.4)	*0.70*	
TNFα *(pg/ml)*	2.5 (1.4-4.4)	2.0 (1.6-4.4)	2.5 (2.0-4.8)	*0.60*	
P-selectin *(ng/ml)*	25.8 (20.3-32.9)	20.8 (19.3-24.6)	23.5 (19.6-29.7)	*0.12*	
PAI-1 *(ng/ml)*	67.6 (36.7-149.8)	85.6 (34.7-138.4)	66.2 (35.6-91.7)	*0.59*	

Table 3
Long adverse events other than death, myocardial infarction and stent thrombosis.

	Overall (n = 206)	Known cardiac death or myocardial infarction or definite stent thrombosis (n = 28; 13%)	Survival free from cardiac death, ami or definite ST (n = 178;87%)	p
Death	30 (14.7)	-	-	
Cardiac death:		-	-	
–non sudden	11 (5.4)			
–sudden	1 (0.5)			
HIV-related death	6 (2.9)	0 (0)	6 (9.2)	0.16
Myocardial infarction	20 (9.8)	-	-	
–only one	16 (7.8)			
–two	4 (2)			
HIV-related death	6 (2.9)	0 (0)	6 (9.2)	0.16
Revascularization:				<0.001
-verall	29 (14.2)	12 (43)	17 (9.8)	
-TVR*	20 (9.8)	5 (22)	15 (8)	
-TLR*	19 (9.3)	9 (38)	10 (7.2)	
Stroke	2 (1)	1 (4.2)	1 (0.6)	0.24
Stent thrombosis				
-definite	7 (3.4)			
–possible	1 (0.5)			

Results

10,050 patients with ACS were screened, and among them a total of 201 (2.0%) fulfilled the inclusion criteria (see Fig. 1). 179 (89%) were men, with median age of 53 (47-62) years (Table 1). Traditional CV risk factors were highly prevalent, with 98 patients (48%) reporting hypertension, and 36 patients (18%) diabetes mellitus. HAART was started 1.4 ± 1.0 years before the ACS current T CD4+ cell count was 651 ± 510 cells/mm^3, with 17% of patients not being fully suppressed that is with a high viral load. STEMI was the most frequent admission diagnosis (71 [35%]), with a high prevalence of left main or multivessel disease (101 [49%]). Percutaneous revascularization was chosen in 154 (76%) of them, and 91 (45%) received a drug-eluting stent (Table 2). After a median of 24 (10–41) months, 30 (15%) patients died, 12 (6%) for cardiac reasons, and 6 (3%) for non cardiac-related causes. MI occurred in 20 (10%), revascularization in 29 (14%), and definite stent thrombosis in 7 (3%) (Table 3).

Patients dying or experiencing myocardial infarction more frequently had chronic renal failure (7 [25%] versus 11 [6%], p = 0.005), and prior coronary revascularization (13 [46%] versus 38 [22%], p = 0.049), than those without such events. Moreover, their T CD4+ cell counts were more commonly below 200 cells/mm^3 (6 [25%] versus 12 [10%], p = 0.04). Multivessel/left main disease (20 [71%] versus 81 [47%], p = 0.013), and LVSD were also more prevalent in these subjects (8 [28%] versus 20 [12%], p = 0.023) (Tables 1-3).

Notably, patients with CD4+ counts < 200 cells/mm^3 did not differ significantly in their CV risk factor profile, but showed a longer time on HAART (1.3 ± 1.7 years vs 0.5 ± 0.6 years, p = 0.007) and were treated less frequently with NRTI-containing regimens (12 [67%] versus 23 [88%], p = 0.03). After admission, these patients underwent a non-invasive strategy more often (7 [39%] versus 19 [12%], p = 0.010); had higher rates of in-hospital major bleeds (2 [13%] versus 7 [2%], p = 0.034) and were discharged less frequently on dual antiplatelet therapy (10 [53%] versus 148 [88%], p < 0.001) and statins (11 [64%] versus 142 [89%]; p = 0.002) (Web Only Tables A and B). At follow-up, these patients also experienced higher rates of cardiac death (2 [12%] versus 10 [6%], p = 0.024) and MI (7 [31%] versus 13 [9%], p = 0.024) (Table 4).

Patients managed in the USA (Web Only Tables C and D, and Table 5) showed a similar CV risk profile, a longer duration of HIV (time from diagnosis 8.7 ± 4.8 vs 3.4 ± 3.6; p = 0.006) with lower CD4 cell count (492 ± 349 vs 728 ± 557; p = 0.008), higher rates of surgical revascularization during the index admission and fewer revascularizations during follow-up than subjects managed in Europe.

Other than LVSD (hazard ratio = 6.4 [95% confidence interval [CI]: 1.6-26: p = 0.009), the only other independent predictor of cardiac death was not being treated with NRTIs (hazard ratio = 9.9 [95% CI: 2.1-46: p = 0.03), whereas T CD4+ count below 200 cells/mm^3 (hazard ratio = 5.9 [95% CI: 1.4-25: p = 0.016) was the only predictor of

Table 4
Cox multivariate analysis for cardiac death.

	HR	LCI	UCI	P
Ejection fraction less than 35%	6.4	1.6	26	**0.009**
CD4+ count less than 200 cells/ mm^3	1.4	0.3	8.3	0.69
Nucleoside-reverse transcriptase inhibitors sparing	9.9	2.1	46	**0.003**
Chronic renal failure	11.47	1.3	54	0.025
USA recruitment center	2.8	0.4	6.7	0.45

HR; Hazard Ratio. LCI; Lower Confidence Interval; UCI; Upper Confidence Interval.

Table 5
Cox multivariate analysis for myocardial infarction.

	HR	LCI	UCI	P
Ejection fraction less than 35%	0.13	0.7	24	0.73
CD4+ count less than 200 cells/ mm^3	5.9	1.4	25	**0.016**
Absence of therapy with nucleoside-reverse transcriptase inhibitors	2.6	0.5	13.5	0.22
Chronic renal failure	1.6	0.4	6.9	0.47
USA recruitment center	1.06	0.2	5.2	0.94

HR; Hazard Ratio. LCI; Lower Confidence Interval; UCI; Upper Confidence Interval

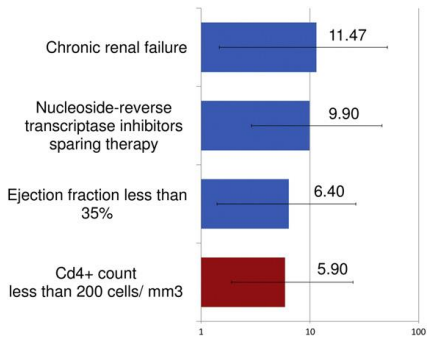

Fig. 2. Independent predictors of cardiac death (blue) and of myocardial infarction (red).

Table 6
Cox multivariate analysis for non cardiac death.

	HR	LCI	UCI	P
Ejection fraction less than 35%	**3.4**	**0.9**	**4.5**	**0.56**
CD4+ count less than 200 cells/ mm^3	**1.3**	**0.3**	**3.2**	**0.45**
Nucleoside-reverse transcriptase inhibitors sparing	**4.3**	**0.9**	**6.5**	**0.76**
Chronic renal failure	**1.4**	**0.6**	**3.2**	**0.35**
USA recruitment center	**1.7**	**0.8**	**3.4**	**0.33**

MI (Tables 4 and 5; Fig. 2). After adjusting for different interventions and pharmacological choices, a low T CD4+ cell count remained an independent negative prognostic factor of subsequent MI (hazard ratio = 4.29 [95% CI: 1.4-17: p = 0.012) (Table 6, Figs. 3, 4 and web only appendix Table E). **When including also revascularization, no independent predictors were found, as for non-cardiac death** (Tables 6 and 7).

Discussion

To the best of our knowledge, this is the largest study with HIV-positive patients presenting with ACS in the contemporary era.

The main findings are: a) this population presents with a high prevalence of high-.risk clinical features and of subsequent thrombotic events; b) CD4 cell count <200 cells/mm^3 and not being treated with NRTI represents a powerful predictor of cardiac prognosis.

HIV patients are exposed to higher rates of recurrence of ischemic events, particularly if presenting with a reduced T CD4+ cell count. A close relationship between HIV and atherosclerotic disease represents a largely investigated yet not completely clarified topic, with three concurrent etiological causes; traditional risk factors, HIV infections itself and antiretroviral drugs.

Concerning the risk profile, our patients, compared to those of the GRACE investigators [31,32], despite their significantly younger age, presented with a relevant prevalence of CV risk factors. Data about prevalence of hypertension are conflicting [33–36], showing traditional relationship with dyslipidemia and with initial kidney disease [37], but with an unclear causal association with HAART; on the contrary high rates of smoking habit [34] and of uncontrolled lipid levels [38–41] have often been reported, the latter being mainly related to exposure to antiretroviral drugs. The same critical interactions between chronic immune-activation and drugs play a crucial role in the development of diabetes mellitus [42]; since this data was confirmed in a relevant percentage of our patients we highlight the need for an accurate preventive control of these modifiable factors.

HIV infection seems to play a crucial role to the development of atherosclerosis. In non HIV-infected animals and men, CD4+ cells were demonstrated to modulate inflammation and consequently atherosclerosis, an equilibrium that is shattered in HIV, with inflammatory process and opportunistic infections leading to increased cytokine expression and vascular damage [43,44]. HIV-RNA levels and degree of T CD4 count were partially demonstrated to correlate with CV events in a setting of primary prevention [43–46], and, more recently, in the SMART trial [47]. This randomized controlled trial showed that individuals randomized to structured interruptions of antiretroviral therapy guided by the CD4+ T-cell count had replicative HIV and reduced CD4+ T cell count, increasing risk of major CVD events as compared with those randomized to continuous therapy. Moreover, in patients with poor immune response to HAART a high intestinal microbial translocation was found [47] supporting a potential higher degree of chronic inflammation and risk of atherogenesis. Finally, some imaging studies have shown that HIV-positive patients, especially those with reduced immunity, present with a more important burden of non-calcified plaque [48], that is prone to rupture.

For the first time, our registry demonstrated the prognostic role of a reduced CD4 cell count after ACS. Patients with CD4 cell count less than 200 cells/mm^3 are burdened with a 30% rate of MI at follow up; this appears to be three-times that of patients with higher level of T CD4+ cells and in HIV negative patients (at 5 year follow up [31] in the Grace registry). Moreover, rates of stent thrombosis were high in all HIV patients (3.4% definite St compared to 1.5% reported in a recent meta-analysis [49] at similar follow-up) and particularly elevated (6%) in individuals with reduced CD4 cells count (200 cells/mm^3). **Finally, CD4 cell count did not relate to risk on subsequent revascularization, but only myocardial infarction. As previously stated, from one side myocardial infarction may be relate to abrupt plaque rupture, in a context of deregulated autoimmunity, while in the other revascularization relate to progression of coronary plaque, mainly due to common cardiovascular risk factors.**

The role of antiretroviral therapy in the reduction of CV events is still debated. Evidence extrapolated from large observational registries have shown that some drug classes, especially protease inhibitors, may enhance the risk of MI [50], while the previously cited SMART tria [47] showed a positive effect of HAART treatment on CV events. Recently, moreover, no relationship have been described with development of

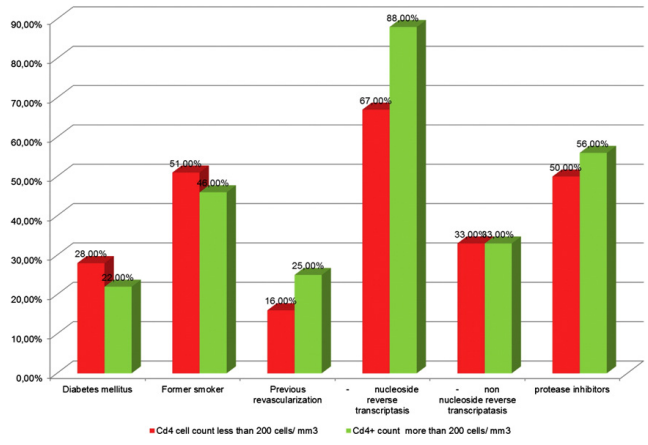

Fig. 3. Main baseline features according to number of CD4 cell count (p 0.03 for nucleoside reverse transciptasis).

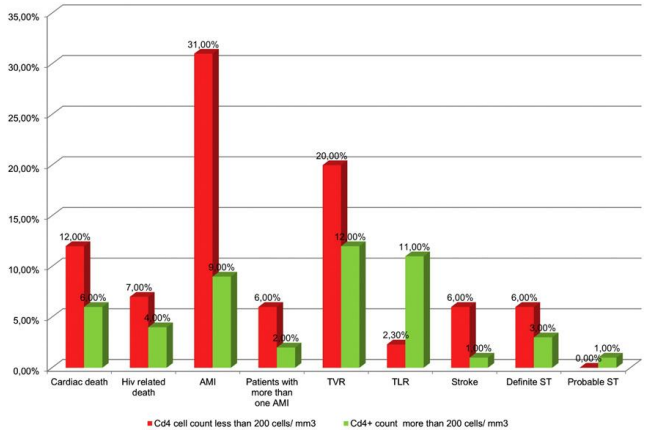

Fig. 4. Outcomes according to number of CD4 cell count (p 0.024 for cardiac death and p 0.024 for myocardial infarction.

heart failure [51]The possible increased risk of developing hyperlipidemia and other risk factors in a setting of secondary prevention like the present registry may increase risk related to lack of control of inflammation. Another potential explanation may relate to section bias; use of NRTIs-sparing regimens is increasing and is generally associated with a longer and more complicated history of HIV infection and treatment, leading to exhaustion of options within the class due to resistance or toxicity, like lipodistrophy, osteoporosis, or renal failure Therefore, NRTI-sparing regimens could identify more fragile patients with an increased risk of CV diseases. Interestingly, in our patients, years from diagnosis were similar (3.46 ± 4.3 vs. 3.9 ± 4.05), and, although kidney disease in NRTIs sparing patients was more frequent (18% vs 9% of those taking NRTIs): at multivariate analysis absence ofNRTI was confirmed to independently predict adverse events However, other possible confounding factors associated with intake of NRTI-free regimens cannot be ruled out.

A high risk of recurrent thrombotic events may have a profound impact in the management of HIV-positive patients presenting with ACS, both in Western Countries and in Africa. Patients with HIV should be closely followed up in order to reduce the burden of traditional risk factors, while randomized controlled trials addressing the use of aspirin and of statin therapy as primary prevention are needed to clarify their potential role in this setting. Furthermore, HIV patients presenting in intensive care units with ACS deserve the evaluation of new antiplatelet drugs reducing thrombotic activation, with a tailored length of double antiaggregant therapy [52] together with a choice of the most appropriate revascularization strategy (including coronary stents with the lotwest risk of subsequent thrombosis) [53]. Finally, HIV-positive patients should be managed jointly by cardiologists and infectious disease specialists, in order to accurately stratify their cardiovascular risk and to avoid under treatment of potential fatal cardiac complications. We advocate the need for long-term management in centers with dedicated specialists (such as Heart Infectious Disease team). Another crucial point is the extent and impact of ACS in limited-resource countries; while the burden of CV disease is still limited, the ongoing rapid urbanization and "westernization" of many African societies may rapidly change this scenario and the prevalence of traditional risk factors.

The main limitation of this registry consists of its observational nature, leading to potential adjudication bias. Moreover the long time of recruitment, and the lack of controls with other chronic infection like hepatitis B and C may represent other limitations. On the contrary, the close collaboration between cardiologists and infectious disease specialists offers accurate and reproducible results.

In conclusion, HIV patients presenting with ACS are at a higher risk of subsequent thrombotic events if they have markedly reduced CD4+ counts and if not treated with NRTI therapy, suggesting that the stage of HIV disease may contribute to cardiovascular instability.

Table 7
Cox multivariate analysis for MACE.

	HR	LCI	UCI	P
Ejection fraction less than 35%	**1.45**	**0.6**	**3.9**	**0.46**
CD4+ count less than 200 cells/ mm^3	**4.3**	**1.3**	**5.7**	**0.26**
Absence of therapy with nucleoside-reverse transcriptase inhibitors	**1.5**	**0.3**	**4.7**	**0.24**
Chronic renal failure	**0.64**	**0.32**	**4.6**	**0.33**
USA recruitment center	**1.45**	**0.34**	**3.2**	**0.35**

HR; Hazard Ratio. LCI; Lower Confidence Interval; UCI; Upper Confidence Interval.

Disclosures

None.

Conflict of Interests

None.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2014.05.037.

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FIGURES

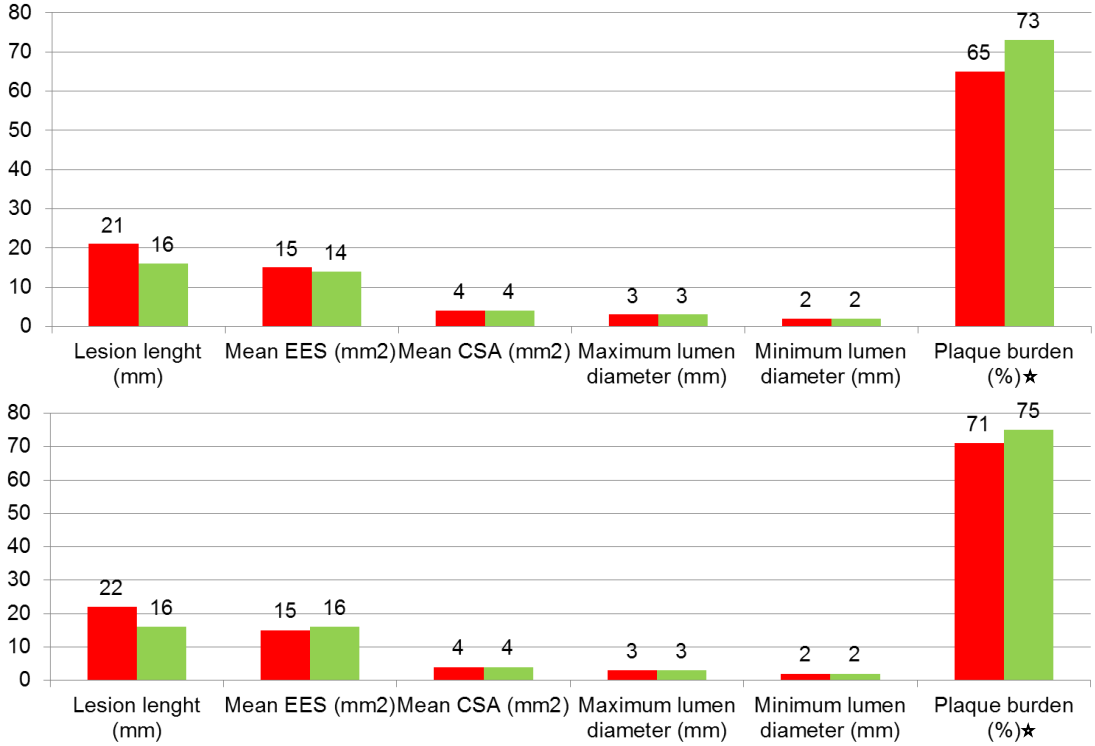

Figure 1: Volumetric analysis before (above) and after (below) propensity score matching between HIV (red) and non HIV (green) patients.

★ p<0.05

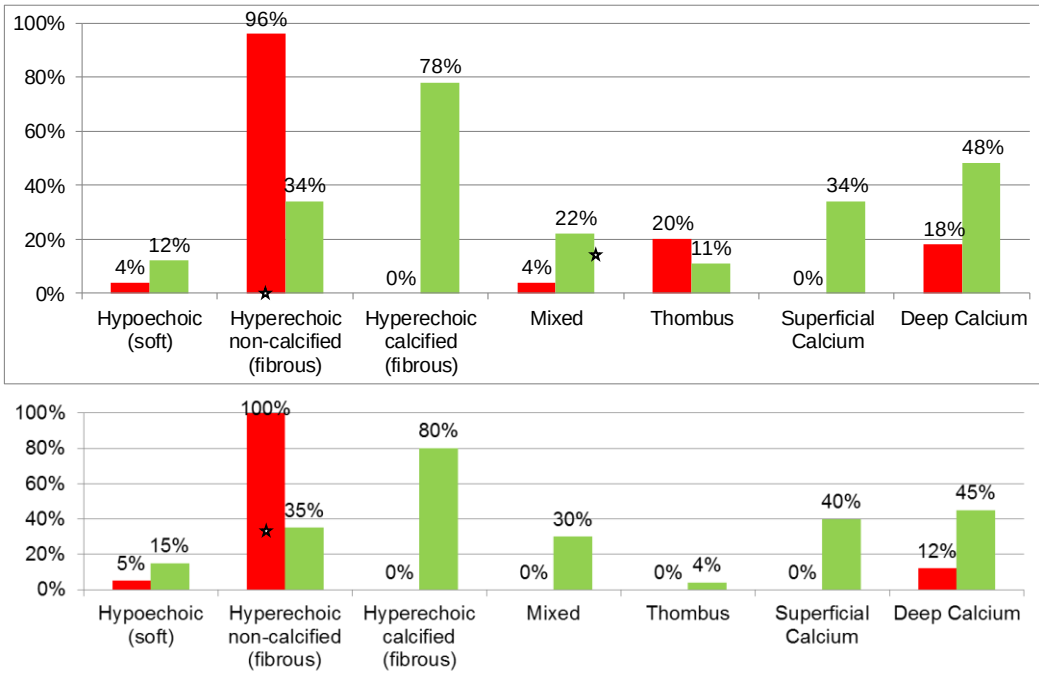

Figure 2: Morphological analysis before (above) and after (below) propensity score matching between HIV (red) and non HIV (green).

⋆p<0.05

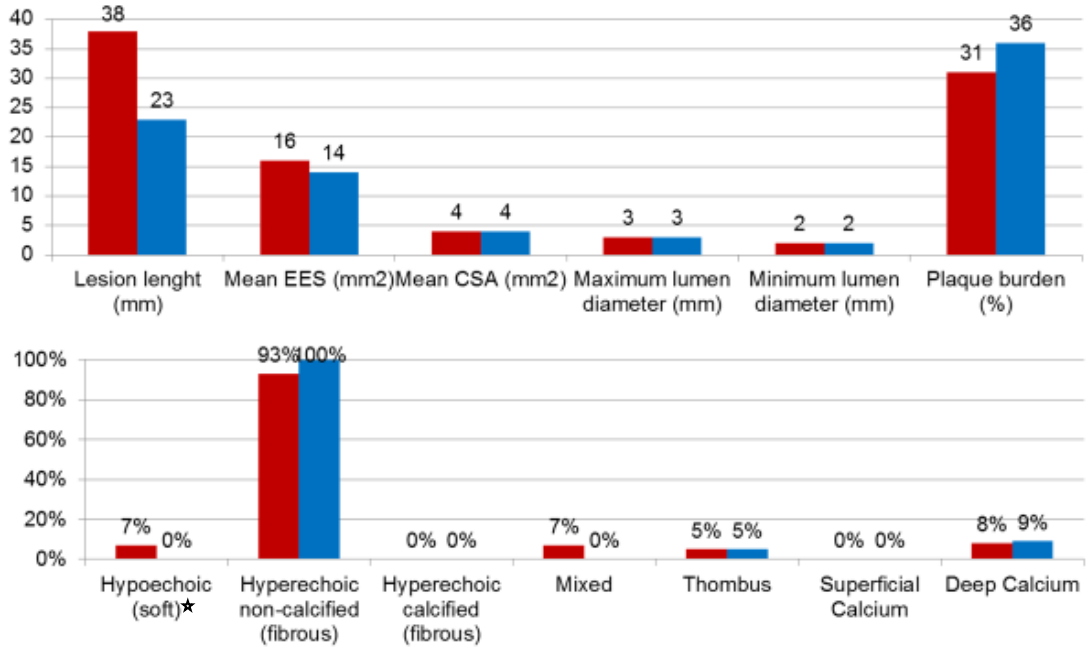

Figure 3: Volumetric (above) and morphological (below) examination between HIV patients with Cd4 cell count less than 200 cells/mm^3 (red) and more than 200 cells/mm^3 (blue).

⋆P<0.05.