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

Ahmed Vachiat



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

DECLARATION

I, Ahmed Vachiat declare that this thesis is my own work. It is being submitted for the Degree of Doctor in Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

Ahmed Vachiat May 2019

I certify that the studies contained in this thesis have the approval of the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg.

Human Research Ethics Committee protocol number: **M111143**

_____

Ahmed Vachiat (Candidate) May 2019

_____

Pravin Manga (Supervisor) May 2019

DEDICATION

To the Almighty who has given me the ability to help others

To my parents, Ismail and Rashida, for investing in the best gift, Education

To my wife, Fatima and children Mohammed, Taskeen and Zahraa for their time, support and love

To my extended family for their support

To Prof Manga and his family

To all my teachers

PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

1) **Africa PCR** 14th March 2014. Oral presentation
   HIV and coronary artery disease

2) **South African Heart Association** 19th October 2014. Oral presentation
   Clinical Characteristics of HIV-positive patients presenting with acute coronary syndromes

3) **South African Heart Association** 25th -28th October 2015. Poster presentation
   Intracoronary lytic in STEMI

4) **South African Heart Association** 9th-12th November 2017. Poster presentation
   Atherosclerotic plaque in HIV-positive patients presenting with acute coronary syndromes

PUBLICATIONS ARISING FROM THIS RESEARCH PROJECT

1) **HIV and Ischemic Heart Disease**

   ***Ahmed Vachiat**, Keir McCutcheon, Nqoba Tsabedze, Don Zachariah, Pravin Manga.*
   ***JACC**. Vol 69. No.1 2017*

2) **New face of Cardiac emergencies Human Immunodeficiency Virus-Related cardiac Disease**

   *Nqoba Tsabedze, **Ahmed Vachiat**, Don Zachariah, Pravin Manga*
   ***Cardiol Clin**. 2018 Feb;36(1):161-170.*

3) **Atherosclerotic plaque in HIV-positive patients presenting with acute coronary syndromes**

   ***Ahmed Vachiat**, Keir McCutcheon, Nqoba Tsabedze, Don Zachariah, Pravin Manga*
   *(Accepted **Cardiovascular Journal of Africa**)*

4) **Endothelial dysfunction in HIV patients presenting with acute coronary syndromes**

   ***Ahmed Vachiat**, Therese Dix-Peek, Raquel Duarte, Pravin Manga*
   *(Accepted **Cardiovascular Journal of Africa**)*

5) **Prognostic indicators for recurrent thrombotic events in HIV-infected Patients with acute coronary syndromes: Use of registry data from 12 sites in Europe, South Africa and the United States.**

   *Fabrizio D'Ascenzo , Enrico Cerrato, Darryn Appleton, Moretti C, Calcagno A, Abouzaki N, Vetrovec G, Lhermusier T, Carrie D, Das Neves B, Escaned J, Casese S, Kastrati A, Chinaglia A, Belli R, Capodanno D, Tamburino C, Santilli F, Parodi G, **Vachiat A**, Manga P, Vignali L, Mancone M, Sardella G, Fedele F, DiNicolantonio JJ, Omede P, Bonora S, Gaita F, Abbate A, Zocczai GB; Percutaneous coronary intervention and surgical revascularization in HIV Database (PHD) Study Investigators.et al.*
   ***Thrombosis Research** 134 (2014) 558-564*

6) **Evaluation *of Coronary featUres of HIV patients pREsenting with ACS : the CUORE a multicenter study***

Mattia Peyracchia MD, Giulia De Lio MD, Chiara Montrucchio MD, Pierluigi Omedè MD, Gabriella d'Ettore MD, Andrea Calcagno MD, Vincenzo Vullo Prof, Enrico Cerrato MD, Mauro Pennacchi MD, Gennaro Sardella Prof, Pravin Manga Prof, Walter GrossoMarra MD, Francesco Vullo MD, Francesco Fedele Prof, Giuseppe Biondi Zoccai MD MStat, Claudio Moretti MD, ***Ahmed Vachiat MD****, Stefano Bonora Prof and Massimo Mancone MD PhD and Fabrizio D'Ascenzo MD.*

Atherosclerosis *2018 Jul; 274:218-226*

7) Clinical Characteristics of HIV-positive patients presenting with acute coronary syndromes

Ahmed Vachiat*, Pravin Manga, Keir McCutcheon et al. SAHJ Vol 11, No 4 (2014): SA Heart Journal Spring 2014. pg. 205 (Abstract)*

8) Atherosclerotic plaque in HIV-positive patients presenting with acute coronary syndromes

Ahmed Vachiat*, Pravin Manga. SAHJ Vol 14, No 4 (2017): SA Heart Journal Spring 2017. pg. 251 (Abstract)*

ABSTRACT

Background

There are approximately 37 million HIV-positive patients worldwide, of whom 70% live in sub-Saharan Africa. Data from developed nations suggest that acute coronary syndromes (ACS) in HIV-positive patients are more prevalent in younger patients who have a high coronary risk factor profile. In developing countries data about HIV and coronary artery disease is very sparse. Furthermore, it is unclear whether the severity and characteristics of atherosclerosis in symptomatic HIV-positive patients is similar to that found in HIV-negative patients.

Methods

A prospective study of all HIV-positive patients with ACS presenting to a large public hospital in Johannesburg, South Africa, was performed over 3 years (July 2012- July 2015). Firstly, intravascular ultrasound and virtual histology was used to perform a detailed analysis of the plaque characteristics and burden of atherosclerotic disease in the culprit and non-culprit arteries in this group (HIV+/ACS) of patients. Secondly, in this cohort, surrogate markers of atherosclerosis such as carotid intima media thickness (CIMT), brachial flow mediated dilatation (FMD), pulse wave velocity (PWV) and endothelial biomarkers were also measured. The latter group of measurements were then compared with two groups of 20 patients each, namely HIV-negative patients presenting with ACS (HIV-/ACS) and HIV-positive patients presenting without ACS (HIV+/no ACS).

Results

The mean ages of the patients were 51.1 (sd=8.1) years, 52.3 (sd=9.0) years, 36.0 (sd=6.8) years in the HIV+/ACS, HIV-/ACS and HIV+/no ACS groups, respectively ($p<0.0001$). In the HIV+/ACS cohort, the predominant manifestation of ACS was ST-segment elevation

myocardial infarction (75%), followed by non ST-segment elevation myocardial infarction (15%) and 10% presented with unstable angina. Risk factors included smoking in 11 (55%), hypertension in 6 (30%), diabetes in 2/20 (10%), dyslipidaemia in 2 patients (10%) and 1 (5%) patient had a family history of ischaemic heart disease. The left anterior descending artery was the most common artery involved (60%).

The total plaque burden in the HIV+/ACS cohort consisted of moderate plaque in 60% of patients, followed by mild plaque in 35% and severe plaque in 5% of cases. The total plaque burden was significantly higher in the proximal than in the mid portion of coronary artery ($p=0.010$). Furthermore, it was significantly higher in the mid than in the distal part of the coronary artery ($p=0.0006$). The predominant plaque morphology in the entire coronary vasculature consisted of fibrous plaque (55.4%). Fibro-fatty plaques were found in 26.6% of patients, while necrotic core plaques were present in 13.3% and dense calcific plaques were present in only 4.7%. In the culprit coronary arteries, the major plaque morphology remained fibrous plaques (56.5%), whilst fibro-fatty (21.2%), necrotic core (14.4%) and dense calcific (3.6%) plaques constituted the remainder.

There was no difference in the mean CIMT of the two groups of patients with ACS. The CIMT in the group without ACS (0.50; sd=0.08 mm) was marginally but significantly lower than the CIMT of both the HIV+/ACS group (0.66; sd=0.16 mm) and the HIV-/ACS group (0.70; sd=0.06 mm), ($p=0.0005$ and $p<0.0001$, respectively). There was no evidence of arterial stiffness as measured by pulse wave velocity in all 3 groups; 4.1 (sd=1.1) m/s, 4.6 (sd=1.1) m/s and 3.9 (sd=1.1) m/s, respectively ($p=0.12$).

Endothelial dysfunction as assessed by FMD was similar in the HIV+/ACS and the HIV-/ACS patients. The HIV+/ACS patients did, however, have fewer coronary risk factors (hypertension, diabetes, dyslipidaemia) compared to the HIV-/ACS patients. Vascular cell adhesion molecule-1 (VCAM-1) levels in the two HIV-positive cohorts were significantly

higher than the HIV-negative cohort. There were no significant differences in the levels of IL1 β, IL1ra, MCP-1, TNFα, P-selectin and PAI-1 between the three cohorts.

Conclusion

Atherosclerotic plaque in HIV-positive patients presenting with ACS is predominantly comprised of non-calcified fibrous and fibrofatty plaque. In addition, these patients have a high degree of atherosclerotic plaque burden. Surprisingly, HIV-positive patients had low carotid intima media thickness and there was no significant arterial stiffness as measured by PWV. Non-invasive investigations like FMD, CIMT and PWV did not identify patients with HIV who are at high risk of ACS. The endothelial biomarker, VCAM-1 may be a useful biomarker to identify HIV patients who have endothelial dysfunction and have increased risk of ACS.

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ABBREVIATIONS

ACS:	Acute coronary syndromes
CIMT:	Carotid intima media thickness
CD4:	Cluster of differentiation 4
cART:	Combination anti-retroviral therapy
CABG:	Coronary artery bypass graft
CAD:	Coronary artery disease
DC:	Dense calcium
DBP:	Diastolic blood pressure
FF:	Fibro fatty plaque
FI:	Fibrous plaque
FMD:	Flow mediated dilatation
HDL:	High density lipoprotein
HIV:	Human immunodeficiency virus
ICAM-1:	Intercellular adhesion molecule-1
IL:	Interleukin
IVUS:	Intravascular ultrasound
LAD:	Left anterior descending coronary artery
LCx:	Left circumflex coronary artery
LDL:	Low density lipoprotein
MCP-1:	Macrophage chemoattractant protein-1
MI:	Myocardial infarction
NC:	Necrotic core
NSTEMI:	Non-ST segment myocardial infarction
NRTI:	Nucleoside reverse transcription inhibitor
PAI-1:	Plasminogen activation factor-1
PCI:	Percutaneous intervention
PWV:	Pulse wave velocity
RCA:	Right coronary artery
STEMI:	ST-segment elevation myocardial infarction
SBP:	Systolic blood pressure
TNT:	Glyceryl trinitrate
TNFα:	Tumour necrosis factor alpha
UA:	Unstable angina
VCAM-1:	Vascular cellular adhesion molecule-1
VH:	Virtual histology

CHAPTER 1 : LITERATURE REVIEW

1.1 Introduction

Human immunodeficiency virus (HIV) is a global problem with an estimated 37 million individuals living with the disease, of whom 70% live in sub-Saharan Africa (World Health Organisation, UNAIDS, 2015b). The association of HIV infection and coronary artery disease (CAD) is well recognized. Increased life expectancy globally as a result of better access to combination anti-retroviral therapy (cART) and high levels of traditional cardiovascular (CV) risk factors has increased the prevalence of CAD in this population (Gill J et al., 2010, Lang et al., 2015a). As a result there is concern about the impact of the rising prevalence of CAD on morbidity and mortality as well its effect on health systems around the world (Vachiat et al., 2017).

HIV may also cause non-ischaemic heart disease. HIV affects the heart structure and function by various mechanisms such as induction of inflammatory or abnormal immune responses, direct invasion of the myocardial cells, increased susceptibility to opportunistic infections and effects of cART. This can lead to HIV-associated cardiomyopathy, pulmonary hypertension, aortopathy, pericardial disease or conduction disease (Figure 1.1). However, non-ischaemic heart disease will not be further addressed in this thesis.

The focus of this thesis is on HIV and CAD (Figure 1.2). The burden of HIV disease is evident in that sub-Saharan Africa, while having over 10% of the world's population, accounts for more than two-thirds of those infected with HIV. The prevalence of HIV infection exceeds 10% in nine countries in Southern Africa. With an estimated 5.6 million HIV-positive population, South Africa continues to have the world's largest HIV epidemic (UNAIDS, 2010).

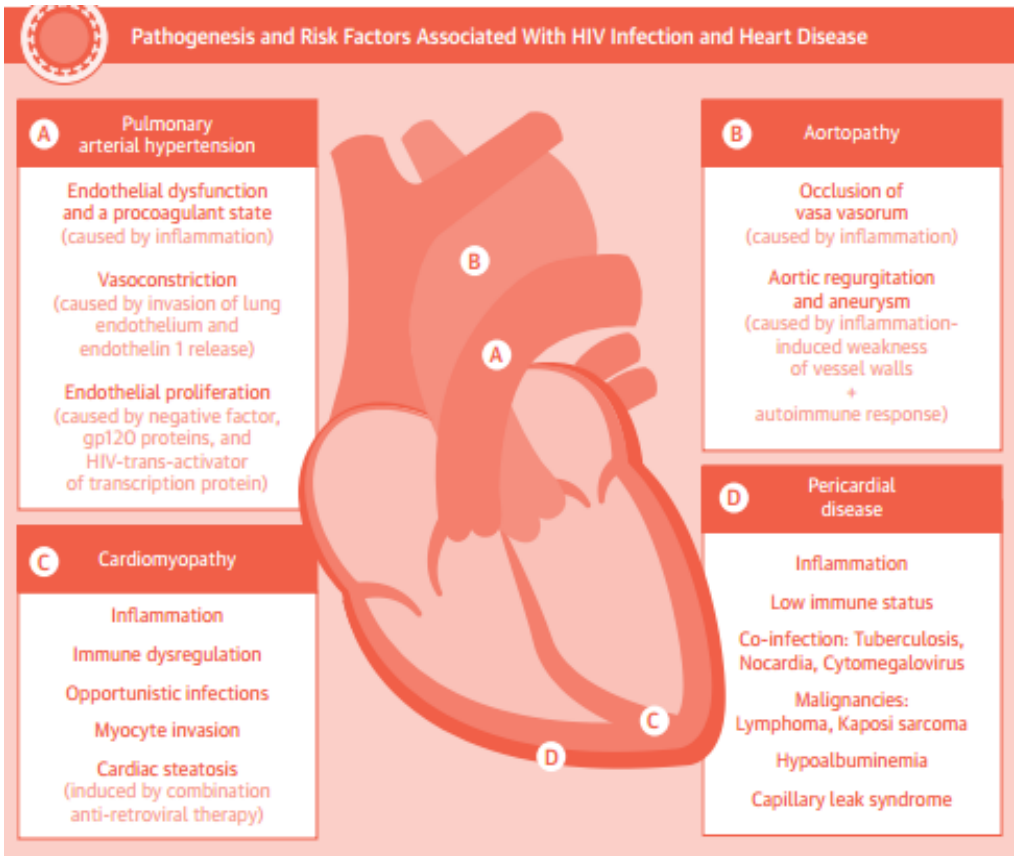


Figure 1.1 : Pathogenesis of HIV and Non-ischaemic Heart Disease (Manga et al., 2017)

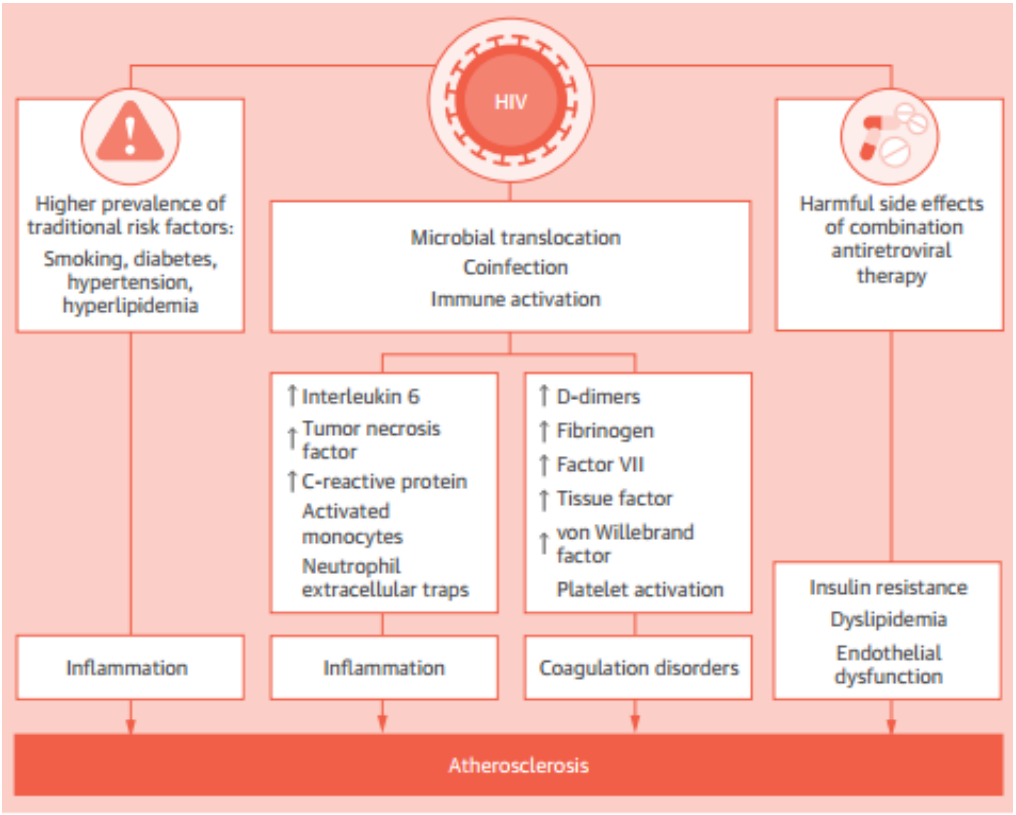


Figure 1.2: Pathogenesis of HIV and coronary artery disease (Vachiat et al., 2017)

South Africa, as in many other developing countries, is in a health transition to a rise in non-communicable diseases such as CAD (Mayosi et al., 2009). The CV burden is accentuated by hypertension and emergence of obesity and diabetes.

Developed nations have considerable data on CAD in HIV-positive patients. There is a noticeable disparity on the prevalence of CAD between developed and developing nations. Developed countries generally have an older HIV-positive population with a higher CV risk profile compared to a younger HIV-positive population in the developing world with a lower CV risk profile (Becker et al., 2010). There have been very few reviews of literature addressing CAD in HIV-positive patients in Africa (Ntsekhe and Hakim, 2005). Despite regional differences in CAD burden, HIV and CAD cause great morbidity and mortality globally (Gill J et al., 2010).

HIV infection accelerates atherosclerosis by a factor of 1.5-2.0 (Triant et al., 2007). However, the mechanisms are poorly understood. The proposed mechanisms include dyslipidaemia, endothelial dysfunction, inflammation, immune activation and hypercoagulability. HIV has been shown to initiate an inflammatory response in the coronary circulation, inducing endothelial dysfunction and promoting atherosclerosis (Boccara et al., 2013). In HIV-negative patients with atherosclerosis the vascular characteristics such as coronary plaque composition, endothelial dysfunction and intimal thickening are well described. However, in HIV-infected populations these are not described at all, or are poorly defined. For example, coronary plaque characteristics are unknown in HIV-positive patients with established CAD. There is data with regards to endothelial function (Cotter, 2006) but the role of endothelial function in patients with known CAD in HIV-infected groups is also largely unknown.

1.2 Epidemiology of Ischaemic Heart Disease and HIV

HIV/AIDS is a global problem with sub-Saharan Africa having the greatest burden of disease with 25.8 million infected individuals (World Health Organisation). The prevalence is also high in Asia and the Pacific region with 5 million HIV-infected people. Latin America has 1.7 million people infected, while Western Europe and North America have a total of 2.4 million who are HIV-positive (UNAIDS, 2015a). As HIV has become a medically controllable chronic disease, (Zanni et al., 2014) there has been a rise in the incidence of non-communicable diseases in this population, especially CAD (Reinsch et al., 2012). This trend is currently noted in high income countries and is expected to emerge in developing nations where cART coverage is increasing (Zanni et al., 2014). It is predicted that HIV-associated CAD will contribute to global morbidity and mortality burden by the year 2030 (Mathers and Loncar, 2006). As the prevalence of CAD rises in the HIV patients, it is anticipated that it will strain the already burdened health systems worldwide especially in sub-Saharan Africa (Mathers and Loncar, 2006).

There are several observational studies (Table 1.1 and 1.2) investigating HIV and CAD. A large data registry from two tertiary care hospitals in the USA compared myocardial infarction (MI) events and cardiovascular risk factors between 3851 HIV-positive and 1044589 HIV-negative patients between 1996 and 2004 (Triant et al., 2007). Myocardial infarction was identified in 189 HIV-positive patients (HR 11.13 CI 9.58-12.68) and 26142 HIV-negative patients (HR 6.98 CI 6.89-7.06) indicating almost a doubling in the risk of MI in HIV-positive patients (Triant et al., 2009). A large prospective longitudinal analysis, the Veterans Aging Cohort Study, of 82459 patients including 27350 predominantly male HIV-positive patients with matched controls and a follow-up of almost 6 years, demonstrated that HIV-positive patients had a higher risk of MI compared with HIV-negative patients with a hazard ratio of 1.48 (95% CI 1.27-1.72) (Freiberg et al., 2013). These and other studies suggest an overall 1.5 – 2.0 fold increased risk of CAD conferred by HIV.

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

1.3 Risk Factors of Ischaemic Heart Disease and HIV

There have been many studies indicating a high prevalence of traditional CAD risk factors in HIV-positive patients. These include smoking, hypertension, dyslipidaemia and obesity, which are probably related to socioeconomic factors as well as metabolic derangements caused by cART (Islam et al., 2012, Freiberg et al., 2013). HIV-positive patients had a greater risk of developing cardiovascular complications compared to HIV-negative patients (Lang et al., 2015a).

In a large US health care data registry, HIV-positive patients had significantly more hypertension (21.0 vs 15.9%), dyslipidaemia (23.3 vs 17.6%) and diabetes (11.5 vs 6.6%) than the HIV-negative patients ($p<0.0001$). The criticism of this study is that they did not include smoking as a risk factor. After adjusting for age, gender, hypertension, dyslipidaemia and diabetes, the difference in MI rates were increased, with a relative risk of 1.75 ($p<0.0001$).

In San Francisco over a decade, between 1993 and 2003, HIV-positive patients were found to have a lower Thrombolysis in Myocardial Infarction risk score on presentation. HIV-positive patients were likely to be young, male, white and more likely to have smoking as a risk factor and less likely to have traditional risk factors such as hypertension, dyslipidaemia and diabetes. High-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were lower and hs-CRP was increased in the HIV-positive patients. A French study found that HIV-positive patients had less hypertension, lower HDL levels, a higher mean triglyceride (TG) level and a higher prevalence of smoking (Saves et al., 2003). A study from Switzerland of 8033 HIV-positive individuals found that the most important risk factors included smoking (57%), lower HDL levels (37.2%), higher TG levels (35.7%) and hypertension (26.1%) (Glass et al., 2006).

There were two large cohorts of HIV-positive patients (Women's Interagency HIV Study and the Multicenter AIDS cohort Study) comparing major risk factors with HIV-negative controls. HIV-positive patients more frequently had lower HDL and elevated TG levels. The risk of CAD was significantly lower in cART-naïve compared to those taking protease inhibitors (odds ratio 0.57). Predictors of elevated risk included low-income status and elevated body mass index. More than 40% of HIV men and more than 60% of HIV women were overweight or obese (Kaplan et al., 2007). Smoking rates were considerably high in the HIV-positive group. A survey of 4000 HIV-positive patients in the US found that 42% were current smokers compared to 21% in the HIV-negative patients (Mdodo et al., 2015).

There is limited data of HIV-positive patients with ACS from developing nations. A study of 30 cART naïve HIV-positive patients presenting with ACS also showed that HIV-positive patients were younger and that besides smoking, had fewer coronary risk factors with less hypertension, diabetes and LDL hyperlipidaemia. The HIV-positive group had lower HDL levels, a lower body mass index and anthropometric measurements (Becker et al., 2010). In HIV-positive patients, African-American race is a predictor of MI with a relative risk of 1.75 (Triant et al., 2007). Framingham risk factors, HCV infection, renal disease and anaemia were found to be independently associated with MI and MI risk was highest among those with CD_4<200 cells/mm^3 (Freiberg et al., 2013).

HIV-positive patients have a unique additional burden of novel risk factors. These include inflammation, immune activation, coagulopathy, chronic kidney disease, cART as well as the direct effect of the HIV virus itself (Triant, 2014). Interestingly, women who are HIV-positive show a greater CAD risk profile than their male counterparts (Lang et al., 2010). It is suggested that this finding is related to higher levels of immune activation in females (Triant, 2014). A similar mechanism has also been proposed for individuals with Hepatitis C virus and HIV co-infection, which is also linked with increased risk of cardiovascular disease (Fernandez-Montero et al., 2016). In the Canadian cohort, 8% of the HIV-positive group were infected with HCV. It

has been suggested that these infections synergistically sustain a chronic low-grade immune activation and worsen CAD risk profile (Freiberg et al., 2011).

A low CD4 cell count and continued HIV replication has been associated with an increased risk of MI, independently of CV risk factors and cART (Lang et al., 2012). However, another study, showed that there was no association between nadir CD4 count (lowest value) or peak HIV viral load and incidence of MI (Friis-Moller et al., 2007). The effects of cART on the CAD have been well studied (Mavroudis et al., 2013, Chastain et al., 2015). In general, the cumulative exposure to protease inhibitors and abacavir has shown to have an additive risk for CAD (Zanni et al., 2014). On the other hand non-nucleoside reverse transcriptase inhibitors, integrase inhibitors and CCR5 antagonists have all been shown to have neutral lipid effects and no increased risk of CAD (Friis-Moller et al., 2007, Chastain et al., 2015, Estrada and Portilla, 2011). In a large prospective study it was shown that cART with indinavir, lopinavir-ritonavir (Kaletra), didanosine and abacavir were also associated with an increased risk of MI (Worm et al., 2010). In the Canadian cohort, there was an increased incidence of MI in HIV-positive patients on cART with an odds ratio with abacavir of 1.79 (1.16 to 2.76 p=0.02), 1.83 (1.21 to 2.76 p=0.004) with efavirenz, 1.98 (1.24 to 3.16 p=0.004) with lopinavir and 2.29 (1.48 to 3.54 p<0.001) with ritonavir (Durand et al., 2011).

1.4 Pathogenesis of Ischaemic Heart Disease and HIV

The underlying mechanisms of atherosclerosis in HIV are multifactorial (Figure 1.2 and 1.3). HIV infection itself can lead to chronic inflammation, immune activation, endothelial dysfunction, athero-thrombosis and dyslipidaemia. These factors acting singly or in combination promote atherosclerosis (Boccara et al., 2013).

Atherosclerosis

Autopsy studies in HIV patients have described coronary lesions as eccentric atherosclerotic plaques with 80-90% reduction of the vascular lumen in coronary vessels, especially in the proximal vessels (Paton et al., 1993). HIV infection of the coronary arteries can lead to proliferation of vascular smooth muscle cells and promote atherosclerosis. In support of this it has been shown that the HIV protein, p24, has been isolated from smooth muscle cells of human atherosclerotic plaques using fluorescence microscopy (Eugenin et al., 2008).

There is no systematic study in HIV-positive patients that has assessed atherosclerosis directly (coronary angiography or intravascular ultrasound). However, an increased prevalence of subclinical atherosclerosis has been reported in HIV-positive patients as compared to HIV-negative patients using non-invasive surrogate tools such as carotid intima media thickness and coronary computer tomography angiography. A meta-analysis of observational studies suggested a trend towards carotid intimal thickening in HIV positive patients (Hulten et al., 2009). Carotid intima media thickness was increased in HIV-infected children receiving cART suggesting that CAD risk may already be increased in HIV patients at a young age (McComsey et al., 2007).

Using computed tomography angiography, a recent meta-analysis of 1229 HIV-positive patients on cART showed three times higher prevalence of non-calcific coronary artery plaques as

compared with HIV-negative controls (D'Ascenzo et al., 2015). Patients with low CD4 counts had more vulnerable plaques suggesting that disease severity may lead to increased CV risk (D'Ascenzo et al., 2015). Prelamin A accumulation which is a marker of vascular aging seen in Progeria patients has been described in patients using protease inhibitors and has been speculated to promote premature aging and early CAD in HIV-positive patients (Lefevre et al., 2010, Boccara et al., 2013).

Inflammation

Higher levels of inflammatory markers such as C-reactive protein (CRP), Interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), plasminogen activator inhibitor-1 (PAI-1), sCD14 have been found in HIV-positive as compared with HIV-negative patients (Triant et al., 2009, Baker et al., 2010, Kelesidis et al., 2012, Knudsen et al., 2014) (Figure 1.2). CRP and IL-6 are increased in HIV-positive patients and can predict increased CV risk and mortality (Kuller et al., 2008). The risk for MI is raised more than 4-fold among HIV-positive patients and elevated CRP compared to HIV-negative patients (Triant et al., 2009). A CD_4 count of < 200 cell/mm^3 and a high HIV viral load have all been implicated in promoting CAD (Lang et al., 2015a). There is still residual risk for CAD even for HIV-positive patients who are compliant on cART with complete virological suppression, since the inflammation and immune activation are not fully suppressed (Lang et al., 2015a).

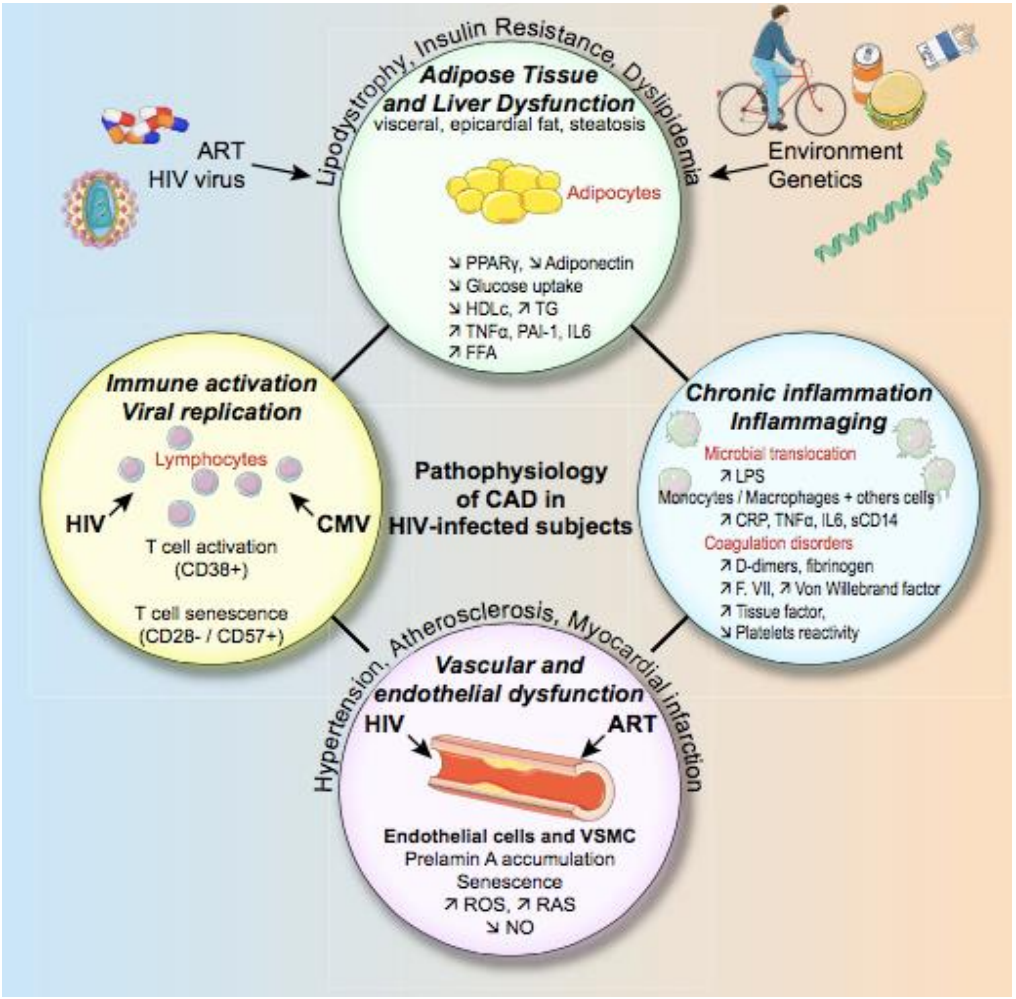


Figure 1.3: Pathophysiology of HIV and Ischaemic heart disease (Boccara 2013)

Endothelial dysfunction

Endothelial function has been studied in HIV-positive patients since the onset of the epidemic (Lafeuillade et al., 1992). There appears to be an intricate interplay between endothelial function and inflammation as markers such as vascular cell adhesion molecule-1 (VCAM-1) and Intercellular adhesion molecule-1 (ICAM-1) are elevated in patients early after HIV infection (Graham et al., 2013). The mechanism of endothelial dysfunction in HIV infected individuals in the development of atherosclerosis is complex but is thought to be related to a number of factors including direct involvement of HIV, endothelial activation and vascular inflammation (Boccara et al., 2013, Palella and Phair, 2011, Conaldi et al., 1995). Endothelial dysfunction is regarded as a link between infection, inflammation and atherosclerosis and there is recent data suggesting the presence of endothelial dysfunction in untreated HIV-positive patients (Fourie et al., 2011). Furthermore, following cART, it has been shown that there is a fall in markers of endothelial dysfunction such as macrophage chemoattractant protein-1 (MCP-1) , P-selectin and VCAM-1 (Graham et al., 2013). There is limited data on endothelial function in HIV-positive patients presenting with acute coronary syndromes. Endothelial dysfunction is associated with raised levels of reactive oxygen species and decreased nitric oxide levels contributing to athero-thrombosis (Verma and Anderson, 2002). A significant improvement in brachial flow mediated dilation has been described in patients in the first 24 weeks after initiation of antiretroviral therapy suggesting that suppression of HIV viraemia leads to improved endothelial function (Murphy and Costagliola, 2008). HIV-positive patients with ACS have been reported to have higher levels of TNFα and VCAM-1 and MCP-1 (Becker et al., 2011a). HIV infection was found to be an independent predictor of a reduced brachial FMD, suggesting a link between HIV and endothelial dysfunction (Cotter, 2006). Peripheral waveform analysis using pulse wave velocity has also been shown to provide a noninvasive method of measuring ‘global’ endothelial function (Lekakis et al., 2011).

Coagulopathy

HIV infection may promote a procoagulant state associated with HIV replication and also immune activation (Baker and Lundgren, 2011). Coagulation abnormalities in HIV-positive patients include raised D-dimers, fibrinogen, Factor VII, von Willebrand Factor (vWF), soluble thrombomodulin and tissue factor (Seigneur et al., 1997, Blann et al., 1997, Ford et al., 2010). In the Strategic Management of AntiRetroviral Therapy study, raised D-dimer levels have been associated with the risk for CV deaths (Kuller et al., 2008). HIV infection may alter coagulation pathways via tissue factor activation. Tissue factor measured 4 months prior to CV events were raised when compared with HIV-positive patients who did not have a subsequent CV event (Ford et al., 2010). In HIV-positive patients, thrombophilia was more common, with lower protein C levels and higher factor VII levels. There were also higher anticardiolipin and antiprothrombin antibodies (Becker et al., 2011b). A positive correlation between HIV infection and prothrombin fragments suggest increasing levels of viraemia could increase the risk of thrombosis (Karmochkine et al., 1998).

Alterations in lipids and lipoproteins

HIV has been associated with a decreased HDL level, increased TG level and pro-atherogenic changes in LDL (mainly due to cART). The HDL atheroprotective effects include reverse cholesterol transport as well as pleiotropic effects such as anti-thrombotic and anti-oxidant effects. Elevated TG level has been described in HIV-positive patients due to decreased clearance (Grunfeld et al., 1992).

In summary, chronic inflammation, immune dysregulation, metabolic disturbances and heightened pro-coagulant factors contribute to an atherothrombotic milieu in HIV-infected patients.

1.5 Clinical Presentation of Ischaemic Heart Disease and HIV

The clinical presentation of HIV-positive patients with CAD includes stable angina and the spectrum of ACS (ST segment myocardial infarction, Non-ST segment myocardial infarction and unstable angina). The presentation of stable angina is not well documented but it appears that angina is under-diagnosed in HIV-positive patients (Zirpoli et al., 2012). HIV-positive patients most commonly present with CAD, which is manifested when they present with an acute episode of ACS. The mean age at presentation of ACS in HIV-positive patients is a decade younger than the general population with the mean age of 50 years (David et al., 2002, Ambrose et al., 2003, Varriale et al., 2004, Becker et al., 2010, Boccara et al., 2011). Furthermore, HIV-positive patients with ACS are more likely to be males, have lower HDL levels and be current smokers. HIV-positive patients often present with low TIMI risk scores with single vessel disease on coronary angiography (Ho and Hsue, 2009). The most common mode presentation of ACS is ST-segment elevation MI followed by non-ST segment MI and unstable angina (David et al., 2002, Ambrose et al., 2003, Varriale et al., 2004, Becker et al., 2010, Boccara et al., 2011). HIV-positive patients are most often treated with cART (54% to 96%) and mainly taking protease inhibitors (>59%). HIV patients are more likely smokers and cocaine users (Lang et al., 2015a).

There is usually a large burden of thrombus in HIV-positive patients who present with ST segment elevation myocardial infarction in developing nations (Becker et al., 2010). This may be due to the increased thrombotic profile of these patients together with an underlying inflammatory background. It has been suggested that HIV-positive patients have less atherosclerotic disease and a high thrombotic burden implicating a pro-thrombotic state (Becker et al., 2010). The HIV virus subtype infection may also play a role as the HIV virus subtype infection differs in various regions. In developed countries the infection is with HIV 1 subtype B, but in Africa it is HIV 1 subtype C. Thus genetic factors may also play a role in the different forms of presentations (Manga, 2015).

1.6 Management of Ischaemic Heart Disease and HIV

The basic management of HIV-positive patients presenting with ACS is no different to HIV-negative patients with ACS. This includes initial diagnosis of the type of ACS and necessary triage. Patients should be given dual antiplatelet therapy (aspirin and P2Y12 inhibitor), statins and follow standard management of basic care. HIV-positive patients presenting with ACS may present without classic atheromatous plaques but with a large burden of thrombus in infarct related artery (Becker et al., 2010). How this high thrombus burden should optimally be managed is unclear but intra-coronary lytic and thrombectomy devices have been utilized in several cases to limit thrombus burden and improve TIMI flow prior to stent implantation with good outcomes (Kayima et al., 2015, Vachiat A et al., 2015).

Revascularization

Drug eluting stents appear to be as safe and efficacious in patients with HIV as in non-HIV patients (Ren et al., 2009). There is conflicting data on the incidence of clinical restenosis and the need for target vessel revascularization among HIV-positive patients during long-term follow up. Several studies demonstrated increased incidence of restenosis but unfortunately these were small studies and used first generation stent technology (Escaut et al., 2003, Segev et al., 2006, Hsue et al., 2004a). This is in contrast to the data from two more recent studies which showed that there was no significant difference in recurrent coronary revascularization post stent implantation between HIV-positive and HIV-negative patients at long-term follow up (Boccara et al., 2006, Boccara et al., 2011). Data from the Percutaneous intervention and surgical revascularization in HIV Database (PHD) study showed a target revascularization rate of 9.8% out to a median of 24 months follow-up (D'Ascenzo et al., 2014). There is scant data regarding stent thrombosis but studies suggest a higher rate of stent thrombosis in HIV-positive patients (Matetzky et al., 2003). Stent thrombosis rate was recently found to be 3.4% at 24 months, which is more than double the rate found in the HIV-negative patients (D'Ascenzo et al., 2014). There are very few studies that

have included HIV-positive patients for coronary artery bypass grafting (CABG) (Boccara et al., 2008, Jimenez-Exposito et al., 2006). These studies suggest that CABG is feasible and intraoperative and postoperative periods are no different from those in HIV-negative patients (Blyth et al., 2006, Castillo et al., 2008).

Prevalence of ischemic cardiomyopathy is increased in HIV-positive patients because of the increased risk of ACS (Bloomfield et al., 2015). While there are no studies specific to the treatment of ischemic cardiomyopathy in HIV-positive patients the management should follow the recommended heart failure guidelines (Yancy et al., 2013). Heart transplantation could be considered in HIV-positive patients but current evidence comes from small retrospective studies and case reports (Uriel et al., 2009, Castel et al., 2011, Calabrese et al., 2003). To date, 15 HIV-positive patients are reported to have undergone heart transplantation in the cART era. At a follow-up of 40 months, 13 were reported to be still alive without progression to AIDS (Aguero et al., 2015).

Risk Factors

Traditional risk factors appear to pose an equal CAD risk to HIV-positive as in HIV-negative patients (Stein, 2012). Therefore aggressive secondary risk factor modification should be promoted in all HIV-patients. In particular, smoking cessation should be advocated since there appears to be a higher prevalence of smoking among HIV-positive patients (Becker et al., 2010, Perello et al., 2011). The HIV focused guideline for the management of dyslipidemia and the European Society of Cardiology and European Atherosclerosis Society guideline on management of dyslipidemia essentially follow the treatment algorithm for HIV-positive patients as those for the HIV-negative patients with dyslipidemia (Dubé et al., 2003, Reiner et al., 2011). Lifestyle modification should be advocated in the first instance and statin therapy for all ACS patients and for those not reaching target levels (Stone et al., 2014, Lang et al., 2015b). At present, atorvastatin and rosuvastatin are the safest and most efficacious statins in patients on cART but

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

Combination antiretroviral therapy is proven to improve outcomes in HIV-positive patients and should be prescribed (Günthard et al., 2014). Treatment with these agents increases long-term survival by reducing opportunistic HIV-related illnesses. Side effects and drug interactions are an important and complex aspect of the management of HIV patients with CAD and therefore the involvement of an HIV specialist is prudent in the care of the HIV patient with CAD (Koganti et al., 2015). A full review of potential drug interactions can be accessed from recent comprehensive reviews on cardiac drugs and antiretroviral medications (Egan et al., 2014, Wang et al., 2015, Feinstein et al., 2015). Protease inhibitors, in particular, increase the risk of rhabdomyolysis when used with certain statins and thus should be avoided (Mavroudis et al., 2013). Furthermore, indinavir and lopinavir-ritonavir may increase the risk of dyslipidemia, thereby increasing CAD risk. However, the risk of CAD associated with anti-retroviral therapy is small compared with the impressive reductions in all-cause mortality with cART (Stein, 2012). The D.A.D study demonstrated that long-term exposure to indinavir, lopinavir-ritonavir or abacavir is associated with an increased risk of MI, which may be important to consider in intermediate to high CAD risk patients (Worm et al., 2010).

Antiplatelet agents are frequently indicated in HIV patients with ACS and should be prescribed according to current ACS guidelines. However, the thienopyridines are predisposed to interactions with antiviral agents such as efavirenz and agents used to treat opportunistic infections including rifampicin, isoniazid and azole antifungals (Wang et al., 2015). There are a number of potential drug interactions with clopidogrel as it is significantly metabolized by CYP2C19 and CYP2C9. Prasugrel levels could fall if it is combined with ritonavir (Daali et al., 2011). Ticagrelor should also not be used in patients receiving protease inhibitor therapy, as it is predominantly metabolized by the CYP3A4/5 isoenzyme (Zhou et al., 2011), Lastly, Rifampicin has been reported to reduce ticagrelor levels and this combination should also be avoided (Teng et al., 2013).

1.7 Prognosis of Ischaemic Heart Disease and HIV

Although death due to AIDS is decreasing as HIV becomes a chronic disease, cardiovascular disease has increased among HIV-infected adults (Lewden et al., 2008). A meta-analysis of HIV-positive patients with ACS (n=2442) demonstrated an in-hospital cardiovascular death rate of 7.9% (D'Ascenzo et al., 2012). In-hospital mortality was also found to be similar in 23 HIV-positive patients with ACS compared with 60 HIV-negative patients (Martin-Reyes et al., 2010). A similar finding was found in Denmark where the 90-day mortality was similar in 44 HIV-positive patients compared with HIV-negative controls (Rasmussen et al., 2007). Of patients who are successfully resuscitated after cardiac arrest, intensive care unit mortality was no worse in HIV-positive patients compared with HIV-negative patients (Mongardon et al., 2015).

There have been conflicting data on long-term mortality outcomes in HIV-positive patients with ACS. No deaths were reported at 25.5 months in a meta-analysis including 2442 HIV-positive patients (D'Ascenzo et al., 2012) or at 12-month follow up in the Prognosis of Acute Coronary Syndrome in HIV-infected patients (PACS) study (Boccara et al., 2011). Similarly, 1-year mortality rates were found to be low (3.1% versus 2.1%) in 608 sex-and age-matched HIV patients (Lorgis et al., 2013). In contrast, in the Percutaneous intervention and surgical revascularization in HIV Database (PHD) retrospective registry of 201 HIV patients with ACS, 30 patients died of whom 12 were from cardiac causes (D'Ascenzo et al., 2014). This study found that the most common risk factors for death were the presence of low ejection fraction, renal failure, nucleoside reverse transcriptase inhibitor-sparing therapy and $CD4<200 cells/mm^3$ (D'Ascenzo et al., 2014).

There is more recurrent MI post ACS in HIV-positive than in HIV-negative patients (Boccara et al., 2011). Patients with $CD4<200 cells/mm^3$ had a 30% rate of recurrent MI at follow up, which is 3-times that seen in patients with higher CD4 counts or HIV-negative patients (D'Ascenzo et

al., 2014). It has been demonstrated that hospitalizations for episodes of heart failure were twice as likely in HIV-positive patients as HIV-negative patients (Lorgis et al., 2013). Furthermore, prior ischemic cardiomyopathy was more common among the HIV-positive patients with ACS, which would contribute to the higher rates of heart failure in the follow up period (Lorgis et al., 2013).

1.8 Conclusion

HIV and CAD are major global health problems and as the HIV population grows older, the increase in cardiovascular risk and subsequent disease will pose significant challenges to clinicians worldwide. The challenge will be particularly greater in developing nations such as South Africa due to the increased burden of disease as well as having limited health care resources. Thus the findings from this thesis will add to the knowledge base of HIV and CAD and possibly help in some small measure in the diagnosis and treatment of these patients.

CHAPTER 2 : OBJECTIVES

As alluded in Chapter 1, in HIV-negative patients the vascular characteristics of atherosclerosis such as coronary plaque composition, endothelial dysfunction and intimal thickening are well described. However, in HIV-infected populations, these are poorly defined or not described at all.

Thus this study aimed to assess the following in HIV-positive patients with ACS:

1) A detailed virtual histological characterization of the atherosclerotic plaque and its burden in the coronary circulation.

2) Endothelial function in the coronary and peripheral circulation.

3) Carotid IMT assessment.

4) Biomarkers in the assessment of endothelial function.

Ethics Approval

Ethical approval for the study was submitted to the University of the Witwatersrand Human Research Ethics Committee and the study was approved unconditionally

(Ethics clearance number M111143).

CHAPTER 3 : METHODS

3.1 Study design

A prospective single center study of HIV-positive patients with ACS presenting to the cardiology division at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) (tertiary referral hospital draining the greater Johannesburg area, South Africa) conducted during the period 1st July 2012 to 30th June 2015. The main aim of the study was to elucidate the atherosclerotic plaque tissue characteristics as well as the burden of atherosclerotic disease in HIV-positive patients with ACS. The plaque characterization was assessed using intravascular ultrasound (IVUS) and more specifically virtual histology (VH). This is the largest study using VH in HIV-positive patients presenting with ACS. Furthermore the study also assessed carotid intima media thickness (CIMT) as a surrogate of atherosclerosis. Endothelial function was assessed by coronary reactivity, and non-invasively by brachial flow mediated dilatation (FMD) and analysis of endothelial biomarkers.

There were three groups of 20 patients each, namely:

1) **HIV-positive patients presenting with ACS (HIV+/ACS)**

2) **HIV-negative patients presenting with ACS (HIV-/ACS)**

3) **HIV-positive patients without ACS (HIV+/no ACS)**

These sixty patients were prospectively and voluntarily recruited over 36 months. The intention of this study was to contribute to the epidemiologic data linking HIV infection and CAD. The study also reviewed our understanding of the factors and pathogenesis associated with HIV and CAD. The study also highlighted the modes of presentation of HIV-positive patients presenting with CAD, in a developing world setting, where the major part of the HIV epidemic resides.

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

HIV+/ ACS patients:

Inclusion criteria

- HIV-positive patients presenting with ACS
- Age ≥ 18years old

ACS includes ST elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA).

STEMI includes those patients presenting with ST elevation 1mm or more in at least two contiguous leads for most leads except leads V2,3 where the criteria is >2mm in a male patient <40 years or >2.5mm in a male patient >40 years and 1.5mm in a female patient.

NSTEMI includes those patients presenting with angina without ST elevation but with positive cardiac enzymes.

UA includes those patients hospitalized with worsening angina or new onset angina at rest without troponin elevations.

Risk factors for CAD that was studied included age (men ≥ 55 years; women ≥ 65 years of age), smoking, hypertension, diabetes and family history of premature CAD.

Informed consent was obtained from all the participants.

Exclusion criteria

- Prior MI
- Life-threatening disease that prevented a 2 year follow up
- Known carotid artery disease

DATA Collection

Demographic data:

- age
- sex
- race

Risk factors:

- smoking (current)
- hypertension (BP>140/90 or on antihypertensive medication)
- diabetes mellitus (symptoms of diabetes plus random plasma glucose ≥ 11.1mmol/l or fasting plasma glucose ≥ 7.1mmol/l)
- dyslipidaemia (Total cholesterol >5mmol/l or LDL>3mmol/l)
- family history of premature coronary heart disease (male first degree relative <55 years of age or female first degree relative <65 years of age)

Clinical data:

- SBP and DBP
- co-morbidities
- cART

Electrocardiography : 12 lead ECG

Echocardiography:

- Left atrial diameter
- Left ventricular internal diameter (diastole)
- Left ventricular internal diameter (systole)
- Ejection fraction

Laboratory data:

As part of the standard of care, the following blood tests were performed at the National Health Laboratory Services, South Africa:

- HIV ELISA, CD4 count
- FBC, U&E, INR, CRP, Trop T, lipogram

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).

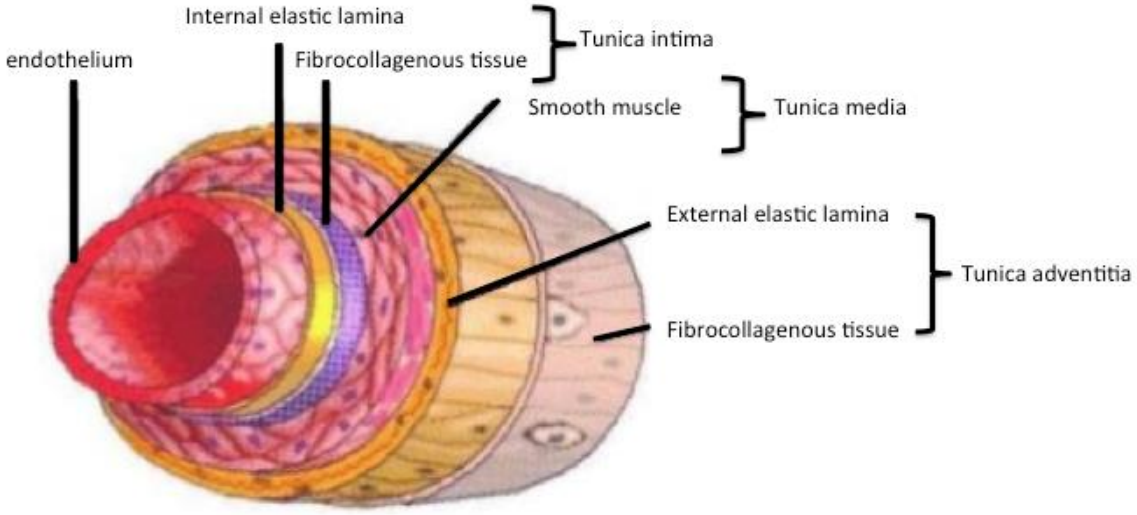


Figure 3.1: Arterial layers

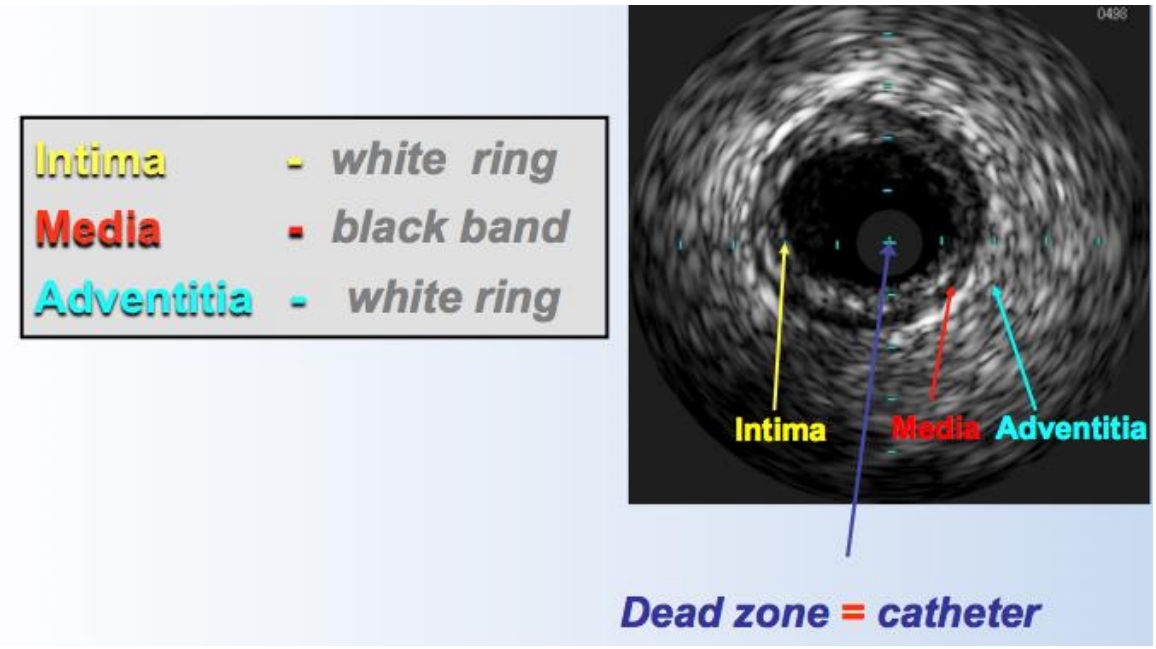


Figure 3.2 : Intravascular ultrasound : arterial layers description

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).

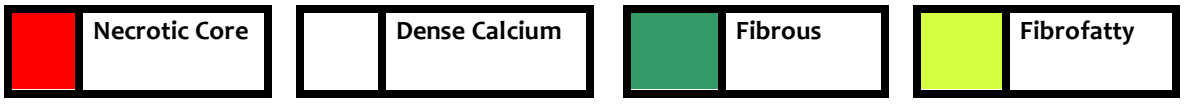


Figure 3.3: Virtual histology plaque colour description

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).

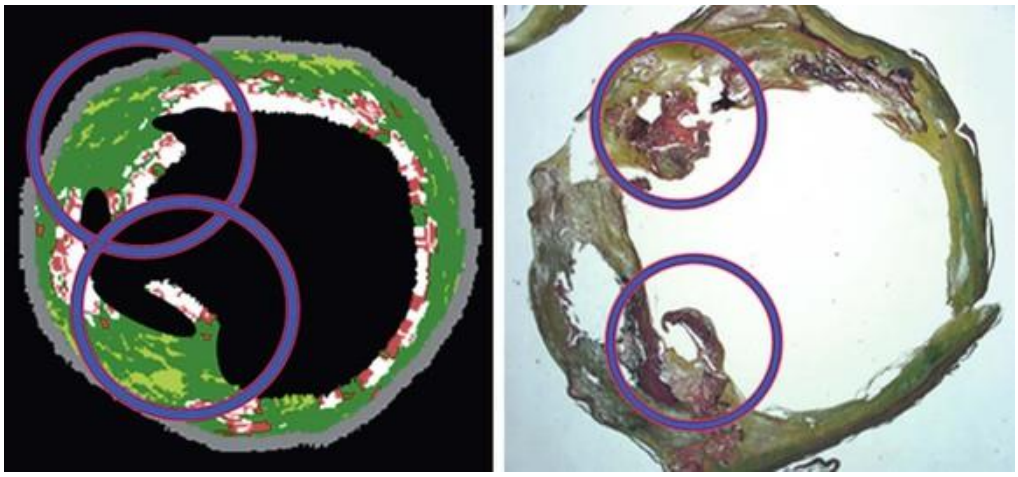


Figure 3.4: Intravascular ultrasound virtual histology and a histological specimen (Diethrich et al., 2007)

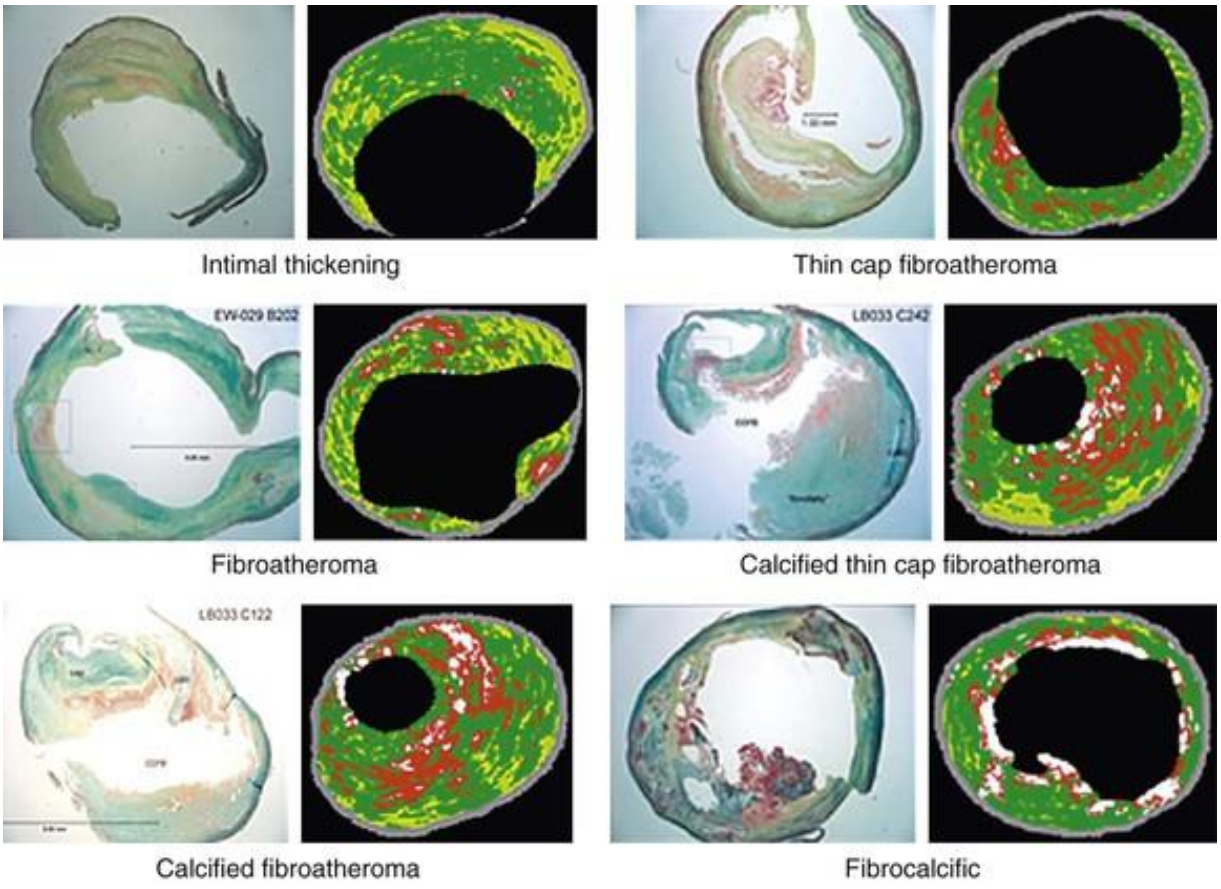


Figure 3.5: Correlation of virtual histology and histological specimens (Diethrich et al., 2007)

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.

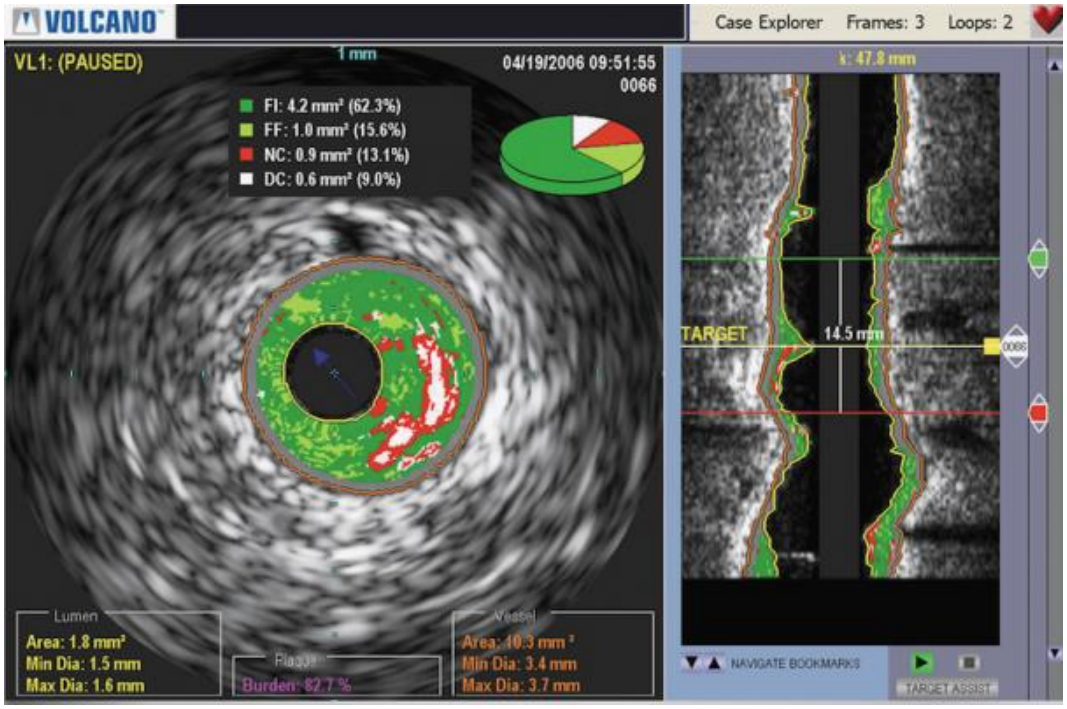


Figure 3.6 : Intravascular ultrasound interface

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

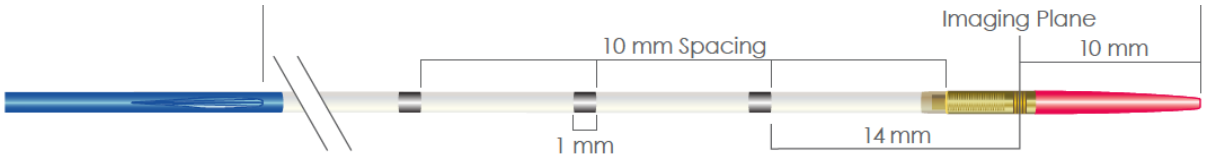


Figure 3.8 : Intravascular ultrasound catheter

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.

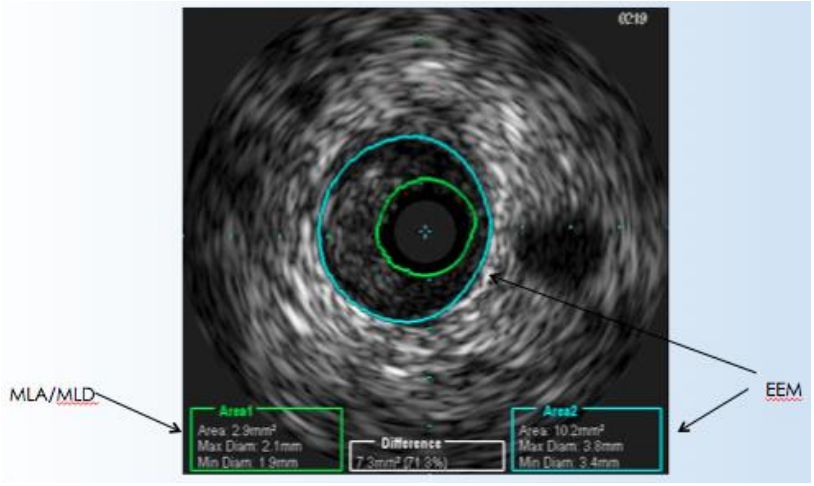


Figure 3.9: Intravascular ultrasound frame :

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

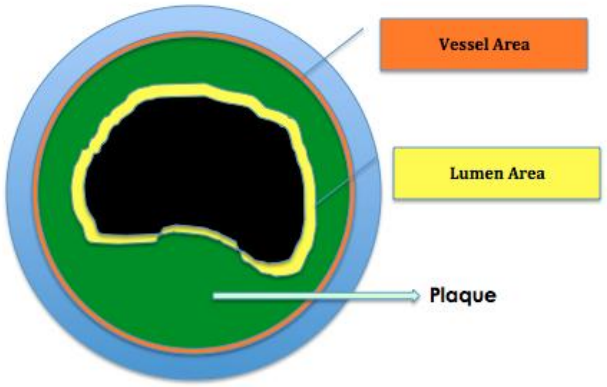


Figure 3.10: Intravasular ultrasound measurements

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.

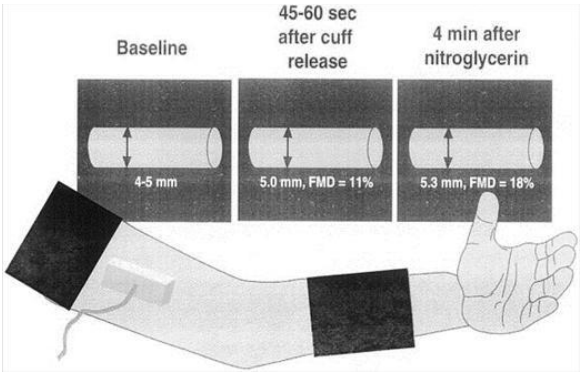


Figure 3.11 : Brachial flow mediated dilatation (Corretti et al., 2002)

3.3.2 Endothelial Biomarkers

The endothelial markers measured included : IL-1B, IL1ra, IL-6, TNFα, MCP-1, PAI-1, E-selectin, P-selectin, VCAM-1 and ICAM-1.

Blood preparation

Blood was collected from all 60 patients using EDTA tubes. Specimens were centrifuged for 20min at 4˚C at 1000 X G (2300rpm). The specimens were decanted into 1,5ml microcentrifuge tubes and stored at -70^{o}C.

Endothelial Biomarker Measurements

IL-1β; IL-ra and IL-6, MCP1, TNFα concentrations were quantified using the Bio-Plex Pro Human Cytokine Standard 27-Plex (Bio-Rad Laboratories, Inc., Hercules, CA) as per manufacturer's instructions. The bead regions were 39 for IL-1b, 25 for IL-ra, 19 for IL-6, 53 for MCP-1 and 36 for TNFα. Briefly, the serum was diluted 4-fold. Standards were prepared by diluting the standard cocktail in sample diluent (1 in 4). Wells were prewet in 100µl assay buffer, 50µl coupled beads were transferred the assay plates, followed by 50 µl of standard or sample and incubated for 1 hour.. The wells were washed 3 times with 100µl of wash buffer. Biotin conjugated detection antibody (25µl) was added to the wells and incubated for 30 minutes. The wells were washed again 3 times with 100µl of wash buffer. Streptavidin-Phycoerythrin (50µl) was added and incubated for 10 minutes. The wells were washed again 3 times and resuspended in 125 µl of assay buffer before loading onto the Bio-Plex 200 (Bio-Rad Laboratories, Inc).

E-selectin and P-selectin were quantified using Luminex assays (R&D systems, Minneapolis, MN) . The bead regions were 26 for E-selectin and 29 for P-selectin. The blood plasma was

diluted 1 in 2. Briefly, the wells were pre-wet with 100µl wash buffer, and 50 µl microparticles and 50 µl sample or standard was incubated at room temperature for 2 hours. The wells were washed 3 times and 50µl diluted biotin antibody cocktail was added. This was incubated for 1 hour, and the wells were washed again. 50 µl of diluted streptavidin-PE was added and incubated for 30min. This was washed again. The beads were resuspended in 100µl wash buffer before loading onto the Bio-Plex 200 (Bio-Rad Laboratories, Inc).

ICAM-1, V-CAM-1 and PAI-1 levels were measured using the human Sepsis Magnetic bead panel (Milliplex, Merck Millipore, Darmstadt, Germany) as per manufacturer's instructions. The bead regions were 35 for ICAM-1, 37 for V-CAM-1 and 76 for PAI-1. The plasma was diluted 40 X. Briefly, the wells were pre-wet with 200µl assay buffer, 25µl standard and samples diluted in 25µl buffer were added to the wells and incubated overnight with 25µl of the beads at 4°C. The wells were washed twice in 200µl wash buffer, followed by incubation for 1 hour with 25µl biotin conjugated detection antibodies. Streptavidin-phycoerthrin (25µl) was added to the wells and incubated for 30 minutes. The wells were washed twice with wash buffer and the beads were resuspended in 100 µl sheath fluid before loading onto the Bio-Plex 200 (Bio-Rad Laboratories, Inc).

The Bio-Plex 200 system measured the fluorescence of all bioanalytes referred to above, and the concentrations of the plasma biomarkers were calculated using a 5-PL logarithm using the Bio-Plex Manager 5.0.

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.

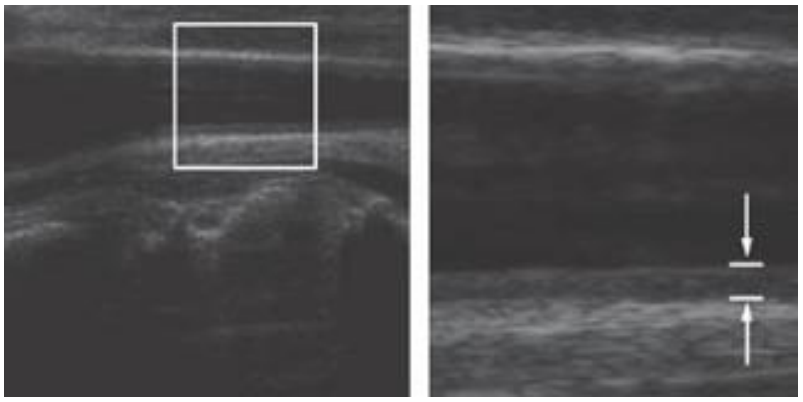


Figure 3.12 : Carotid intima media thickness

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).

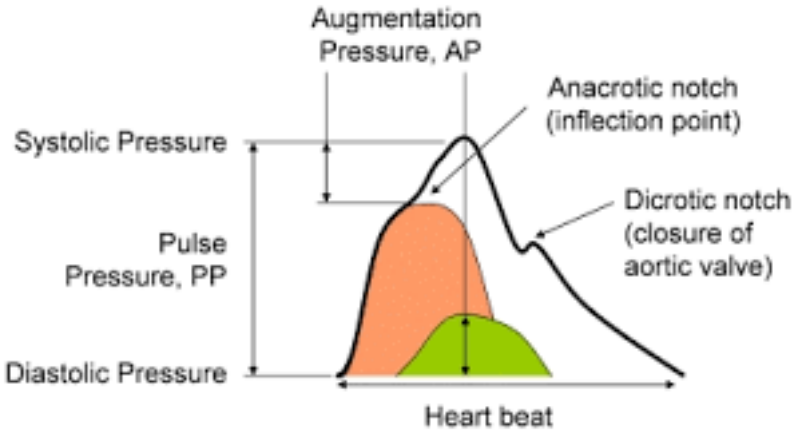


Figure 3.13 : Aortic pressure waveform

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).

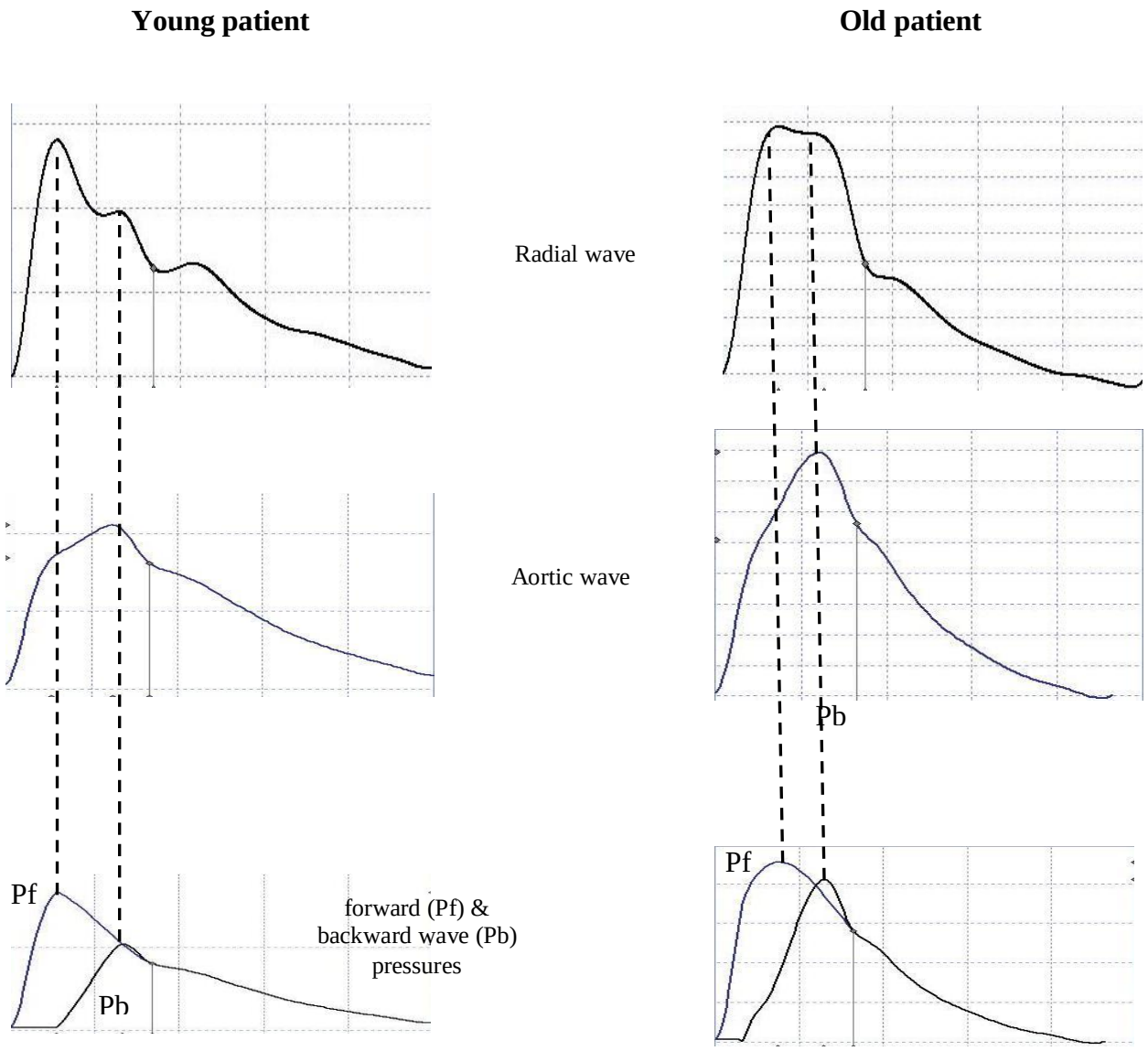


Figure 3.14 : Pressure waveforms in young and old patients

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).

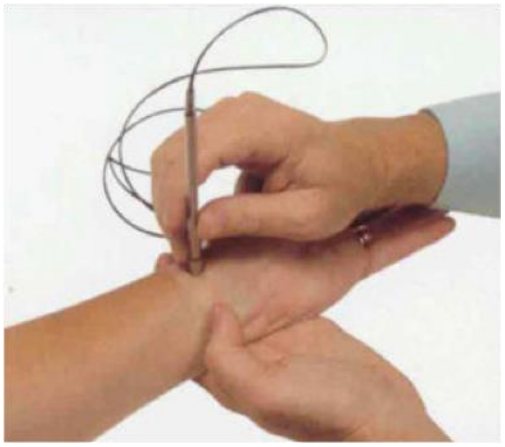


Figure 3.15 : Radial artery applanation tonometry

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.

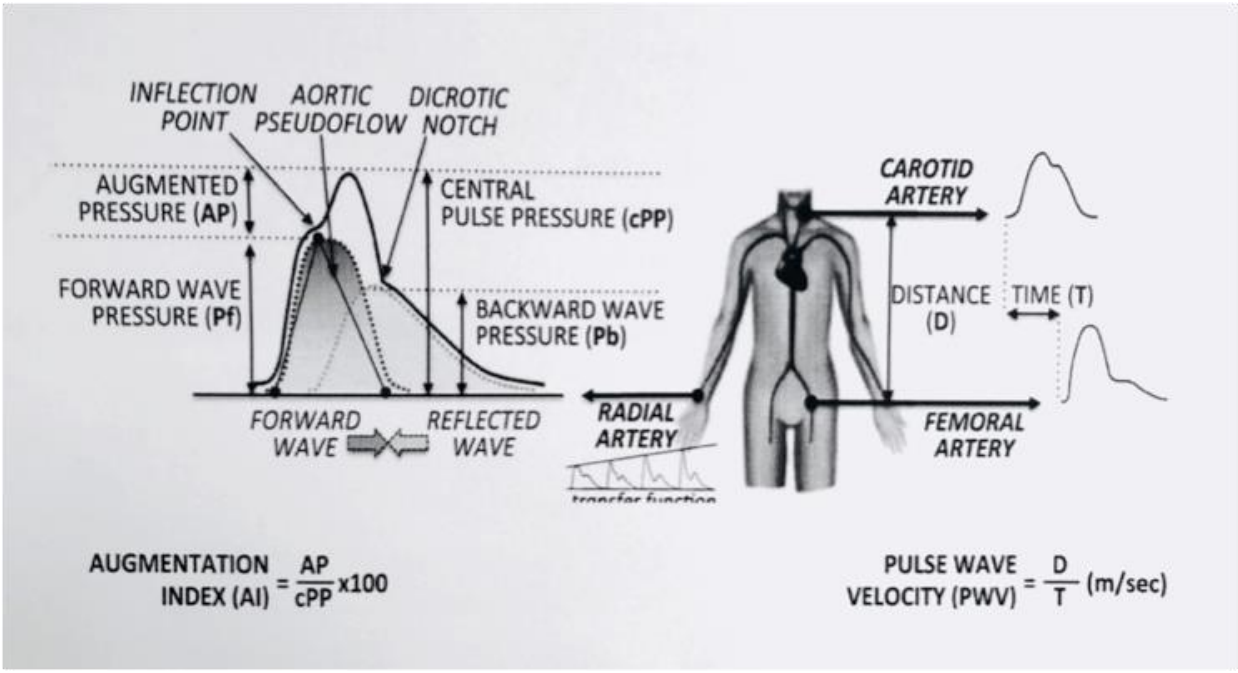


Figure 3.16 : Applanation tonometry. Adapted from (Canepa and AlGhatrif, 2015)

3.6 Statistics

Descriptive analysis of the data was carried out as follows: Categorical variables were summarized by frequency and percentage tabulation, and illustrated by means of bar charts. The mean, standard deviation, median and interquartile ranges summarized continuous variables, and their distribution illustrated by means of histograms.

The X^2 test was used to assess the relationships between categorical variables and group. Fisher's exact test was used for 2 x 2 tables or where the requirements for the X^2 test could not be met. The strength of the associations was measured by Cramer's V and the phi coefficient respectively. The following scale of interpretation was used:

0.50 and above	high/strong association
0.30 to 0.49	moderate association
0.10 to 0.29	weak association
below 0.10	little if any association

One-way Analysis of Variance (ANOVA) for three groups and the unpaired t-test for two groups assessed the relationship between continuous variables and group. Post-hoc tests for ANOVA were conducted using the Tukey-Kramer adjustment for multiple comparisons. Where the data did not meet the assumptions of the test, a non-parametric alternative, the Kruskal-Wallis test was used for three groups, and the Wilcoxon rank sum test for two groups. The Cohen's d for parametric tests and the r-value for the non-parametric tests measured the strength of the associations. The following scale of interpretation was used:

0.80 and above	large effect
0.50 to 0.79	moderate effect

0.20 to 0.49	small effect
below 0.20	near zero effect

Paired comparisons between continuous variables were carried out with the paired t-test or the Wilcoxon matched paired test where the assumptions of the paired t-test were not met.

Data analysis was carried out using SAS version 9.4 for Windows and a 5% significance level was used. *In other words, p-values <0.05 indicate significant results.*

Sample size

Most study variables were continuous, thus a one-way ANOVA was required. For the detection of small, medium and large effect sizes (f=0.10, 0.25, and 0.40 respectively) with 80% power at the 5% significance level, sample sizes of 966, 157 and 63 are required. Typically we aim for the detection of at least a medium effect size. The actual sample size of 60, which was used in this study, allows the detection of only large effect sizes, which is a limitation of the study.

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).

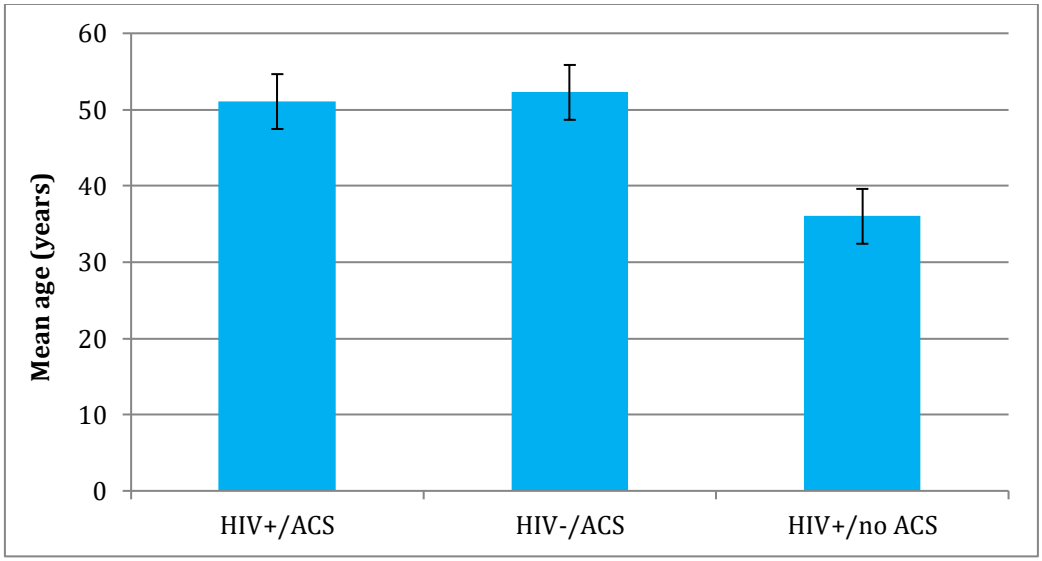


Figure 4.1: Comparison of age

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.

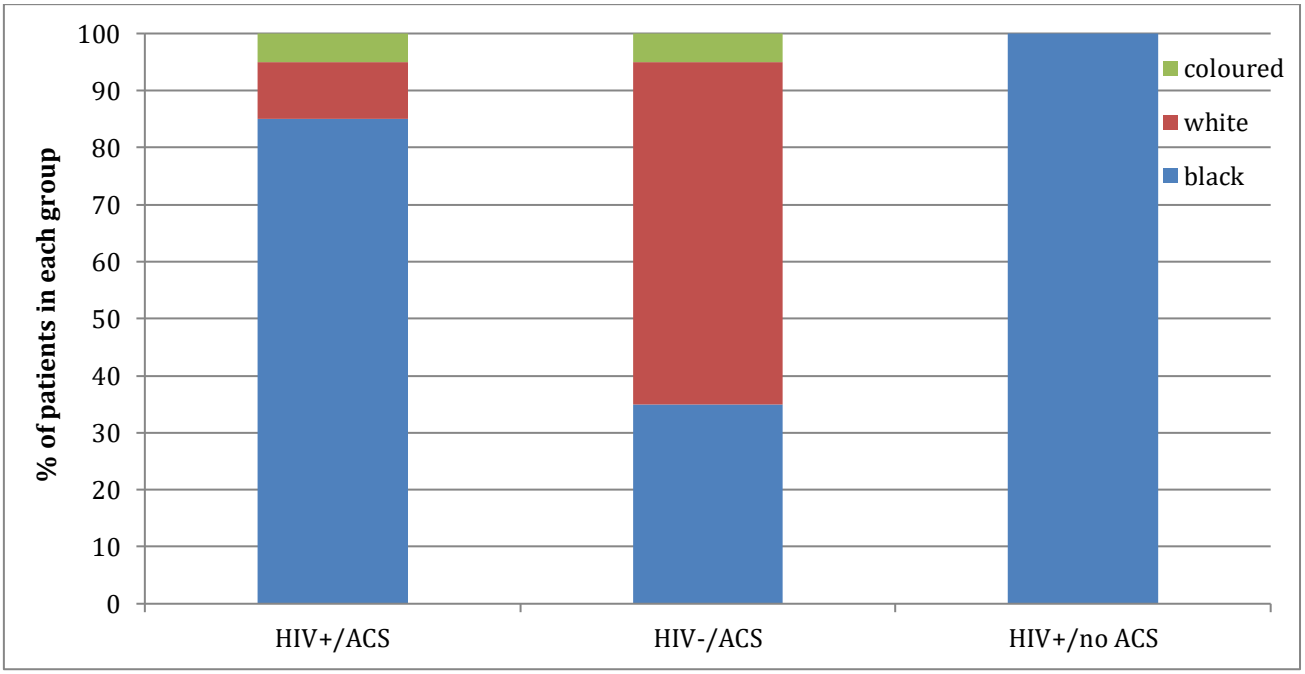


Figure 4.2 : Comparison of race

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.

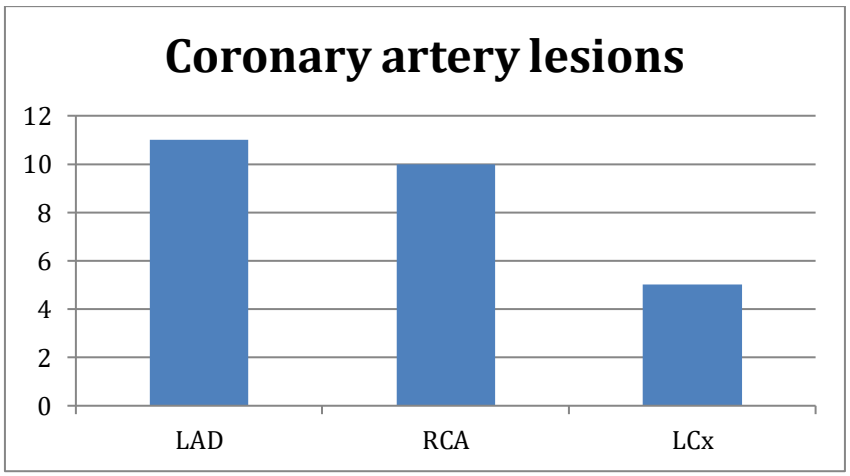


Figure 4.3: Coronary artery lesions

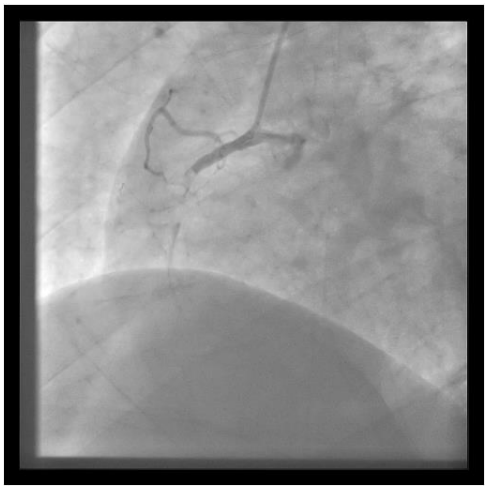


Figure 4.4 : STEMI : complete occlusion of the right coronary artery

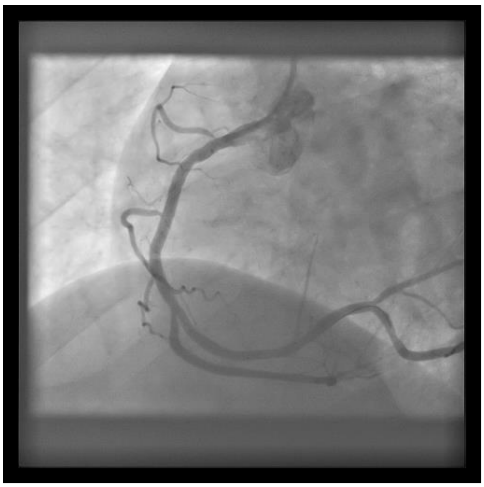


Figure 4.5 : Post intracoronary lytic and stent

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):

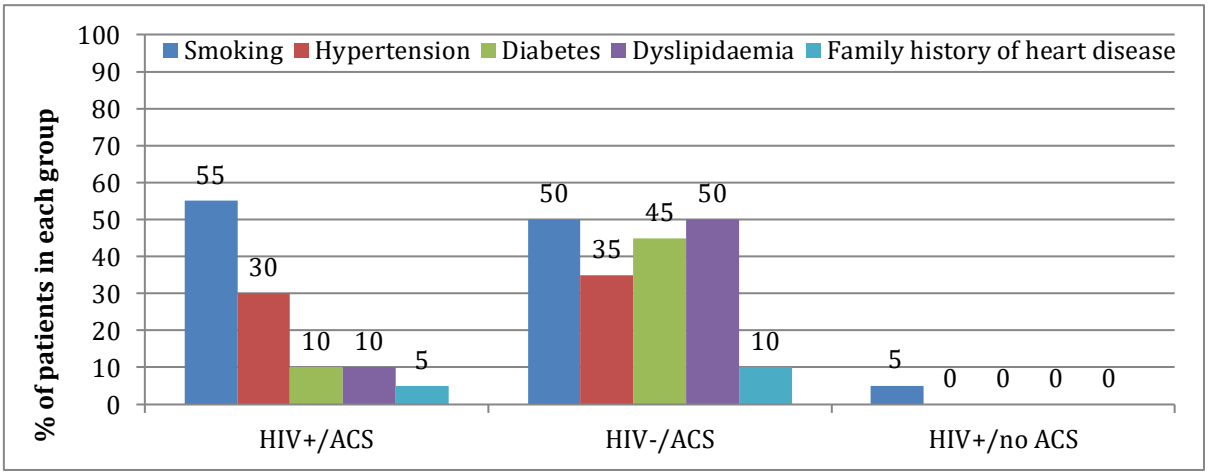


Figure 4.6 : Comparison of traditional risk factors

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).

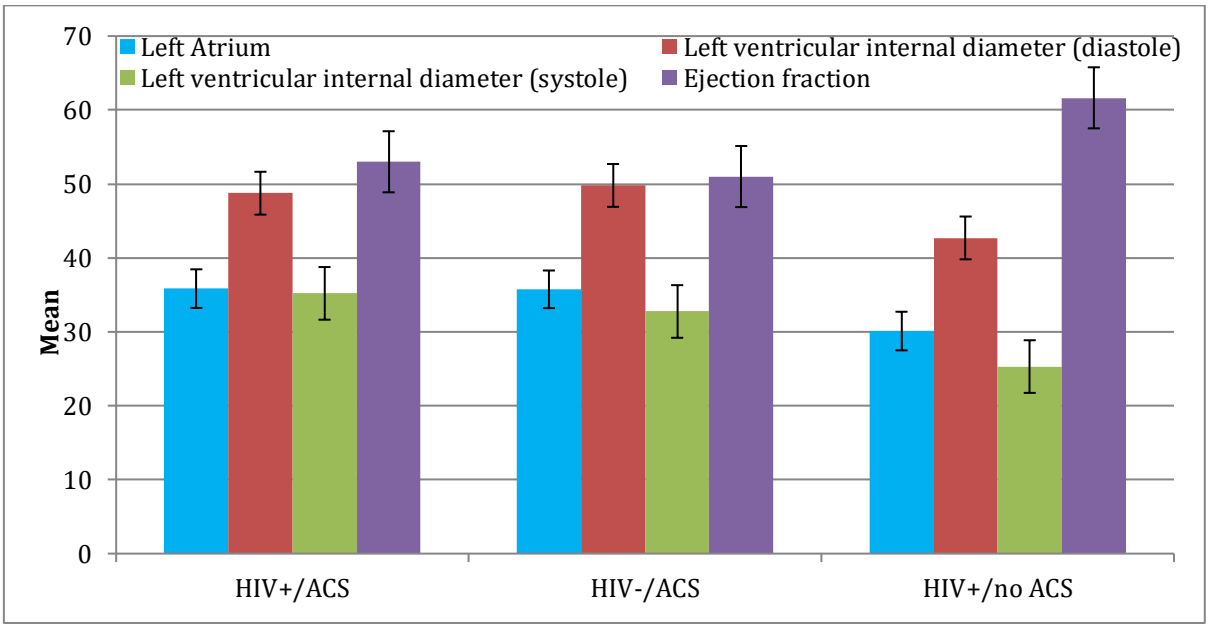


Figure 4.7: Echocardiographic measurements

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).

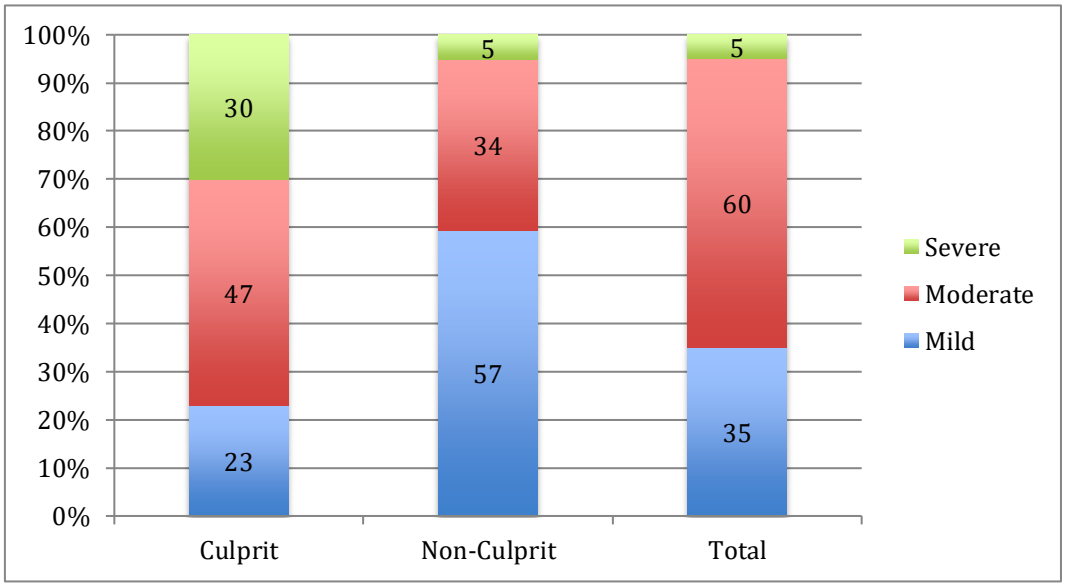


Figure 4.8 : Comparison of plaque burden

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).

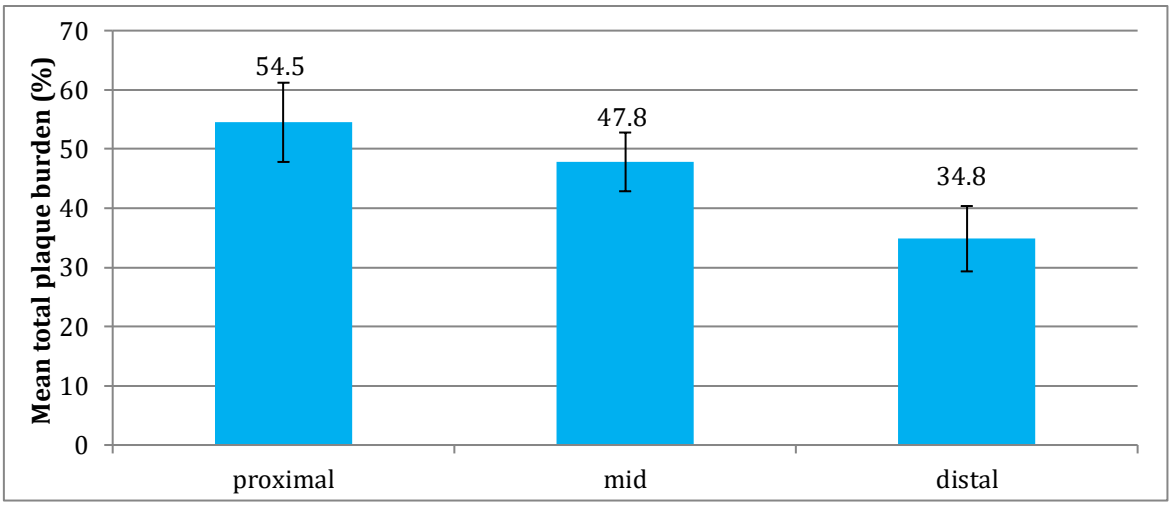


Figure 4.9 : Mean total plaque burden (%)

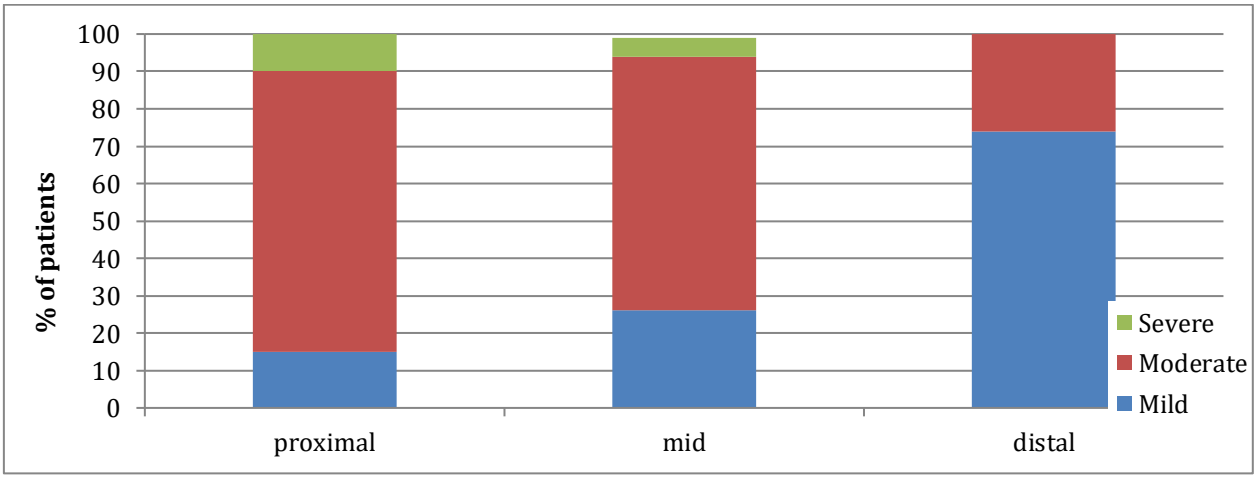


Figure 4.10 : Comparison of plaque burden per segment

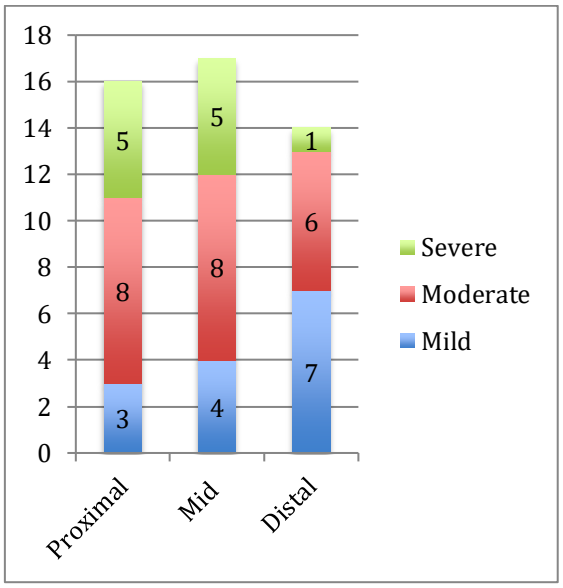


Figure 4.11 : Plaque burden (culprit vessel) per segment

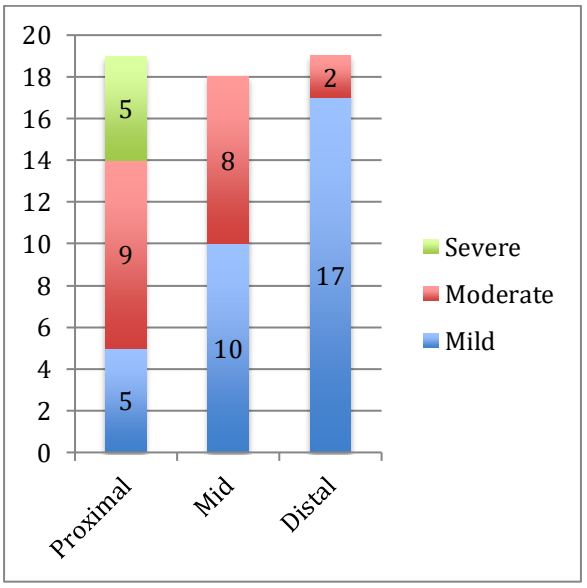


Figure 4.12: Plaque burden (non culprit vessels) per segment

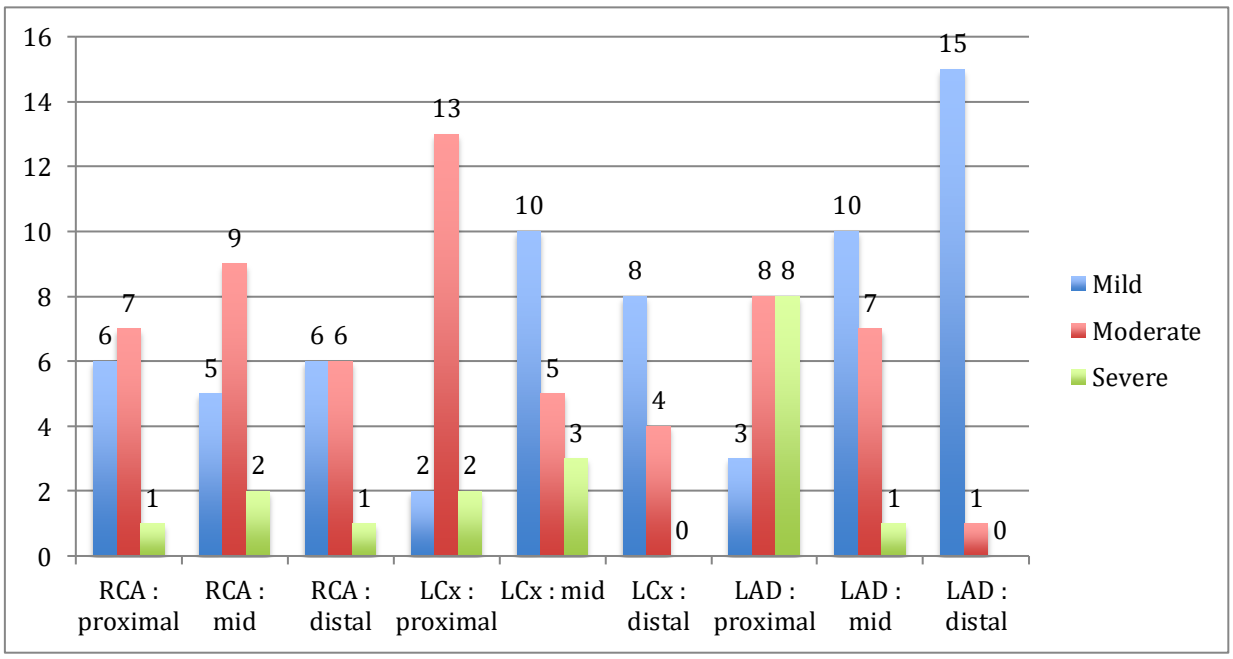


Figure 4.13: Plaque burden (specific coronary artery)

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).

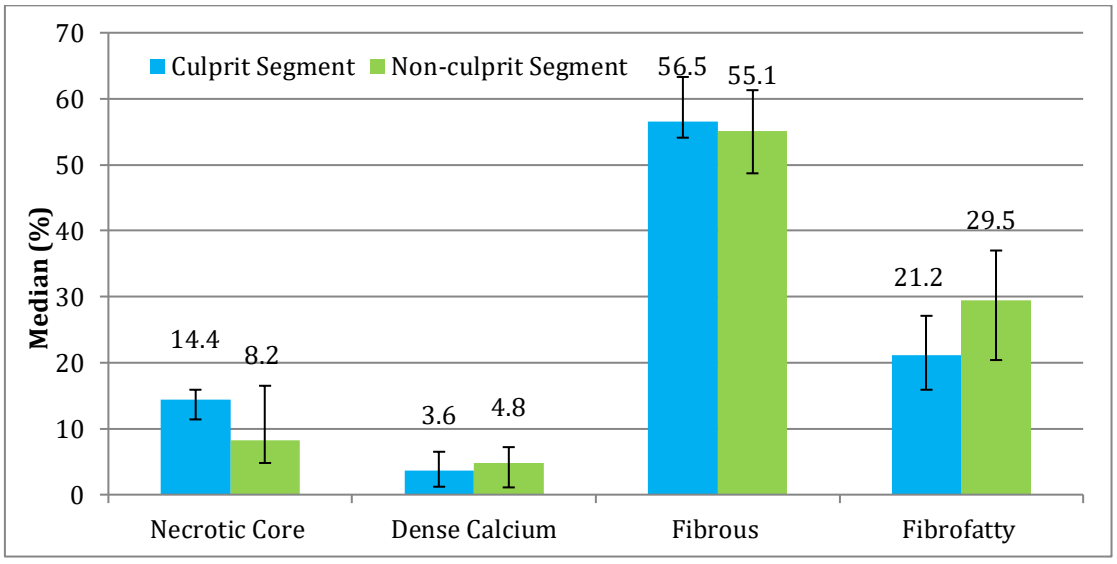


Figure 4.14 : Virtual Histology of the culprit and non-culprit segments

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).

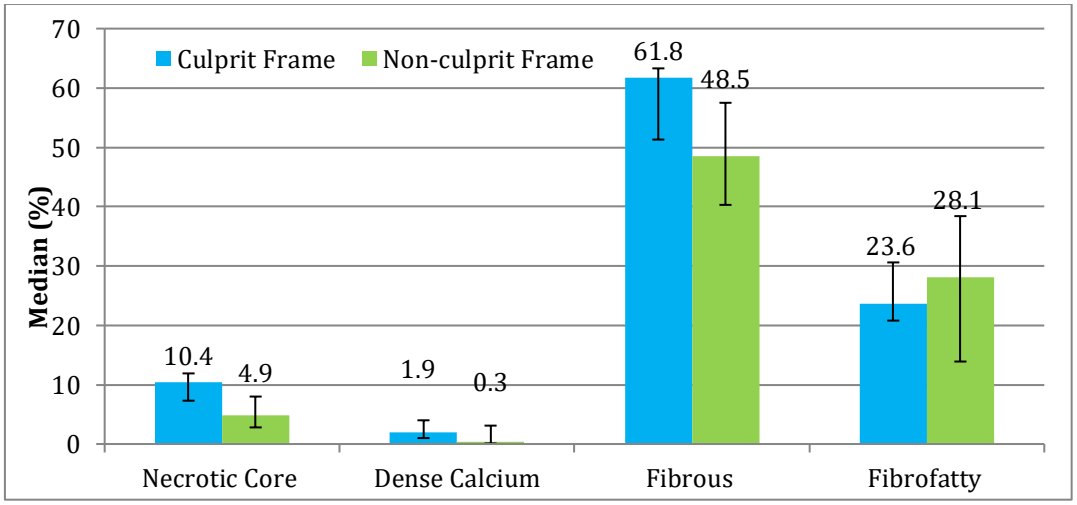


Figure 4.15 : Virtual Histology of the culprit and non-culprit frame

Frame and segment:

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

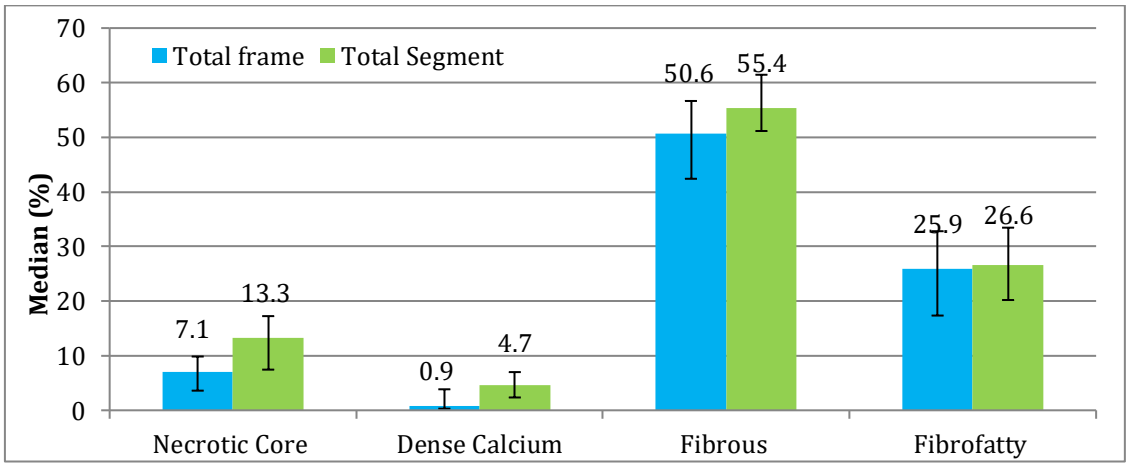


Figure 4.16: Virtual histology of the total frame and segment

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.

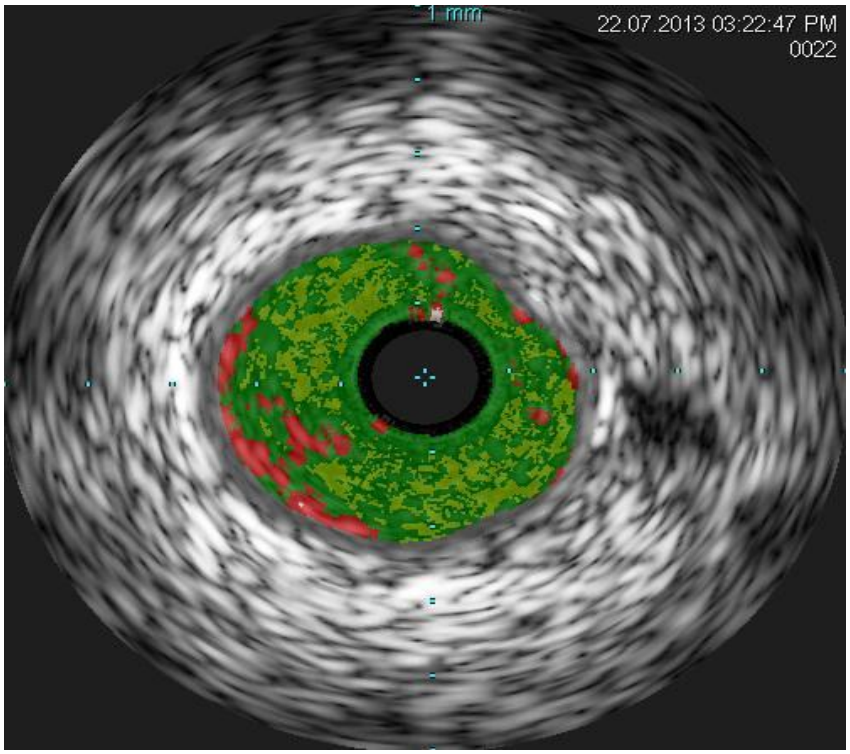


Figure 4.17: Virtual histology (fibrous/fibro-fatty plaque) in an HIV+/ACS patient

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.

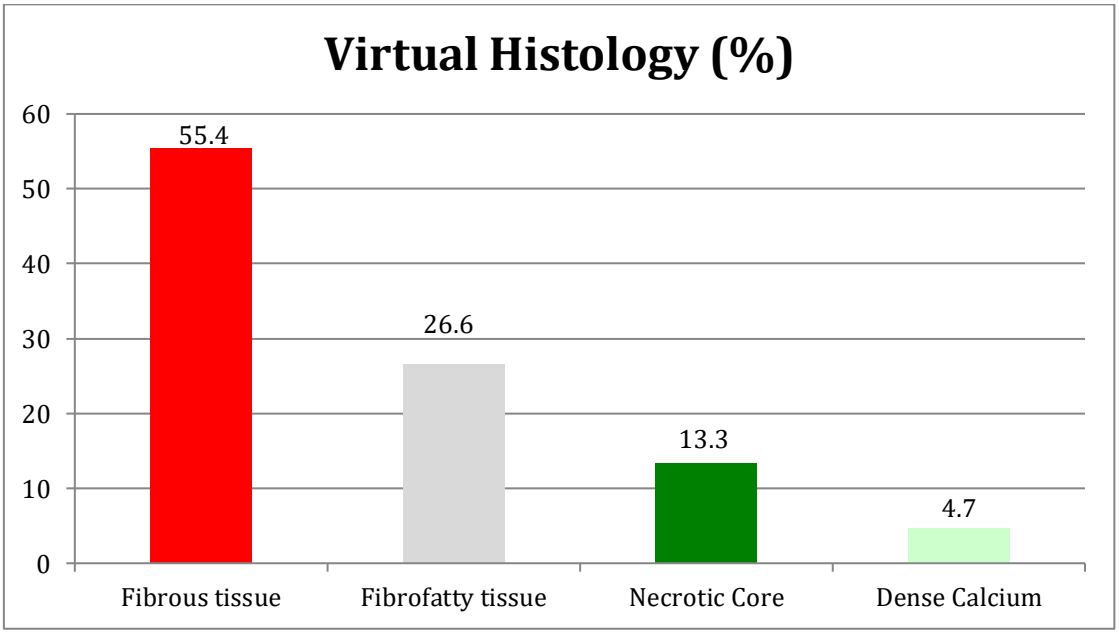


Figure 4.18: Virtual Histology of the atherosclerotic plaque in HIV-positive patients presenting with ACS

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)

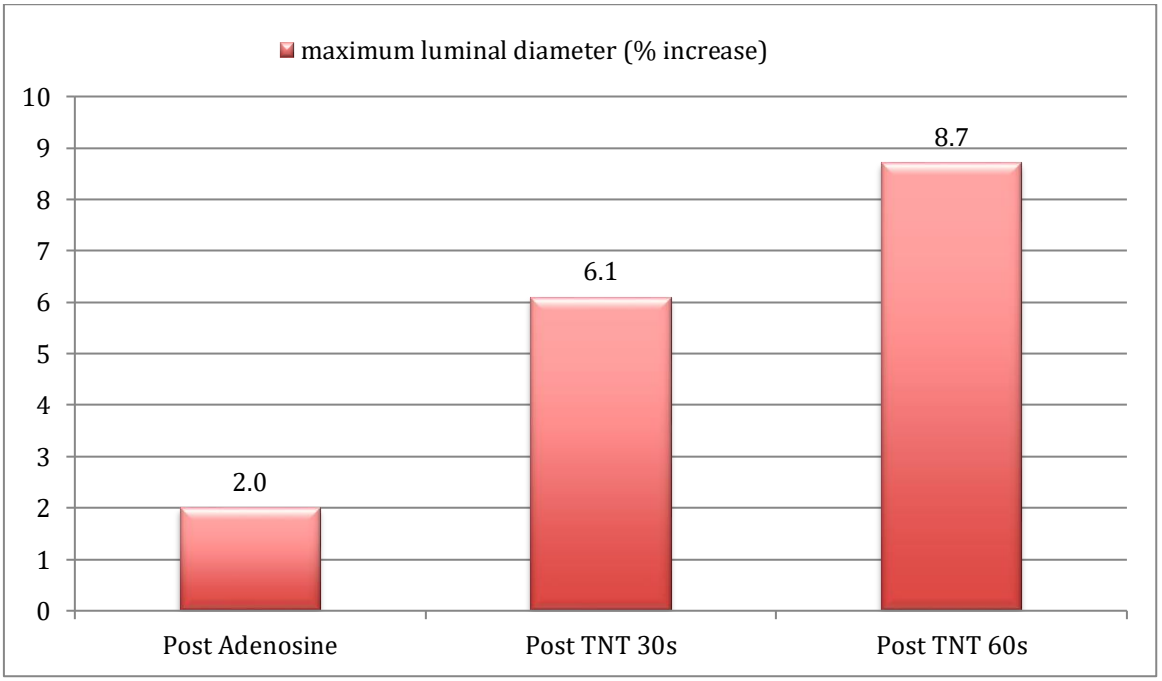


Figure 4.19: Coronary endothelial reactivity in HIV+/ACS group

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).

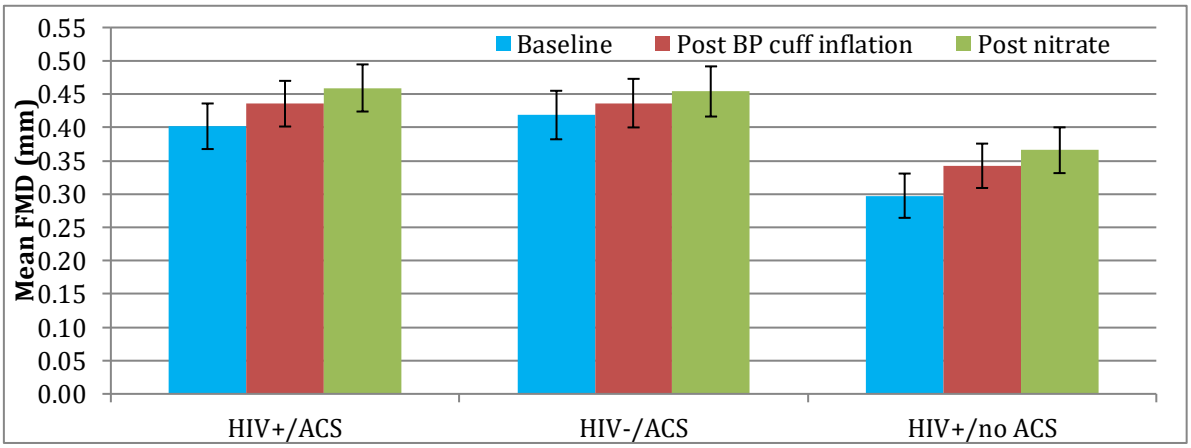


Figure 4.20: Brachial flow mediated dilatation post BP cuff inflation and post TNT

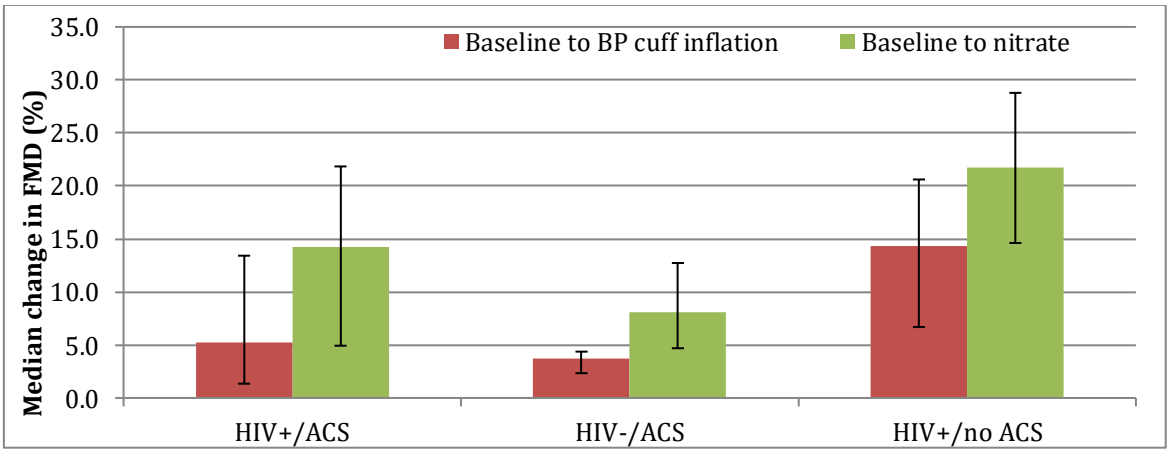


Figure 4.21: Median change in brachial flow mediated dilatation post BP cuff inflation and post TNT

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).

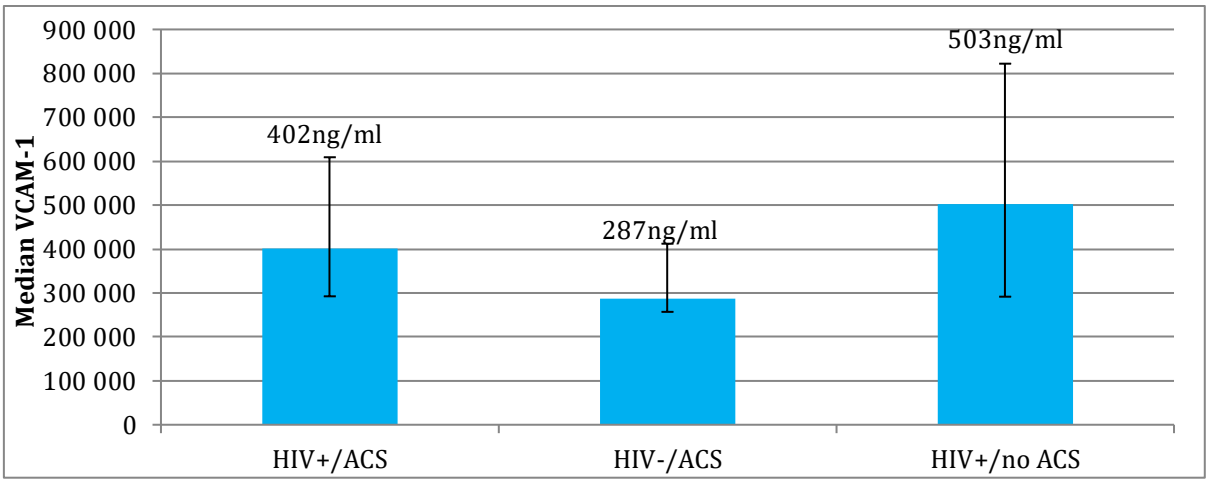


Figure 4.22: VCAM-1(pg/ml): HIV+/ACS and HIV+/no ACS had significantly higher levels than HIV-/ACS patients

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).

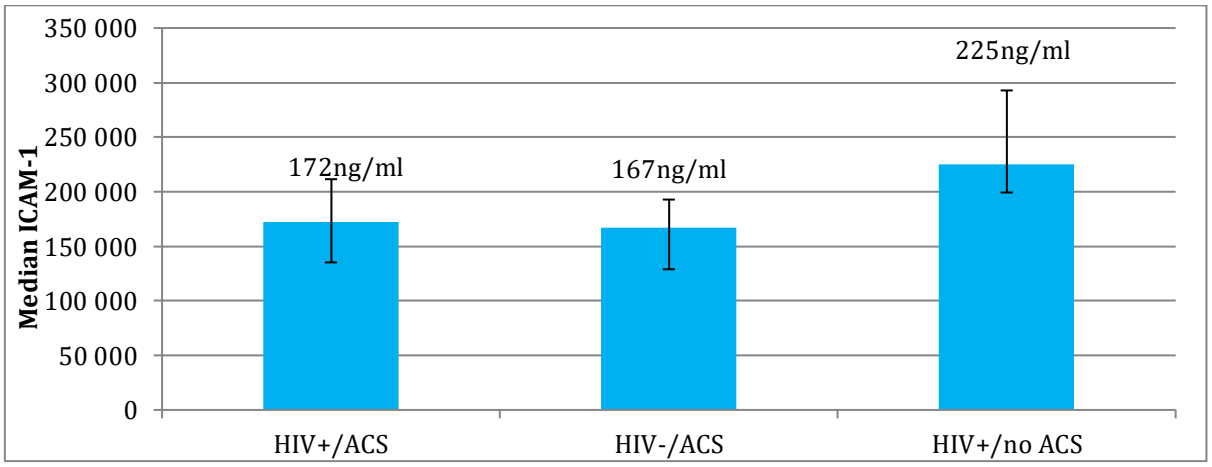


Figure 4.23: ICAM-1 (pg/ml): ACS patients had lower levels compared to the HIV+/no ACS group

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).

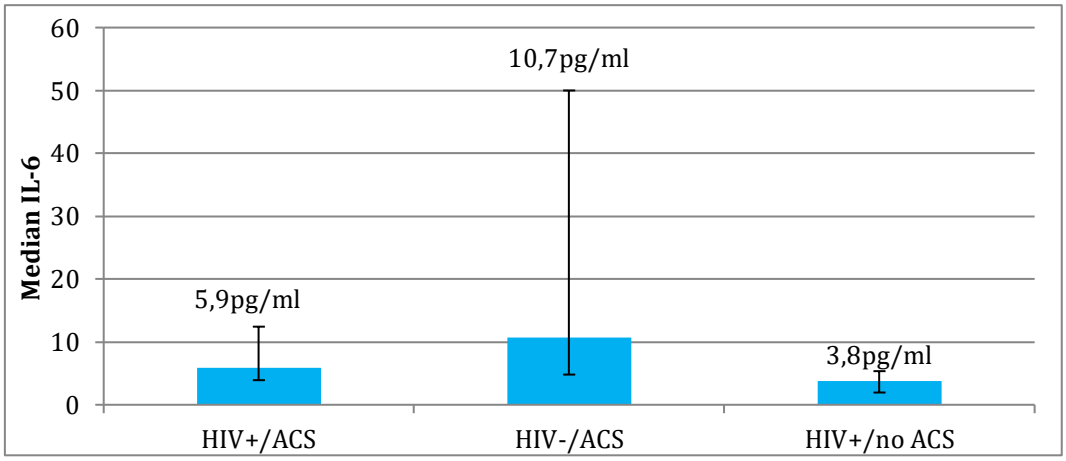


Figure 4.24 : IL-6 (pg/ml): ACS levels were higher than the HIV+/no ACS patients

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).

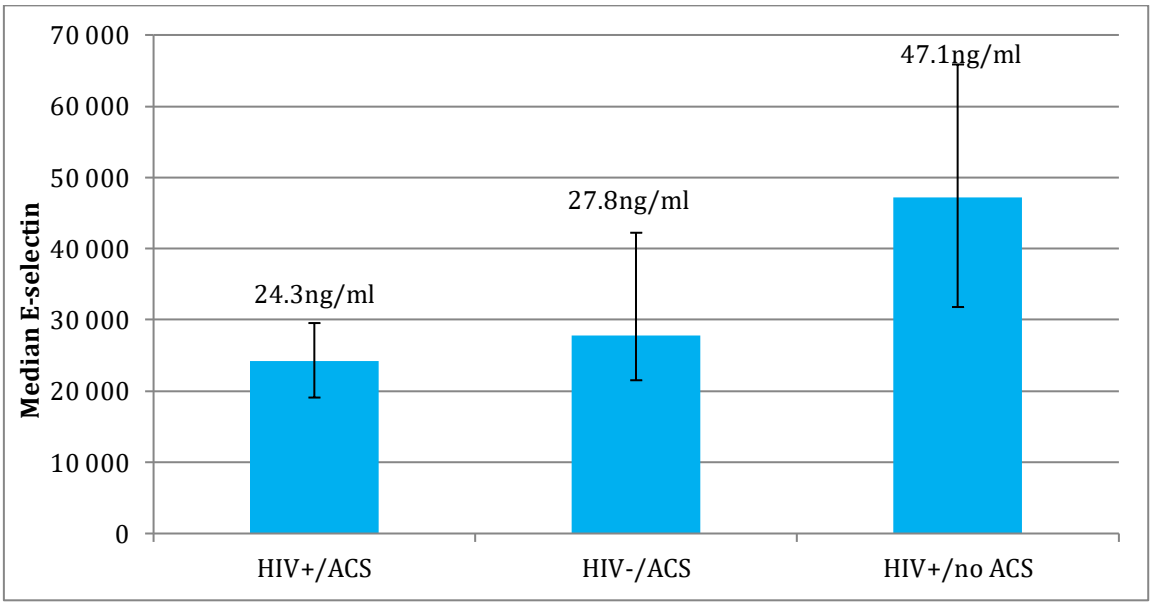


Figure 4.25 : E-selectin (pg/ml): ACS patients levels were lower than the HIV+/no ACS patients

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).

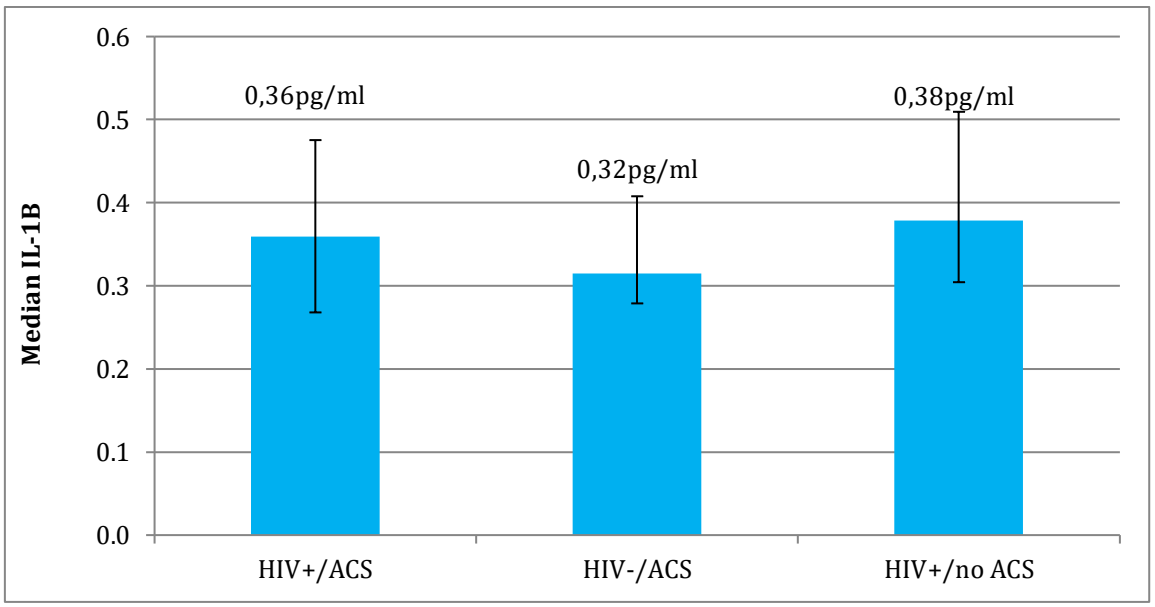


Figure 4.26: IL-1B (pg/ml) : There were no significant differences between the three groups

IL-1ra

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

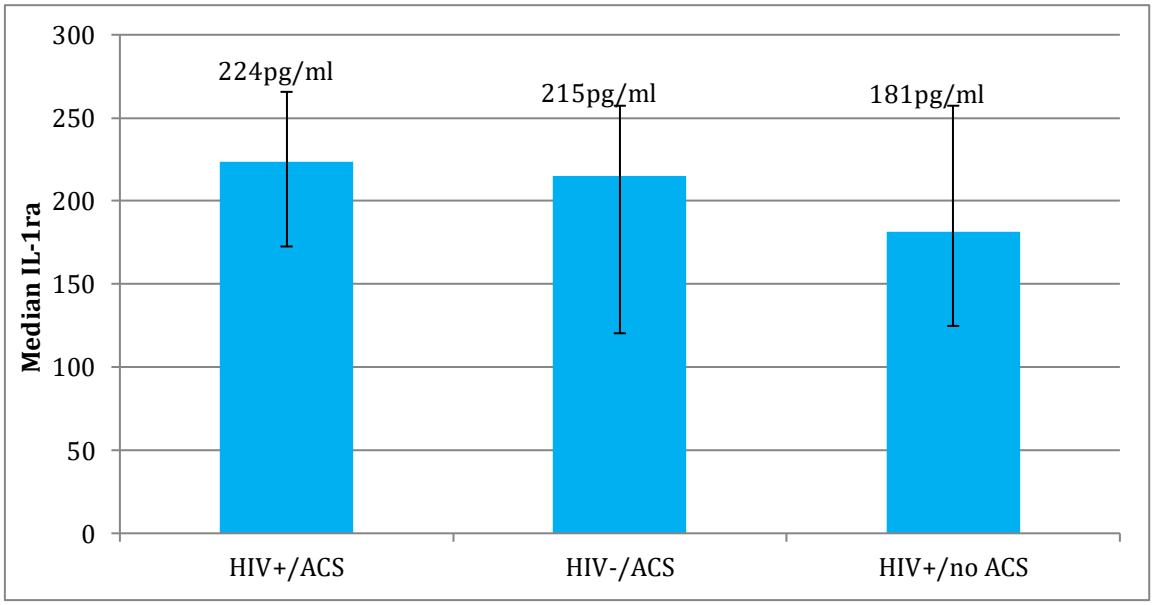


Figure 4.27: IL-ra (pg/ml) : There were no significant differences between the three groups

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).

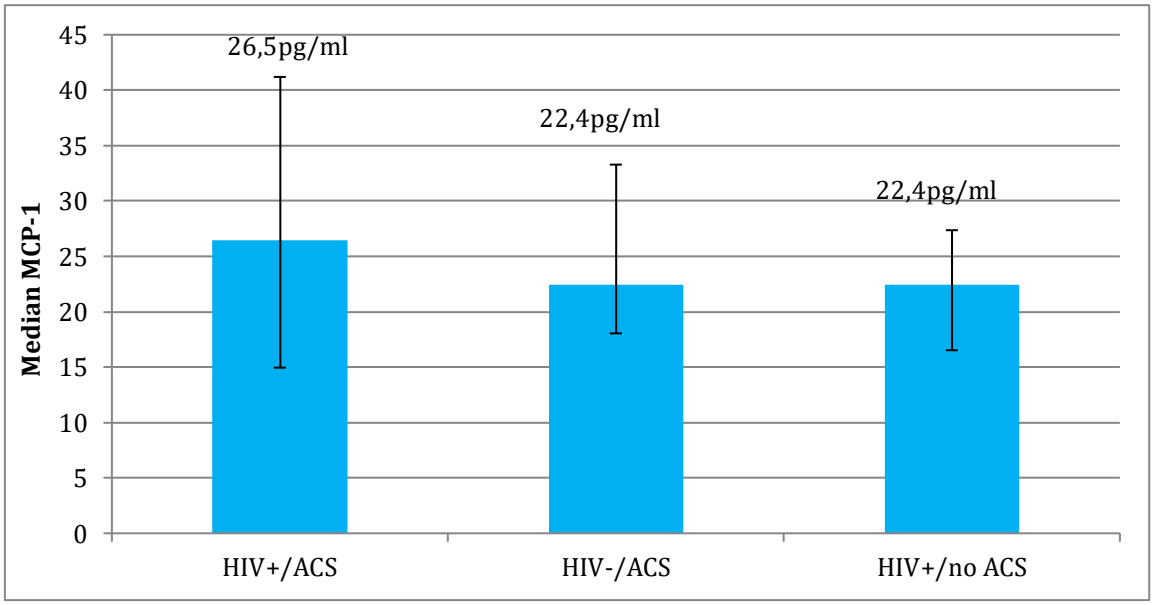


Figure 4.28: MCP-1 (pg/ml) : There were no significant differences between the three groups

TNFα

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

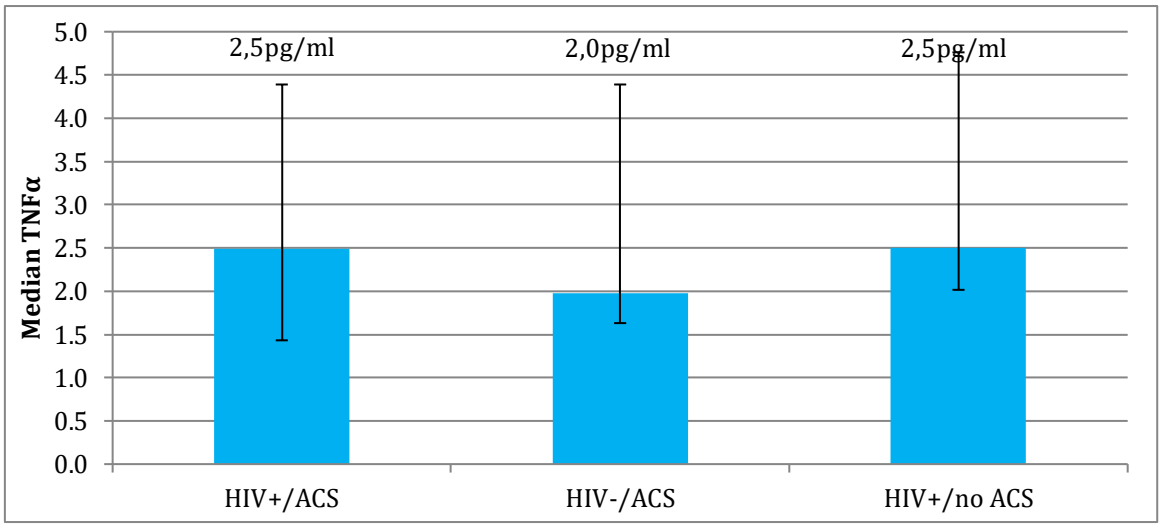


Figure 4.29: TNFα (pg/ml) : There were no significant differences between the three groups

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).

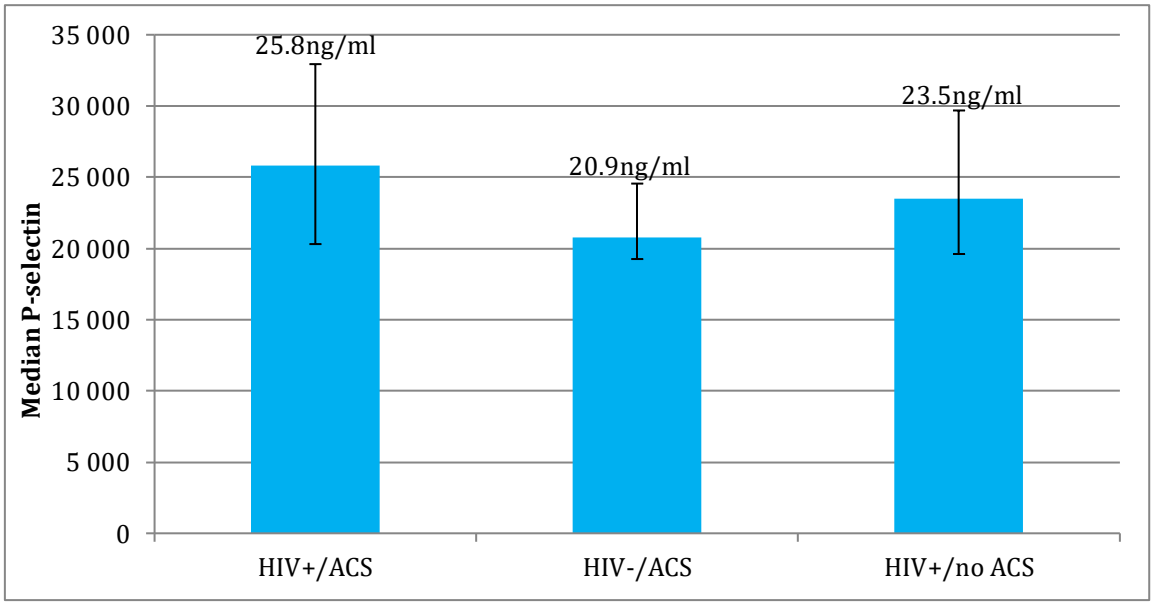


Figure 4.30 : P-selectin (pg/ml) : There were no significant differences between the three groups

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).

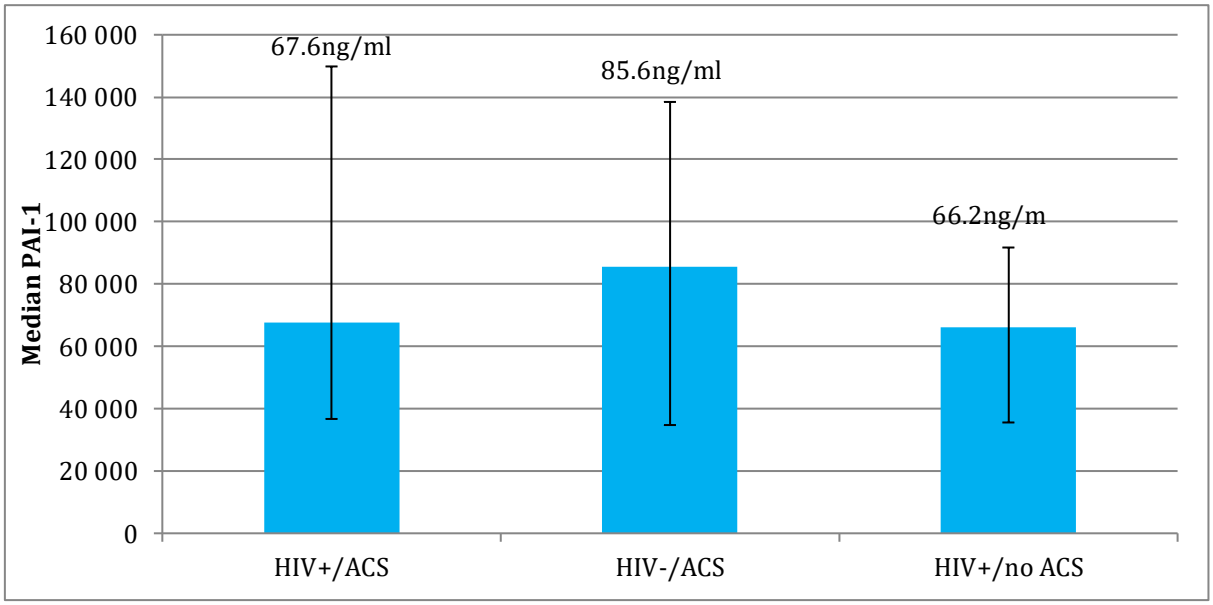


Figure 4.31 : PAI-1(ng/ml) : There were no significant differences between the three groups

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).

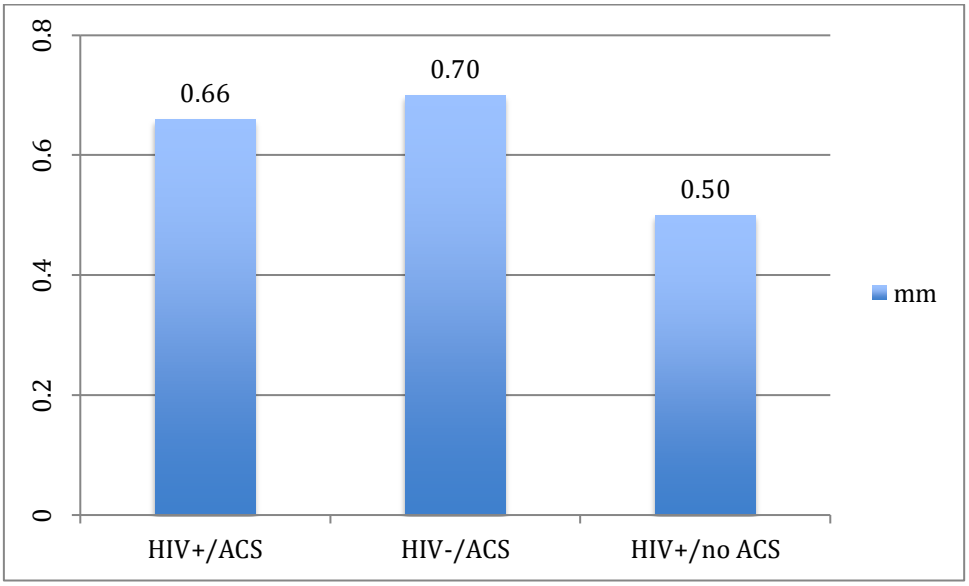


Figure 4.32: Carotid intima media thickness

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).

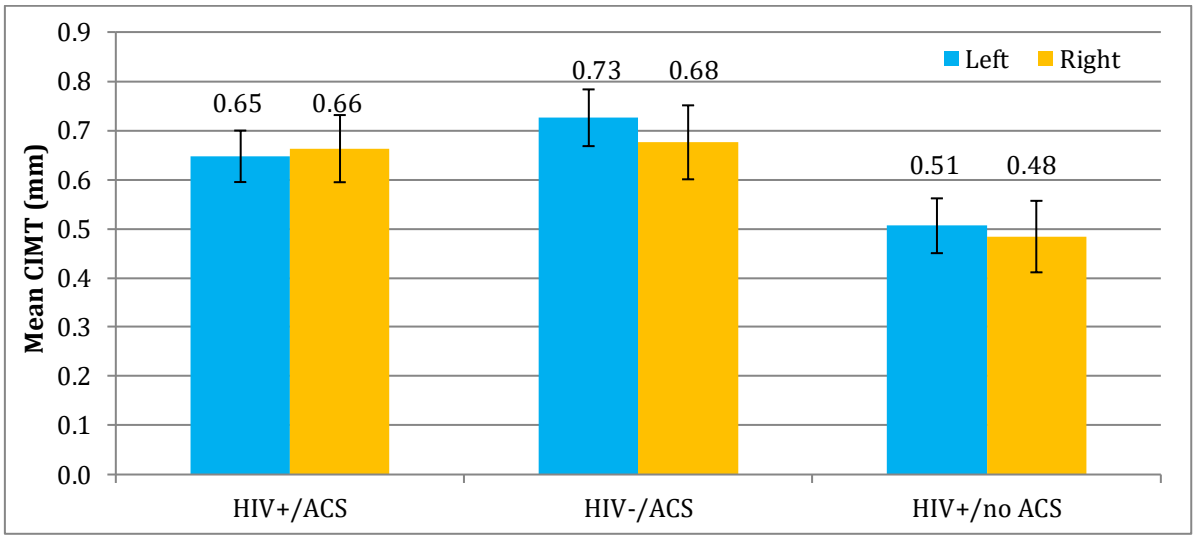


Figure 4.33 : Comparison of left and right carotid artery intima media thickness

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).

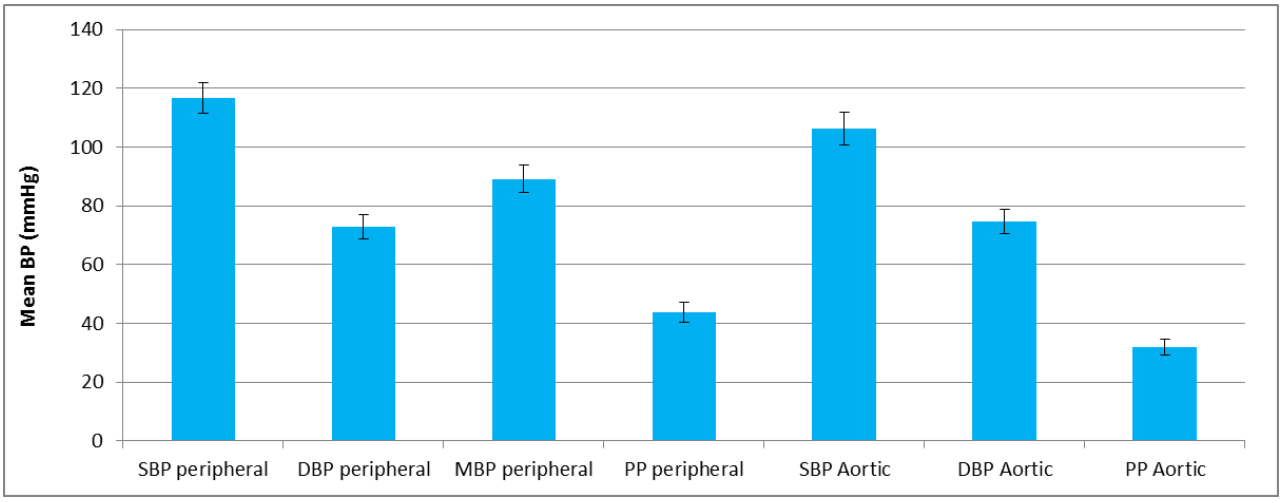


Figure 4.34 : BP measurements (HIV+/ACS patients)

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).

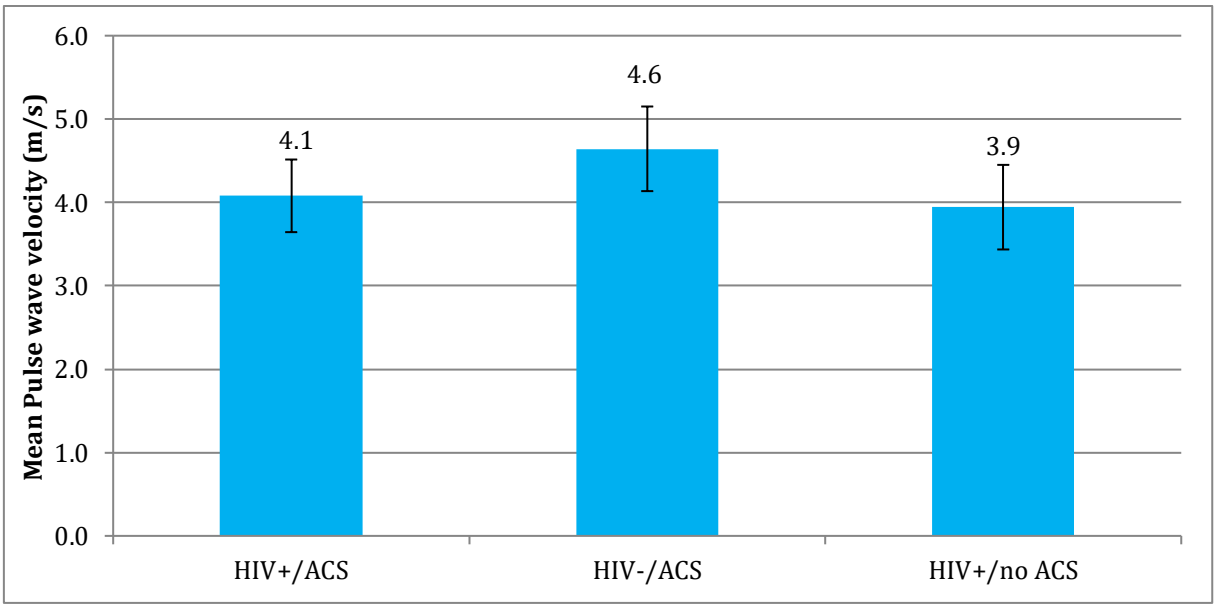


Figure 4.35: Pulse wave velocity

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).

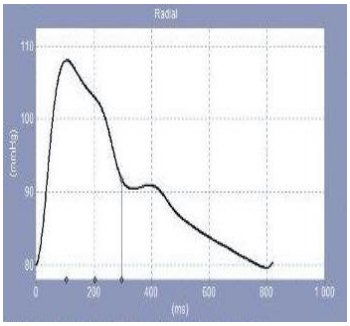


Figure 4.36: Radial waveform

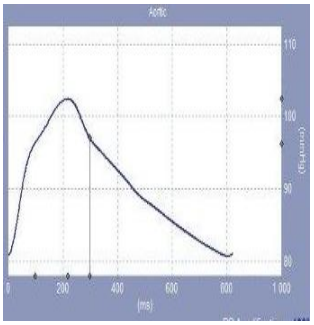


Figure 4.37: Aortic waveform

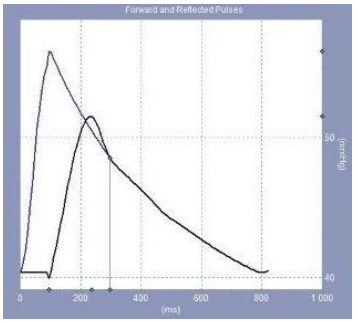


Figure 4.38: Forward and Backward pressures

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).

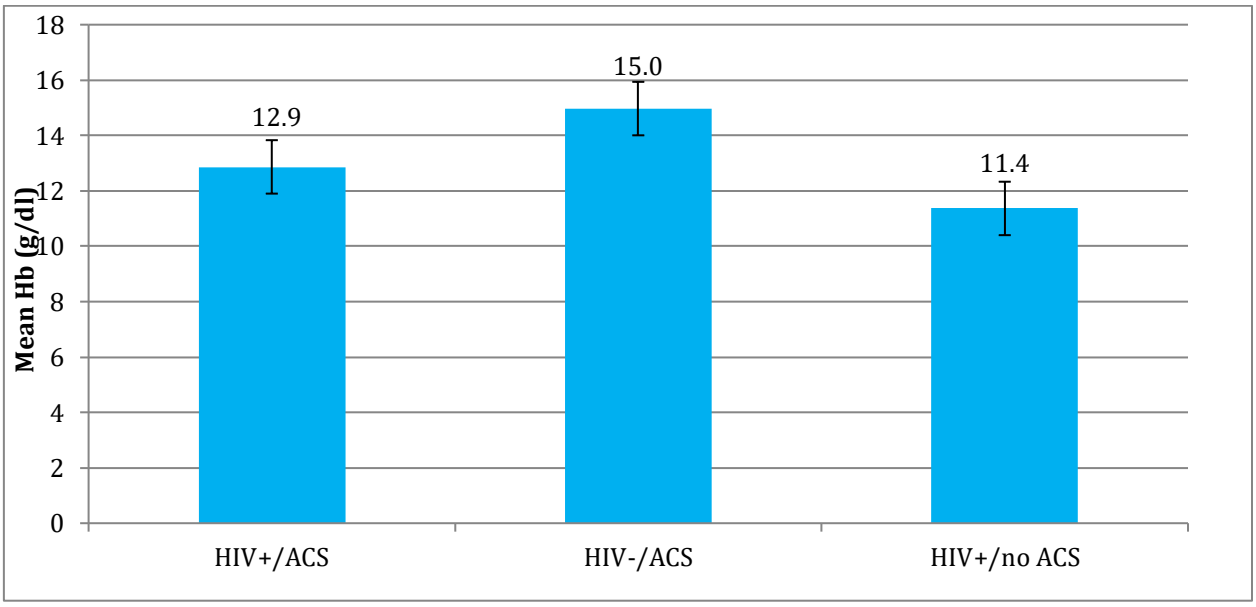


Figure 4.39 : Haemoglobin levels

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).

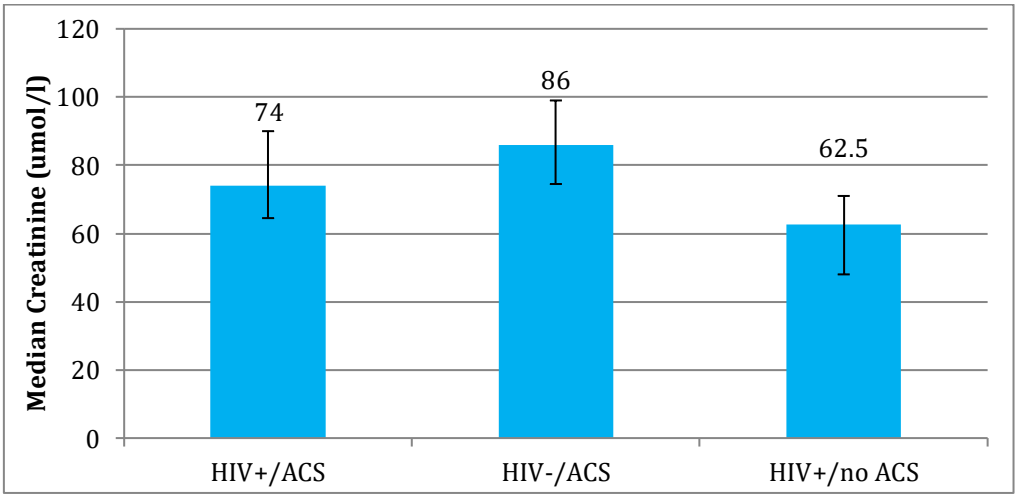


Figure 4.40 : Creatinine levels

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).

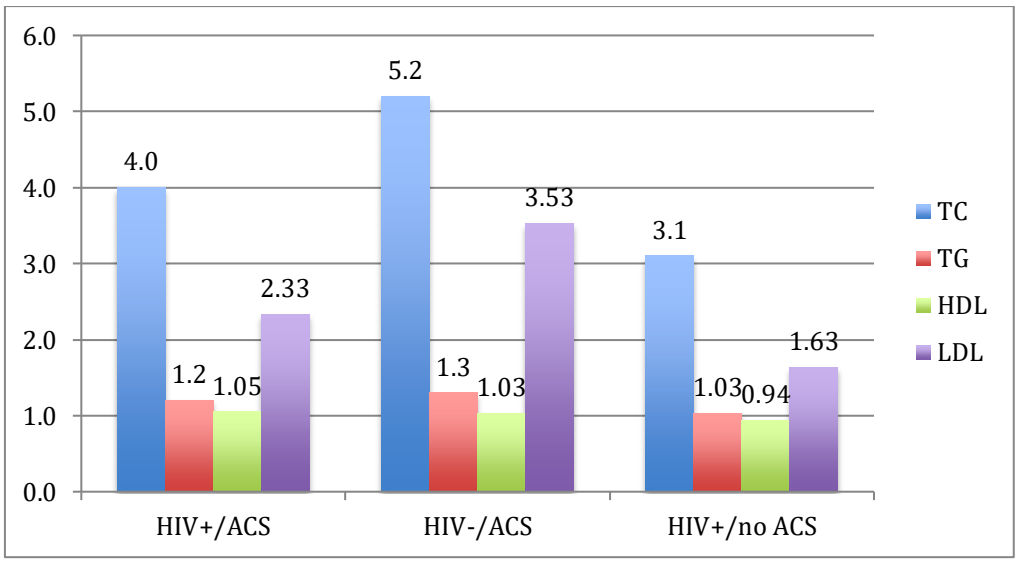


Figure 4.41 : Lipid profile

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).

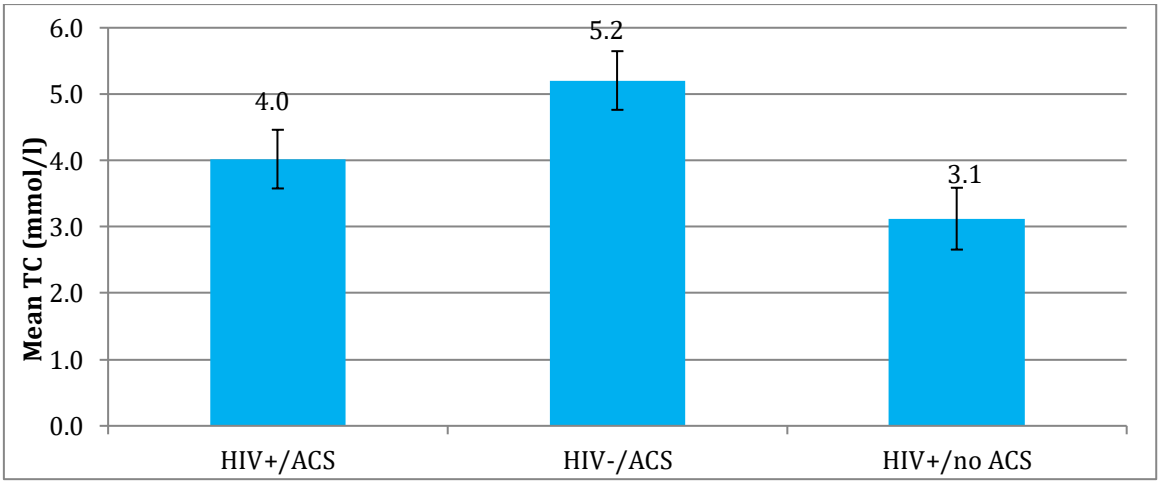


Figure 4.42 : Total cholesterol levels

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).

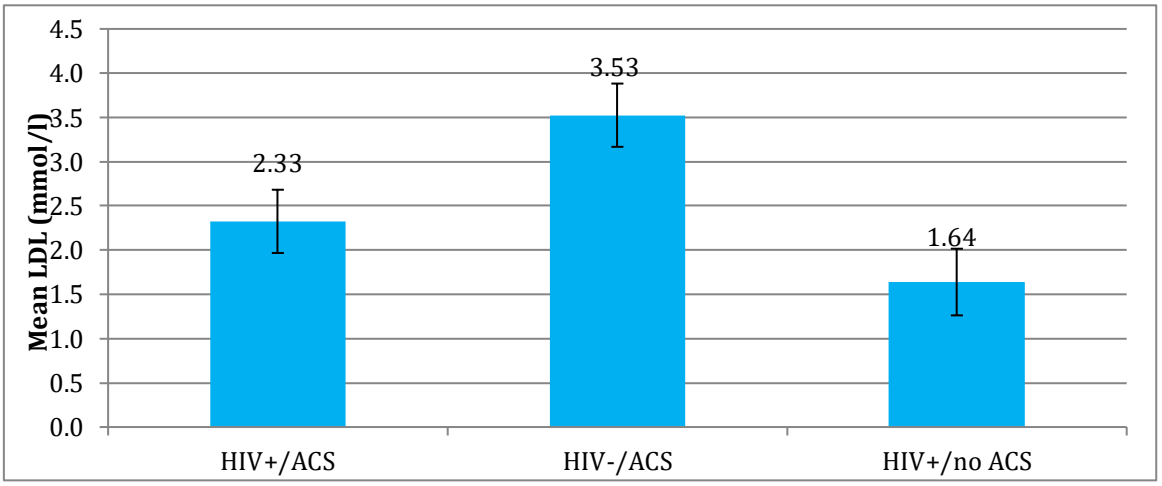


Figure 4.43 : LDL levels

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).

CHAPTER 5 : DISCUSSION AND CONCLUSION

5.1 Clinical presentation

In HIV-positive patients, the presence of CAD initially manifests as a clinical event such as an ACS (Vachiat et al., 2017). In developed countries the typical patient profile of a HIV-positive patient presenting with ACS is a young male patient less than 50 years of age and in more than 90% of cases, HIV has been present for more than 8 years (Boccara et al., 2013). The mean age of 51.1 years in the current study is similar to that reported in the literature. Unfortunately, it was not possible to ascertain how long HIV had been present in our cohort due to poor educational standards.

The mean age of the HIV+/no ACS group (36 years) was significantly lower than that of the HIV+/ACS group (51 years) and the HIV-/ACS group (52 years). The HIV+/no ACS group was much younger as they were recruited from the HIV clinic and were cART naïve. In the current study HIV-positive and HIV-negative patients with ACS were matched for age. 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). The body mass index in the HIV+/ACS patients was 24.4 kg/m^2, findings that are very similar to that found in another study from South Africa (Becker et al., 2010).

As most of the reported series of ACS in HIV-infected individuals arise from Europe or North America, Caucasians form the bulk of these cohorts. The current study is from South Africa and thus the predominant racial group in the study cohort is black. There was a strong association between group and ethnicity. The largest differences were noted between the HIV-/ACS and

HIV+/no ACS groups, the latter group comprised solely black patients, while the former group comprised only 35% black patients and white patients constituted 60% of this group. Ideally it would have been preferable to have balanced ethnicity in the 3 groups of patients studied. However, the ethnicity difference in the different three groups is not surprising as it is a reflection of the disease prevalence in the various ethnic groups in South Africa. Black patients have low prevalence of ACS and high prevalence of HIV, whilst the white patients have a low prevalence of HIV and high prevalence of ACS.

Traditional risk factors for CAD such as hypertension, diabetes and dyslipidaemia are more common in developed regions. The current study had fewer patients with hypertension, diabetes, dyslipidaemia and family history of CAD in HIV-positive patients with ACS. In developing countries, smoking appears to be the dominant risk factor with prevalence rates of 24.4% in HIV-positive males (Becker et al., 2010). In the current study more than half of the HIV+/ACS patients were smokers with fewer other traditional risk factors. This highlights the fact that in developing countries, smoking cessation should become an important health promotion strategy in HIV-positive patients.

Half of HIV+/ACS patients in the current study were on cART whereas other reports of cART use in HIV-positive patients presenting with ACS range from 53-93% (Boccara et al., 2011, Crane et al., 2017). Furthermore, protease inhibitors were not used in patients in the current study compared to 50-83% use in other studies (Hsue et al., 2004a, Boccara et al., 2011). This is most likely due to the fact that in the current study patients were treated with newer cART regimens. Ten of the thirteen patients (77%) who knew their HIV status were already on cART. The median time on cART was 24 months (IQR 5-51). Seven patients (35%) were not aware of their HIV status on admission for ACS. This probably reflects the fact that the majority of patients who access the public health service in South Africa come from poor socio-economic backgrounds and often lack sufficient educational background.

The HIV-positive and HIV-negative patients who presented with ACS each presented predominantly with STEMI (70%). This was followed by NSTEMI (20%) and UA (10%) in the remainder. This finding is similar to other studies, where it was also found that STEMI is the most common presentation in HIV-positive patients (Boccara et al., 2013). Only 4 of the 14 (29%) of the STEMI patients were thrombolysed. Due to low educational standards and poor socio-economic status, many patients present very late to public hospitals following the onset of STEMI and thus do not qualify for reperfusion therapies.

The left anterior descending artery was the most common artery involved (60%), followed by the right coronary artery (35%) and the left circumflex artery (20%). Six drug eluting stents were inserted with an average length of 22mm. In 8 patients (40%) there was a high thrombus burden associated with the infarct related artery and one patient was given an intracoronary thrombolytic as reperfusion therapy. Thrombosis of the infarct related artery has also been reported to be common in a study from Soweto, South Africa (Becker et al., 2010) as well as anecdotal reports from many other centers in developing countries. Management of such thrombosis is unclear but thrombus aspiration, GpIIb/IIIa inhibitors as well as intracoronary lytic therapy have all been suggested. One patient had sudden cardiac death two weeks after discharge in the HIV+/ACS group and the overall 5% mortality is similar to a meta-analysis of 11 studies on HIV-positive patients presenting with ACS (n=2442), which demonstrated a cardiovascular death rate of 7.9% (D'Ascenzo et al., 2012).

The rate of primary PCI was similar in our study to the Percutaneous intervention and surgical revascularization in HIV Database (PHD) registry (Table 5.1). The 20 HIV+/ACS patients from the current study were part of this registry. As can be seen from the table there were fewer percutaneous procedures in our patients with more patients treated conservatively with medical therapy as compared to the patients treated in the entire registry. PCI use was lower due to either

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

5.2 Intravascular ultrasound

There is ample evidence in the literature that HIV infection accelerates atherosclerosis by a factor of 1.5-2.0 (Triant et al., 2007). However, the mechanisms are poorly understood and have been discussed in more detail in Chapter 1.

In normal populations without HIV infection who have atherosclerosis, the vascular characteristics such as coronary plaque composition and endothelial dysfunction are well described. However, in HIV-infected populations these are not described at all or are poorly defined. In some HIV populations without known CAD, there have been descriptions of coronary plaque through non-invasive coronary CT imaging (Stein et al., 2014). However, coronary plaque characteristics are unknown in HIV-positive patients with established CAD. Thus one of the major objectives of this study was to directly assess plaque characteristics in HIV-positive patients presenting with ACS using intravascular ultrasound and virtual histology.

This is the first study that has highlighted through IVUS imaging, that significant atherosclerosis is present in patients who are HIV-positive presenting with an ACS event. This in a cohort of patients whose mean age was only 51 years. Using IVUS, this study has shown that the total plaque burden in HIV-positive patients consisted of moderate plaque in the majority (60%) of patients. In 35% of patients the total plaque burden was of mild degree and in a minority (5%) of patients there was severe plaque burden. Similar to non-HIV populations with ACS there was appropriately more severe plaque burden (30%) in the culprit vessel as opposed to non-culprit vessels (5%).

Furthermore this is the first prospective study which has characterized the coronary plaque morphology in HIV-positive patients presenting with ACS using VH-IVUS. This is also the first

study that has described in detail the total plaque burden both in culprit as well as non-culprit vessels of HIV-positive patients with ACS. Previous description of coronary plaque in autopsy studies in HIV patients only alluded to the fact that coronary lesions were eccentric atherosclerotic plaques with 80-90% reduction of the vascular lumen in coronary vessels, especially in the proximal vessels (Paton et al., 1993). In this study analysis of the entire coronary tree by IVUS demonstrated that the mean total plaque burden was significantly more prevalent in the proximal as compared to the middle and distal coronary artery segments. This is in agreement with findings of the autopsy studies in HIV-positive patients (Paton et al 1993). In the current study the mean plaque burden in the proximal, middle and distal locations was found to be 54.5%, 47.8% and 34.8%, respectively. The total plaque burden was significantly higher in the proximal coronary artery than in the middle segment of the coronary artery. The total plaque burden was also significantly higher in the middle segment compared to the distal segment of the coronary artery.

This study also demonstrated that some form of atherosclerosis is present in all HIV-positive patients presenting with ACS without any prior cardiac history. Even normal vessels by angiography were found to have atherosclerosis and in 5% of these vessels the plaque burden was surprisingly severe. Our findings help explain the discrepancy of lower plaque volumes that have been reported in HIV-positive patients studied angiographically, as coronary angiograms are not accurate in defining minor plaque volumes (O'Dwyer et al., 2016).

Virtual histology of the plaque in HIV-positive patients revealed that the culprit vessel consisted of fibrous plaque (56.5%), fibro-fatty plaque (21.2%), necrotic core plaque (14.4%) and dense calcific (3.6%) plaque. The non-culprit vessels consisted of fibrous plaque (55.1%), fibro-fatty plaque (29.5%), necrotic core plaque (8.2%) and dense calcific plaque (4.8%). The degree of fibrous plaque was significantly greater than fibro-fatty plaque, which in turn was significantly greater than necrotic core plaque, which in turn was significantly greater than dense calcific plaque. In summary, these findings have shown that the predominant plaque morphology in the

coronary arteries of HIV-positive patients presenting with ACS consists of fibrous plaque in just over half of all patients and fibro-fatty plaque in a further quarter. Necrotic core plaque is uncommon and dense calcified plaque is rare. Hence the plaque morphology in HIV-positive patients with an ACS event can be described as predominantly one of non-calcified fibrous and fibro-fatty disease. These finding were found in a group of patients with low prevalence of traditional factors for CAD, other than smoking. is in keeping with the low LDL and low CIMT found in HIV-positive patients in the current study. Thus other drivers of atherosclerosis, such as inflammatory mechanisms for atherosclerotic plaque development may play an important role in plaque formation in HIV-positive patients.

The findings of the current study, that fibrous and fibro-fatty plaque is present in the majority of HIV-positive patients presenting with a coronary event, are supported by non-invasive imaging such as coronary computer tomography angiography (CCTA) which has shown an increased prevalence of subclinical atherosclerosis in asymptomatic HIV-positive patients compared with HIV-negative patients (D'Ascenzo et al., 2015, Stein et al., 2014). A recent meta-analysis of 1229 asymptomatic HIV-positive patients on cART, demonstrated a 3–fold higher prevalence of non-calcific coronary artery plaques at CCTA as compared with HIV-negative controls (D'Ascenzo et al., 2015). Even in HIV-infected women, a significantly higher percentage of non-calcified plaque has been found on CCTA as compared to HIV-negative women (Fitch et al., 2013).

Using dual-source CCTA, features of non-calcified plaque have also been found in early atherosclerosis of healthy HIV-negative populations with a family history of early onset of coronary artery disease (Kral et al., 2014). Thus, the plaque morphology of atherosclerosis in HIV-positive populations, as found in the current study, is very similar to that found in early atherosclerosis of HIV-negative populations. One of the important findings of the current study is that the atherosclerosis in HIV-positive patients is more extensive and with less calcification as compared to atherosclerosis in HIV-negative populations. The reasons for these differences are

unclear but are probably related to the link between HIV infection and atherosclerosis, independent of traditional cardiovascular risk factors.

Higher rates of ACS in the general population without HIV infection have been reported in a number of studies to be associated with fibrous and fibro-fatty plaque as compared to mixed or calcified plaques (Lo et al., 2010, D'Ascenzo et al., 2015, Post et al., 2014). Non-calcified plaques, as found in our cohort, represents an earlier stage of atherosclerosis and is more prone to rupture, leading to ACS (Ahmadi et al., 2011). The presence of non-calcific or low attenuation coronary plaques in normal populations with ACS has also been shown by optical coherence tomography to correlate better with ruptured fibrous caps (Ozaki et al., 2011). Furthermore, the presence of non-calcific coronary plaques as diagnosed by CCT at time of ACS presentation in HIV-negative patients, has shown to predict recurrent coronary events after ACS (Kristensen et al., 2011). Importantly, HIV-positive patients have a larger burden of coronary atherosclerosis, particularly non-calcified plaque as compared to HIV-negative patients with similar cardiovascular risk factors (Lo et al., 2010). Thus, the dual risks of the presence of more extensive non-calcific fibrous and fibro-fatty plaque and its vulnerability to plaque rupture could explain the higher prevalence of ACS and earlier onset of ACS in HIV-positive patients as compared with HIV negative patients.

Of interest is that the profile of ACS in HIV-positive patients in developed countries is changing. In a recent study from 6 United States centers, half (50.4%) of all HIV-positive patients presenting with an ACS had type 2 myocardial infarction, which occurs in the setting of supply and demand mismatch (Crane et al., 2017). This is probably a reflection of the fact that HIV-positive patients in the United States are better controlled with regards to cART and have a far more comprehensive CAD risk factor management program as compared to developing countries.

5.3 Endothelial dysfunction

The endothelium lines the internal surface of blood vessels and is responsible for vascular homeostasis, such as maintenance of vascular tone, non-thrombotic vascular surfaces as well as immunomodulation. With the onset of endothelial dysfunction, the vasculature is predisposed to vasoconstriction, platelet activation, leukocyte adherence, pro-oxidation, impaired coagulation, thrombosis and vascular inflammation (Verma and Anderson, 2002). Endothelial dysfunction has thus been identified as a key step in promoting atherogenesis, and is well described to be an early predictor of future cardiovascular events both in patients with established and those without established cardiovascular disease (Schachinger et al., 2000, Neunteufl et al., 2000, Gokce et al., 2003).

Endothelial function can be measured in many different ways. One approach is to assess it invasively by assessing blood flow responses, either intra-arterial or intracoronary, to infusions of methacholine chloride, sodium nitroprusside and N^G-mono-methyl-L-arginine. The more common technique and one which is well validated, is the non-invasive measurement of endothelial function which relies on high resolution ultrasound of the brachial artery (Verma and Anderson, 2002).

Endothelial dysfunction is associated with increased levels of reactive oxygen species and decreased nitric oxide levels and hence decreased vascular reactivity (Verma and Anderson, 2002). HIV itself has been linked to endothelial dysfunction (Cotter, 2006, Boccara et al., 2013). This is supported by findings of a significant improvement in FMD in patients in the first 24 weeks after initiation of cART, suggesting that suppression of HIV viremia can lead to improved endothelial function (Murphy and Costagliola, 2008). However, undetectable viral loads do not necessarily equate to amelioration of ongoing inflammation and whilst inflammation and immune

activation are diminished with cART, they are not abolished. As HIV predominantly infects T cells and macrophages there is induction of oxidative and endoplasmic reticulum stress, dysregulation of autophagy and inflammasome formation, all of which contribute to HIV-associated atherosclerosis (Kearns et al., 2017). Thus HIV infection, even in the presence of cART, has been described to perpetuate endothelial dysfunction through immune activation mechanisms (Kearns et al., 2017)..

Endothelial dysfunction is well known to be associated with atherosclerosis in HIV-negative populations (Davignon and Ganz, 2004, Vanhoutte, 1997). It has also been described in HIV-positive patients without ACS (Baker and Lundgren, 2011, de Gaetano Donati et al., 2004, Cotter, 2006). In the current study, as assessed by FMD, HIV+/ACS patients had almost the same degree of endothelial dysfunction as the control group of ACS patients without HIV. Although it would appear that endothelial dysfunction was not more prevalent in the HIV-positive group with ACS it must be borne in mind that the latter group had significantly fewer coronary risk factors compared to the HIV-negative patients with ACS, suggesting that HIV infection itself contributed to endothelial dysfunction. HIV-positive patients without ACS had the highest brachial artery vasoreactivity compared to the patients with ACS. This is an interesting finding but is most likely a reflection of the much younger age of this group as compared to the other two groups as it is well known that endothelial reactivity declines with age.

Another approach to study endothelial function is by measuring endothelial biomarkers. Endothelial biomarkers, such as cellular adhesion molecules are either present on the surface of endothelial cells or are expressed on endothelial cells in response to certain stimuli. The endothelial biomarkers include the selectins (P-selectin, L-selectin, E-selectin) and vascular adhesion molecules (VCAM-1, ICAM-1) which are involved in leukocyte rolling, adhesion and transendothelial migration into sub-intimal spaces (Verma and Anderson, 2002). There is evidence that these cellular adhesion molecules can be considered reliable biomarkers for the

development and severity of atherosclerosis and add to the predictive value of the classical risk factors for ischaemic heart disease (Verma and Anderson, 2002, Ridker et al., 1998).

Endothelial function has been studied in HIV-positive patients since the onset of the epidemic (Lafeuillade et al., 1992). Even in untreated HIV-positive patients, endothelial dysfunction had been reported (Fourie et al, 2011). The mechanism of endothelial dysfunction in HIV infected individuals in the development of atherosclerosis is unknown but is thought to be multifactorial and the possible mechanisms include, direct involvement of HIV, endothelial activation and vascular inflammation (Boccara et al., 2013, Palella and Phair, 2011, Conaldi et al., 1995). Endothelial biomarkers such as VCAM-1 and ICAM-1 are elevated in patients early after HIV infection (Graham et al., 2013). In support of aforementioned mechanisms is that following cART, it has been shown that there is a fall in markers of endothelial function such as monocyte chemo-attractant protein, P-selectin and VCAM-1 (Graham et al., 2013).

Interestingly thus far there is a paucity of data on endothelial function in HIV-positive patients presenting with acute coronary syndromes. By studying ACS patients who were HIV-positive and comparing them to ACS patients who were HIV-negative it was possible to assess endothelial activation in both groups of patients. In developing countries high levels of endothelial biomarkers such as IL-6, TNFα, PAI-1, sCD14 have been reported in HIV-positive patients compared with HIV-negative patients (Triant et al., 2009, Baker et al., 2010, Kelesidis et al., 2012, Knudsen et al., 2014). Studies of endothelial function from developing nations have demonstrated that in recently seroconverted Kenyan women, endothelial biomarkers (VCAM-1 and ICAM-1) were significantly elevated in these patients early after HIV infection (Graham et al., 2013). In a recent study from South Africa, HIV-positive patients were found to have higher levels of adhesion molecules compared to HIV-negative patients with an odds ratio of 3.9 (2.2-7.0) for ICAM-1 and 16.2 (7.5-35) for VCAM-1 (Fourie et al., 2015). Furthermore, the same investigators reported that ICAM-1 and VCAM-1 were elevated in both treated and cART naïve patients with odds being greater for the never treated group. There is only one report in the

literature that studied endothelial biomarkers in HIV-positive patients with ACS (Becker, 2010). This study found significantly elevated VCAM-1 levels in HIV-positive patients with ACS as compared to control patients who were either HIV-negative or HIV-positive without ACS (Becker, 2010). In the cohort of HIV+/ACS patients of the current study, it was found that VCAM-1 levels were significantly higher as compared to HIV-/ACS patients, findings that are in concert with the report of Becker et al. The current study did not show ICAM-1 levels to be significantly elevated in HIV+/ACS patients. This is at odds with the findings of Fourie et al, but it must be borne in mind that the latter study did not include any HIV+ patients who had acute coronary syndromes. It is possible that the VCAM-1 may be stimulated by the occurrence of an ACS event. The endothelial biomarker, VCAM-1, is a member of the immunoglobulin super-family and is involved in cellular adhesion and transmigration of leucocytes through endothelial cells and is thought to play a role in the development of atherosclerosis (de Gaetano Donati et al., 2004). With the stimulation of endothelial cells by inflammatory cytokines there is increased expression of VCAM-1 and this is associated with an increased predictive value for future cardiovascular events (Blankenberg et al., 2003). Thus VCAM-1 may be an informative biomarker for predicting the risk of HIV disease progression, morbidity and mortality (Graham et al., 2013).

The proinflammatory cytokine, IL-6, induces expression of adhesion molecules such as VCAM-1 and ICAM -1 and may be seen as an early modulator of leukocyte trafficking in the vascular wall (Libby et al., 2002). However, the current study did not find significantly elevated levels of IL-6 in HIV-positive and HIV-negative patients with ACS. Lack of significant difference in IL-6 and other markers of endothelial dysfunction in HIV infected and non-infected controls have also been previously reported (Becker, 2010, Knudsen et al., 2014). These differences could be related to differences in risk profiles for , ethnicity and age in reported studies. There was no significant difference between the three groups for the following endothelial biomarkers; P-selectin, PAI-1, IL1B, MCP-1, TNFα and IL1ra. Thus these biomarkers did not prove useful in identifying HIV-

positive patients at high risk of developing ACS, findings which are very similar to those reported in another study from South Africa (Becker, 2010).

Endothelial function was also measured in the coronary circulation of the index patients who were HIV positive and who presented with an ACS event. Coronary endothelial function was measured only in the HIV+/ACS patients using adenosine and glyceryl trinitrate (TNT). The maximum lumen diameter (MLD) for each segment of each coronary artery was measured. Following administration of adenosine, the MLD increased by 2% and following infusion of bolus TNT the MLD increased by 6.1% after 30 seconds and by 8.7% after 1 minute. This is significantly lower than that reported in both atherosclerotic and non-atherosclerotic segments in HIV-negative patients where the percentage increase following TNT administration was found to be 17% and 31% respectively (Yamagishi et al., 1995). This confirmed that significant coronary endothelial dysfunction was present in the cohort of HIV-positive patients who presented with ACS. These findings are the first to describe significant coronary endothelial dysfunction in a cohort of HIV-positive patients presenting with ACS.

5.4 Non-invasive investigations

A meta-analysis of 13 observational studies has suggested a trend towards increased CIMT in HIV-infected patients (Hulten et al., 2009). As early as childhood, HIV-infected children receiving cART were reported to have increased CIMT, indicating that CAD risk may already be heightened in HIV-infected patients at a young age (McComsey et al., 2007). Unfortunately, there have been no other studies that have corroborated these findings. A study assessing CIMT in HIV-positive patients from San Francisco, showed that HIV-positive patients' baseline CIMT (0.91 ± 0.33mm) was significantly greater than CIMT (0.74 ± 0.17) in HIV-negative patients (Hsue et al., 2004b).

Carotid intima media thickness was measured in all three groups in the current study. In the study cohort, CIMT measurements were unexpectedly lower in the HIV+/ACS compared to the HIV-/ACS patients. The HIV+/no ACS patients also had low CIMT measurements. One possible explanation for this finding is the relative lack of traditional risk factors for atherosclerosis, such as hypertension and diabetes in the HIV+/ACS group. In support of this thesis is that it has been shown that the presence of high cardiovascular risk factor profiles in HIV- positive patients is positively associated with increased CIMT (Kablak-Ziembicka et al., 2004). Thus it is not surprising that the study from San Francisco showed increased CIMT in the HIV-positive cohort as the latter group had a higher risk profile for CAD and were older than the current study. Genetic factors may also play a role in the development of CIMT in that the HIV virus subtype differs in developed as compared to developing regions (Manga, 2015).

In HIV-positive patients, endothelial activation may lead to structural and functional vascular changes. Exposure to long-term subclinical inflammation is related to accelerated stiffening of large arteries. Peripheral waveform analysis using PWV has been shown to provide a noninvasive method of measuring 'global' endothelial function (Lekakis et al., 2011). Increasing levels of arterial stiffness are correlated with higher pulse wave velocities. The value for stiff vessels is a PWV >10m/s and this value has been found to be an independent marker of end organ damage (Mancia et al., 2013, Van Bortel et al., 2016). 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 with no differences between groups. This finding is most likely an age-related effect. This is supported by Fourie et al who recently reported increasing PWV velocities only after the age of 50 years in HIV-positive patients who were cART naïve (Fourie et al., 2011).

Disease severity may also contribute to atherosclerosis. An association between reduced CD4 cell count and non-calcified coronary artery plaque as well as the presence of coronary stenosis >50%, in HIV-positive patients as compared to HIV-negative patients, have recently been

reported (D'Ascenzo et al., 2015, Post et al., 2014). The average CD4 count in the current study cohort was low (301 cells/mm^3), despite half of the patients being on cART at the time of presentation with ACS. It is unknown how long the current study cohort were infected with HIV, but the low average CD4 count suggests these patients were possibly at more risk of developing atherosclerosis.

The mean haemoglobin level of the HIV-/ACS group (15.0g/dl) was significantly higher than that of both the HIV+/ACS (12.9g/dl) and HIV+/no ACS groups (11.4g/dl). This is not unusual as HIV+ patients are often anaemic due to numerous reasons including iron deficiency, decreased bone marrow production and increased bleeding. The median creatinine level for the HIV+/ACS and the HIV-/ACS groups were significantly higher than that of the HIV-/no ACS group. This is expected as the ACS patients are more likely to have haemodynamic disturbances as opposed to the stable patients with no ACS.

HIV-positive patients presenting with ACS had lower LDL levels than HIV-negative patients with ACS, findings which are similar to another local study (Becker et al., 2010) . The HIV-positive group pre-cART, had very low LDL levels. This is significantly different to that in developed nations where HIV-positive patients have worse lipid profiles as compared to HIV-negative patients (Boccara et al., 2017). The three groups of patients in the current study had similar HDL levels. These findings are somewhat different from other studies which found lower HDL levels in HIV-positive patients with ACS (Becker et al., 2010). These differences are more than likely related to differing populations and differing time frames of analysis. Inflammatory biomarkers such as hs-CRP have been reported to be elevated in HIV+ patients with ACS. However, in this study only CRP levels were measured and there were no significant differences between the three groups.

HIV-positive patients presenting with ACS have been found to have a 'thrombo-inflammatory' state caused by heightened platelet function, hypercoagulability and inflammation (Hauguel-Moreau et al., 2017). Mechanisms which promote thrombosis such as increased levels of soluble p-selectin, CD-40L and microparticles have been demonstrated in HIV-positive patients with ACS (Hauguel-Moreau et al., 2017). In our patient cohort, 40% of patients had a high thrombus burden associated with the infarct-related artery. This inflammatory and thrombotic milieu may well be important in the pathogenesis of the "athero-thrombotic plaque".

5.5 Limitations

This study had some limitations that deserve to be highlighted. Firstly this was a single centre study. Given the nature of the study it took almost 3 years to prospectively recruit 20 HIV-positive patients presenting with ACS to our centre and thus the small sample size. The time of presentation to angiography was left to the discretion of the treating physician and availability of Catheterisation lab resources. Given the type of the clinical presentation of patients in the study we were unable to completely match case control patients for age, gender and cardiovascular risk factors. Although the HIV+/no ACS group were gender matched, they could not be matched for age as the majority of HIV+/no ACS patients, who were cART-naïve, presenting at the HIV clinic were young. It would have been ideal to have performed IVUS imaging of the HIV-/ACS patients and compare these findings to the HIV+/ACS patients but because of prohibitive cost of IVUS catheters as well as time constraints in a busy catheterisation laboratory in the public hospital, this comparison was not possible. Medication therapy for hypertension and dyslipidaemia can have an impact on arterial compliance and subsequently endothelial function. Although there were no significant differences in the use of these medications in the three groups we did not assess the effect of medication on endothelial function independently.

5.6 Conclusion

The major findings of this study are multifold. Firstly, this is the first study that has highlighted that significant atherosclerosis is present in all patients who are HIV-positive and who present with an ACS event. These findings were found in a cohort of patients who had a relatively low risk profile for CAD. The total plaque burden in the majority of the HIV+/ACS cohort was at least of moderate degree and in a small minority it was severe. The total plaque burden was significantly higher in the proximal coronary artery, particularly the left anterior descending coronary artery.

Secondly, this is the first study that has demonstrated by direct visualization of plaque morphology that in HIV-positive patients with ACS, the predominant plaque morphology consisted of non-calcified fibrous and fibro-fatty plaque. These plaques are prone to rupture and this may explain the early age of onset of ACS in HIV-positive populations.

Thirdly, endothelial dysfunction as assessed by FMD is common in HIV-positive patients. Additionally, this is the first study detailing significant coronary endothelial dysfunction in patients who are HIV-positive and who present with an ACS event. This study has also shown that certain endothelial biomarkers such as VCAM-1, may be useful to identify HIV patients who have endothelial dysfunction and who may be at an increased risk of developing a coronary event.

Based on the findings of this study, several recommendations for the care of such patients in future can be made. Firstly, early identification of HIV+ patients with CAD risk factors is important. These patients should be managed with aggressive primary preventative measures such as cessation of smoking, control of hypertension, diabetes and control of dyslipidemia. Additionally, in high risk HIV+ patients, endothelial biomarkers such as VCAM-1, may prove to be useful in identifying those who have endothelial dysfunction and who may be at increased risk of a coronary event.

It is hoped that the findings of this study contributes to the knowledge base of HIV-associated atherosclerosis and because of the large burden of disease in developing countries, particularly South Africa, the findings from this study will help in some small measure to the management of patients who are HIV infected.

Appendices

Appendix 1

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Ahmed Ismail Vachiat

CLEARANCE CERTIFICATE	M111143
PROJECT	The Histological Characterization and Coronary Endothelial Function in HIV Positive Patients Presenting with Acute Coronary Syndromes
INVESTIGATORS	Dr Ahmed Ismail Vachiat
DEPARTMENT	Department of Internal Medicine/Cardiology
DATE CONSIDERED	25/11/2011
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 16/07/2012 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof Pravin Manga

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 2

CONSENT TO ACT AS A SUBJECT IN RESEARCH

I, _____ being 18 years or older, consent to participating in a research project entitled: **"The histological characterization and coronary endothelial function in HIV positive patients presenting with acute coronary syndromes."**

The procedures have been explained to me and I understand and appreciate their purpose, any risks involved, and the extent of my involvement. I have read and understood the attached information leaflet. I understand that the procedures form part of a research project, and may not provide any direct benefit to me.

I understand that all experimental procedures have been reviewed and approved by the Human Research Ethics Committee, University of Witwatersrand, Johannesburg.

I understand that my participation is voluntary, and that I am free to withdraw from the project at anytime without prejudice.

_____	_____
Participant name and signature	Date
_____	_____
Investigator name and signature	Date

Appendix 3

Patient Information Sheet

Title of research project:

"The histological characterization and endothelial function in HIV-positive patients presenting with acute coronary syndromes"

Dear participant

I am currently a Physician training in cardiology, conducting a research project on the effect of HIV, in patients presenting with an acute coronary syndrome (ACS) / heart attack, on atherosclerosis (thickening and hardening of the arteries) and endothelial function (the inner lining of the blood vessels). This research will help us better understand why HIV-positive patients present with ACS. I would like you to please participate in this study to further help with research in this field.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. Participation in this study is entirely voluntary and you are allowed to withdraw at any time. If after reading the information sheet you decide against participating in this study please be assured that any further treatment will not be affected. The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. There are no re-imbursements. The routine follow up will be at our cardiac clinic after 1 month and 6 monthly thereafter.

The study involves twenty HIV-positive and twenty HIV-negative patients that present with ACS. Prior to the routine angiogram, additional blood test of approximately 20ml of blood (4 teaspoons) will be taken for analysis. The twenty HIV-positive patients will have the routine angiogram and in addition an intravascular ultrasound (camera) will be used to image the plaque, and a flow wire will be used to assess the narrowing and reactivity. There is no additional risk to the standard coronary angiogram and this will in fact provide us with more information on the narrowing. As part of the study after the angiogram, a carotid IMT (camera to your neck vessel) will be performed together with a BP measurement of your arm to assess dilation (non-invasive).

All the data will be put together, analyzed and the results presented in my thesis and possibly published in a research paper written for the scientific community.

I have obtained approval for my study from the Human Research Ethics Committee of the University of the Witwatersrand. If you have any questions regarding your rights as a participant in this study or any complaints please contact Prof P Cleaton-Jones (011) 717 2301

I would like to ask you please to participate in the study and confirm your willingness to do so by signing the consent form.

Sincerely

Dr Ahmed Vachiat
MBBCh (Wits) MMed FCP (SA)
011 488 3611
Email : ahmed.vachiat@wits.ac.za

Appendix 4

DATA COLLECTION SHEET

Patient Study number_____ HIV **Yes**☐ **No**☐
Date of admission: _____
Age: ____
Sex: M☐ F☐ Race: B ☐ W☐ C☐ I☐
STEMI ☐
NSTEMI ☐
UA ☐
No ACS ☐
Chest pain onset _____ duration _____ Radiation _____

Date HIV diagnosed _____
CD4 (diagnosis) _____
Last CD4 _____
cART yes☐ no☐ if yes initiation date _____
ARV _____

Medication

Risk factors:

- ☐previous MI
- ☐smoking
- ☐hypertension
- ☐diabetes mellitus
- ☐dyslipidaemia
- ☐family history of premature coronary heart disease
- ☐obesity

Allergies: _____

Examination

Weight _____ Height _____ Body mass index_____
Abd circum _____
SBP _____ pulse _____
DBP _____

ECG

Rate Rhythm
Axis
Intervals PR QRS _____ QT _____
ST elevation leads _____ Inverted T waves _____

ECHO

Left ventricular internal diameter (diastole) _____

Left ventricular internal diameter (systole) _____
Ejection fraction _____
Regional wall motion abnormalities _____
Valvular lesions _____
Pericardial effusions _____
Pulmonary artery pressure _____

Laboratory data

FBC: Hb ____ platelets ____
U&E: Na ___K ____Cl ____ CO2____Urea ____Creatinine _____
CRP ____ ____ ____
Lipogram Chol ___ TG___ HDL___ LDL___
CD4 ____

Carotid IMT R CCA _____ L CCA _____

Flow Mediated Dilation

Baseline _____

BP cuff inflated_____

TNT _____

Pulse wave velocity _____

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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

HIV and Ischemic Heart Disease

Ahmed Vachiat, MBBCh, Keir McCutcheon, MBBCh, Nqoba Tsabedze, MBBCh, Don Zachariah, MBBCh, Pravin Manga, MBBCh, PhD

ABSTRACT

The association of coronary heart disease (CHD) and human immunodeficiency virus (HIV) infection has been well recognized for many years. The etiology of the increased prevalence of CHD in HIV-infected populations is the result of complex interactions among the viral infection, host factors, traditional risk factors, and therapies for HIV. As the HIV population is living longer, largely attributable to combination antiretroviral therapy, there is concern about the effect of the rising prevalence of CHD on morbidity and mortality, as well its effect on health systems around the world. This review will highlight the epidemiological evidence linking HIV infection and CHD. It will also focus on our current understanding of the pathogenesis and factors associated with HIV infection and CHD. In addition, the review will highlight modes of presentation and management strategies for mitigating risk and treatment of HIV-positive patients presenting with CHD. (J Am Coll Cardiol 2017;69:73–82) © 2017 by the American College of Cardiology Foundation.

Of the approximately 37 million people in the world living with human immunodeficiency virus (HIV), 70% live in sub-Saharan Africa (1,2). The increased prevalence of coronary heart disease (CHD) in this population is due to increased life expectancy globally, resulting from better access to combination antiretroviral therapy (cART) and high levels of traditional cardiovascular disease (CVD) risk factors (3). Although North America and Europe have substantial data on CHD in the HIV-infected population, there is a paucity of data regarding HIV-associated CHD from developing regions.

Despite the evidence that HIV infection carries a higher risk of developing coronary artery disease (CAD), the mechanisms responsible for the heightened risk are not well understood. The etiopathogenesis of HIV and atherosclerosis is secondary to the highly complex interplay between numerous factors (**Central Illustration**). It has been well recognized for many years that there is increased prevalence of traditional risk factors in HIV-infected individuals (4,5). In addition, the effects of certain cART treatment regimens lead to dyslipidemia, insulin resistance, and endothelial dysfunction (6,7). However, the role of HIV-related inflammation and immune activation is central to the increased risk of CAD (8). Furthermore, the outcome of the interaction between the different factors in an individual or population is also dependent on other variables, particularly environmental and genetic factors.

This review focuses on epidemiological evidence linking HIV infection and CHD, and on our current understanding of the pathogenesis and associated factors. We will also highlight modes of presentation and management strategies for mitigating risk and treatment of HIV-positive patients presenting with CHD. HIV and nonischemic heart disease are discussed in the accompanying review in this issue of the *Journal* (9).

EPIDEMIOLOGY

HIV infection has become a medically controllable chronic disease with non-acquired immunodeficiency syndrome (AIDS) defining illnesses as the main cause of morbidity and mortality (10). This is observed in regions with wide cART coverage, and is associated

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the Division of Cardiology, Department of Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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.

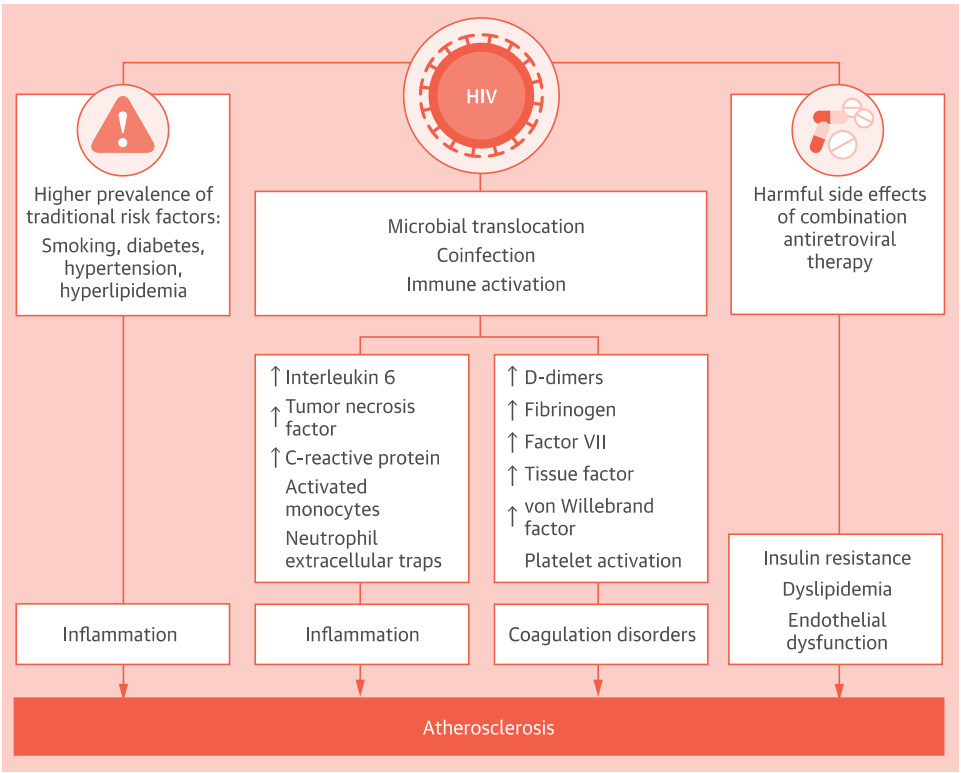
INFLAMMATION AND IMMUNE ACTIVATION. HIV infection, through attendant inflammation and immune dysfunction, is an independent predictor of CVD. Two recent large cohort studies found a strong and consistent association of HIV with a 44% to 48% increased risk of MI, independent of traditional risk factors, 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

and budgets. Thus, research from these regions is clearly needed. Current data suggests that management of HIV-positive patients with CHD is similar to that of HIV-negative patients. Our knowledge of the complex interaction of traditional factors, inflammation and immune activation, cART, and HIV infection itself in the progression of atherosclerosis has grown over the past 2 decades. However, more investigation and study are required to understand the critical pathways in the pathogenesis of the atherosclerotic process in the HIV population, the role of aggressive primary and secondary preventative measures for CHD, and the role of current and newer antiretroviral therapies. We hope that these investigations will have a significant effect on long-term outcomes of the HIV-infected population in the future.

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KEY WORDS acquired immunodeficiency syndrome, antiretroviral agents, atherosclerosis, coronary heart disease, drug interactions, myocardial infarction

A New Face of Cardiac Emergencies

Human Immunodeficiency Virus–Related Cardiac Disease

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KEYWORDS

• Human immunodeficiency virus • HIV-associated acute cardiovascular diseases
• Antiretroviral drug interactions • Emergency department

KEY POINTS

- Patients positive for the human immunodeficiency virus (HIV) present a unique challenge to emergency physicians as they may present to the emergency department with a variety of cardiovascular diseases related to the HIV infection.
- Common cardiovascular emergencies include acute coronary syndromes, HIV-associated cardiomyopathy, pericardial effusion, infective endocarditis, pulmonary embolism, and cardiac arrhythmias.
- Important drug interactions between antiretroviral therapy and common cardiovascular therapies exist and should be taken into consideration when treating such patients.

INTRODUCTION

The human immunodeficiency virus (HIV) epidemic is a major health challenge of the twenty-first century with an estimated 36.7 million people living with HIV globally and more than 1.2 million HIV-positive patients living in the United States.[1,2] The improved access to combination antiretroviral therapy (cART) has not only increased life expectancy, but has also changed the spectrum of disease. Thus HIV-positive patients present a unique challenge to emergency physicians, as they may present with a variety of cardiovascular diseases related to the HIV infection (Fig. 1). In this review we discuss the presentation, management, and prognosis of common acute cardiovascular diseases affecting HIV-positive patients presenting to the emergency department (ED).

CORONARY ARTERY DISEASE

HIV infection carries an overall 1.5 to 2.0-fold increased risk for developing coronary artery disease (CAD).[3] Current data suggest that immunodeficiency (CD4 <200 cells/mm^3) is significantly associated with a higher risk of myocardial infarction (MI).[4,5] HIV-related inflammation and immune activation together with endothelial dysfunction and coagulation abnormalities contribute to CAD in these patients.

Studies indicate a high prevalence of traditional CAD risk factors in HIV-positive populations.[4,6] However, prevalence estimates vary due to differences in study populations, risk cutoffs, genetic background, geographic location, and access to cART. Smoking is the most common risk factor and has been reported to be two-fold higher in

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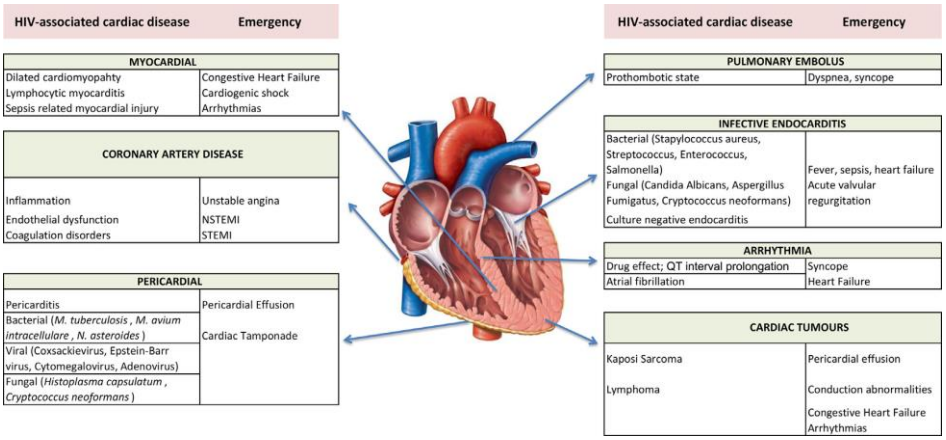


Fig. 1. Cardiac emergencies in HIV. NSTEMI, non-STEMI.

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]

Table 1
Antiretroviral drug interactions with common cardiovascular therapies

Cardiovascular Medications	Non-Nucleoside Reverse Transcriptase Inhibitors	Nucleoside Reverse Transcriptase Inhibitors	Protease Inhibitor	Integrase Inhibitor
Antiplatelets				
Aspirin	No effect	No effect	No effect	No effect
Clopidogrel	Etravirine and efavirenz decrease effect of clopidogrel	No effect	Decreases effect of clopidogrel	Elvitegravir/cobicistat decreases effect of clopidogrel
Prasugrel	No effect	No effect	Decreases effect of prasugrel	No significant effect
Ticagrelor	Decreases effect of ticagrelor	No effect	Increased risk of bleeding	Increased risk of bleeding with elvitegravir/cobicistat
Antifailure				
ACE inhibitors	No effect	No effect	No effect	No effect
Losartan	Efavirenz and etravirine increases effect of losartan	No effect	Decreases effect of losartan	Elvitegravir/cobicistat decreases effect of losartan
Telmisartan	No effect	No effect	No effect	No effect
Valsartan	No effect	No effect	No effect	No effect
Carvedilol	Variable response	No effect	Variable response	Elvitegravir/cobicistat increases effect of carvedilol
Metoprolol	No effect	No effect	Increases effect of metoprolol	Elvitegravir/cobicistat increases effect of metoprolol
Furosemide	No effect	Potential elevated exposure of tenofovir	No effect	No effect
Spironolactone	No effect	No effect	No effect	No effect
Anticoagulants				
Heparin	No effect	No effect	No effect	No effect
Warfarin	Variable response	No effect	Variable response	Elvitegravir/cobicistat decreases effect of warfarin
Dabigatran	No effect	No effect	No effect	No effect
Rivaroxaban	Decreases effect of rivaroxaban	No effect	Increased risk of bleeding	Elvitegravir/cobicistat increases bleeding risk
Apixaban	Decreases effect of apixaban	No effect	Increased risk of bleeding	Elvitegravir/cobicistat increases bleeding risk

Abbreviation: ACE, angiotensin-converting enzyme.

Data from European AIDS Clinical Society. European AIDS Clinical Society guidelines. 2017. Available at: http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Accessed May 23, 2017; and Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2016. Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed May 23, 2017.

Revascularization using drug-eluting stents appears to be safe and efficacious in HIV-positive patients.[26] There is no significant difference in target vessel revascularization rates post stent implantation between HIV-positive and HIV-negative patients.[27,28] However, one study of 201 patients with ACS found a stent thrombosis rate of 3% in HIV-positive patients, which is significantly higher compared with that found in HIV-negative patients.[29] Coronary artery bypass grafting should be considered if clinically indicated. Perioperative complications related to bypass surgery have been found to be no different from those in HIV-negative patients even when CD4 counts are less than 500 cells/mm^3.[30]

Prognosis

Mortality and overall prognosis of HIV-positive patients presenting with ACS is similar to that of HIV-negative counterparts.[31] Long-term outcomes have also been reported to be similar.[31,32] Risk factors for death include the presence of chronic kidney disease, nucleoside reverse transcriptase inhibitors-sparing therapy, low ejection fraction (EF) and CD4 counts less than 200 cells/mm^3.[29] Some studies suggest that HIV-positive patients have higher rates of recurrent MI compared with HIV-negative patients.[29,31] HIV-positive patients have also been reported to have a 4.5-fold increased rate of sudden cardiac death, which is associated with a history of previous MI, cardiomyopathy, heart failure, arrhythmia, hypertension, and dyslipidemia.[33]

HUMAN IMMUNODEFICIENCY VIRUS–ASSOCIATED CARDIOMYOPATHY

Epidemiology

HIV-associated cardiomyopathy encompasses several myocardial disease entities. These include dilated cardiomyopathy (DCM) with reduced EF, lymphocytic myocarditis, sepsis-related myocardial injury, and toxic drug reactions. Right ventricular dysfunction secondary to HIV-associated pulmonary hypertension, other secondary causes of pulmonary hypertension, such as pulmonary infections (tuberculosis) and chronic pulmonary thromboembolic disease, also may lead to right-sided heart failure.

In the pre-cART era, dilated cardiomyopathy with reduced EF was reported to be a common cardiac complication of HIV infection with a prevalence ranging from 10% to 30% and associated with a low CD4 cell count (<100 mm^3) and poor prognosis.[34,35] With increasing availability of cART, the DCM phenotype is now less common, with diastolic dysfunction being the dominant myocardial manifestation.[35,36]

Clinical Presentation

In the ED, these conditions typically manifest as congestive heart failure either as a de novo index presentation or a decompensated state precipitated by a new-onset arrhythmia, infectious process, or CAD. In most developed countries where cART coverage is extensive, HIV-associated cardiomyopathy usually presents with minimal symptoms despite having left ventricular (LV) dysfunction.[37] Therefore, dyspnea of unknown origin may be the only clinical manifestation, requiring echocardiography to better define LV systolic and diastolic function to aid in making a definitive diagnosis.

Congestive heart failure due to DCM with reduced EF is still encountered in regions where cART is less accessible and is frequently associated with a high burden of opportunistic infections.[38,39] Right ventricular dysfunction presenting with pedal edema and a raised jugular venous pressure may be seen in patients with HIV-associated pulmonary hypertension or pulmonary hypertension due to other secondary causes. Echocardiography is essential in delineating raised pulmonary arterial pressures, and confirming a dilated right ventricle and atrium with preserved LV function.

Management and Prognosis

The management of HIV-associated cardiomyopathy in ED should follow current guidelines for the treatment of acute heart failure.[40,41] The primary goal is to screen for cardiogenic shock and respiratory failure and thereafter manage the acute precipitant for acute heart failure. In the HIV population, important precipitants include ACS, opportunistic infections, and drug toxicity.

There are no reported adverse drug interactions between antiretroviral therapies and inotropic agents used for the treatment of cardiogenic shock. However, there are possible drug interactions with certain diuretics, angiotensin receptor antagonists, and B-blockers, which are all key therapies for heart failure. To date, angiotensin-converting enzyme inhibitors have no reported drug interactions with antiretroviral drugs (see Table 1).

Patients on zidovudine, which has been implicated to cause DCM, should be changed to safer new agents with fewer side effects.[42,43] All HIV-positive patients at presentation should be initiated on cART, as antiretroviral therapy has been

reported to reduce the prevalence of HIV-associated DCM by 30%.[36,44]

PERICARDIAL DISEASE

Pericardial involvement in HIV-infected patients is common. The prevalence of pericarditis and subsequent pericardial effusions, before the extensive use of cART, was common and reported to range from 11% to 40%.[45,46] However, following the introduction of cART, the prevalence of pericardial effusions has declined considerably.[47] Poor immune status with low CD4 count is associated with a higher prevalence of pericardial effusion.[45] Fortunately, most pericardial effusions that do develop in HIV-infected patients are small and are largely asymptomatic.[45]

Pericardial effusions may be the result of opportunistic infections. These include bacterial infections, particularly *Mycobacterium tuberculosis*, in developing countries where tuberculosis is endemic. In these countries, reports suggest that large pericardial effusions are related to *M tuberculosis* in up to 90% of cases.[48,49] Other infections, commonly seen in immunocompromised HIV-positive patients, such as *Cryptococcus*, *Nocardia*, *Cytomegalovirus*, and *Toxoplasma* may cause pericarditis. Malignancies, such as lymphoma and Kaposi sarcoma, in HIV-positive patients may also be associated with pericardial effusions. It has been postulated that pericardial effusions may occur in the absence of inflammation of the pericardium, as cytokine activation in advanced HIV infection may cause the capillary leak syndrome.[45,50] Despite aforementioned etiologies, the cause of pericardial effusions in developed countries is not found in up to 80% of patients.[51]

Clinical Presentation in the Emergency Department

Small pericardial effusions are asymptomatic and often diagnosed incidentally, as patients may present with another illness. Larger effusions often present with fever, dyspnea, or chest pain. On clinical examination, the apex beat may be poorly palpable or may be absent. Chest radiography will usually suggest an enlarged cardiac silhouette and there may be electrocardiographic changes of pericarditis, diffuse low voltages, and electrical QRS alternans with large pericardial effusions.

Diagnostic workup in the ED should be guided by clinical presentation and local epidemiology of the region. Pericardiocentesis, ideally under fluoroscopic and or echocardiographic guidance, should be considered only in patients with moderate to large effusions. Contemporary biochemistry, virology, and molecular biological techniques have considerably improved diagnostic yield.[52]

HIV-infected patients with large pericardial effusions may present with cardiac tamponade. This should be suspected if a patient presents with symptoms such as acute dyspnea with tachycardia, hypotension, pulsus paradoxus greater than 10 mm Hg, muffled heart sounds, and jugular venous distension. In this instance, urgent echocardiography is mandatory (Fig. 2). The characteristic features include a moderate to large pericardial effusion with right atrial and right ventricular collapse.[53] Urgent pericardial drainage with appropriate imaging guidance, such as echocardiography or fluoroscopy, is critical in management of such patients.

There is a small group of patients who may develop constrictive pericarditis. This is largely reported to be a sequel to tuberculous pericarditis.[54] They usually present with dyspnea, ankle and abdominal swelling, and on clinical examination have tachycardia, a distended jugular venous pressure, and early third heart sound. Diagnosis can be suggested on chest radiography and confirmed by echocardiography.

Prognosis and Therapy

Pericardial effusion in HIV-infected patients predicts a higher mortality, with one report suggesting a ninefold increased mortality in those HIV-infected AIDS patients with pericardial effusion compared with those without pericardial effusion.[45] In those countries in which tuberculosis is endemic, the mortality from tuberculous pericarditis is extremely high, with mortality ranging from 17% to 40%.[55]

Treatment of pericardial effusions is dependent on the underlying etiology. Bacterial, viral, and other infections need to be treated appropriately.

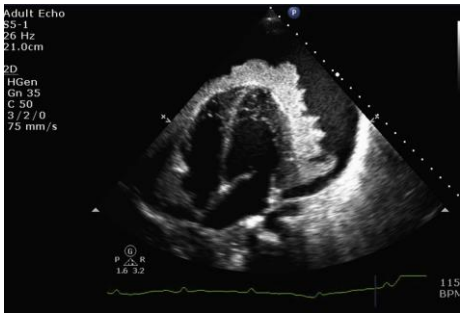


Fig. 2. Echocardiographic image: HIV-positive patient with large tuberculous pericardial effusion with fibrinous strands noted in the pericardial space.

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]

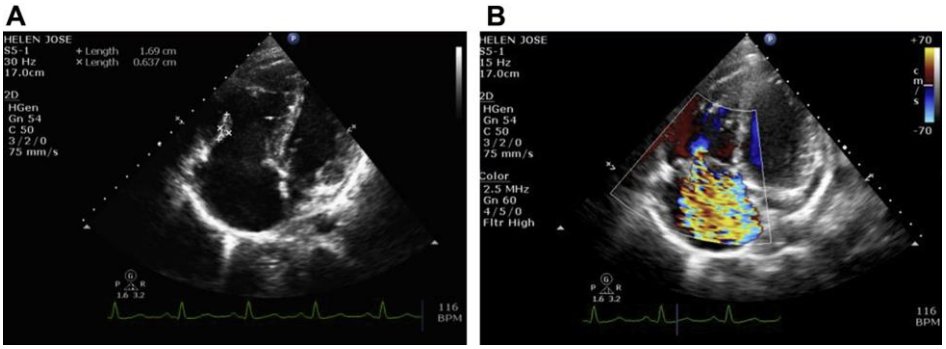


Fig. 3. (*A, B*) Echocardiographic image: HIV-positive, cART-naïve, intravenous drug user showing a large vegetation on tricuspid valve (*A*) caused by *Staphylococcus aureus*, complicated by severe tricuspid insufficiency (*B*).

MISCELLANEOUS CONDITIONS

Pulmonary Embolism

HIV is a prothrombotic state with a 2 to 10-fold increased risk of venothromboembolism and the risk is higher in those with low CD4 counts.[68–70] Pulmonary embolism should be considered when patients with HIV present with unexplained dyspnea or hypoxia. Electrocardiographic findings include tachycardia, with features of right heart strain (right axis deviation, S_I Q_{III} T_{III} pattern, and inverted T waves in the right precordial leads). Pulmonary embolism should be confirmed by computed tomography pulmonary angiography and primary reperfusion therapy with thrombolysis should be considered for those in cardiogenic shock. The initiation of warfarin in patients on cART may lead to clinically significant drug interactions. Agents such as nevirapine and lopinavir/ritonavir can induce warfarin metabolism and hence decrease the efficacy of warfarin, whereas etravirine can inhibit its metabolism (see **Table 1**). Hence, empiric doses are discouraged and careful monitoring of international normalized ratio is advised.

Arrhythmias

HIV-positive patients may present to the ED with tachyarrhythmias or bradyarrhythmias. These may occur in the setting of ACS or in the presence of HIV-associated structural heart disease. Frequent electrocardiographic abnormalities include ventricular ectopy, bundle branch block, and atrioventricular block due to fibrous degeneration of the conduction system.[71] QT prolongation is also noted in HIV-positive patients due to the higher exposure to drugs, such as azoles, and antifungal and macrolide antibiotics. Interestingly, HIV-positive patients are prone to prolonged QT and torsade de pointes, even in the absence of drug therapy. Evidence suggests that the HIV tat protein inhibits KCNH2 protein expression and thereby enhances the predisposition to the prolonged QT syndrome.[72] The overall incidence of atrial fibrillation in HIV-positive patients is low and when present is generally associated with more advanced HIV disease.[73]

Cardiac Tumors

HIV-related malignancies such as Kaposi sarcoma and lymphoma can also affect the heart. Kaposi sarcoma and lymphoma have been shown to involve the pericardium, myocardium, coronary artery adventitia and great vessels.[74] Thus, they may present to the ED with heart failure, superior vena caval syndrome, pericardial effusion, atrial and ventricular arrhythmias and heart block. A detailed history, examination and appropriate investigations will help confirm the diagnosis, followed by appropriate therapy. The introduction of cART and more advanced chemotherapy has significantly improved the prognosis of these conditions.[75]

SUMMARY

Access to cART in many regions of the world has significantly changed the spectrum of cardiovascular disease in HIV-positive populations. HIV-positive patients present less often with infectious complications and more often with noncommunicable diseases, such as CAD. In most instances, the approach to diagnosis and treatment of cardiovascular disease in HIV-positive patients presenting to the ED will be the same as HIV-negative populations. As highlighted, the interactions between cART and common cardiovascular therapies need to be borne in mind. With timely diagnosis and appropriate management, the prognosis of these patients will be significantly improved.

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Atherosclerotic plaque in HIV-positive patients presenting with acute coronary syndromes

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ABSTRACT

Objectives: This study aimed to characterize the atherosclerotic plaque and plaque burden in HIV-positive patients presenting with acute coronary syndromes (ACS).

Methods: We prospectively studied 20 HIV-positive patients with ACS. Intravascular ultrasound (IVUS) and virtual histology (VH) were performed to assess plaque burden and plaque characteristics in the culprit and non-culprit coronary arteries.

Results: HIV-positive patients with ACS had a mean age of 51.1 (± 8.1 years). ST-segment elevation myocardial infarction was the most common presentation (75%) with the left anterior descending artery being the most common culprit artery (60%). In 60% of patients the total plaque burden was of moderate degree (40-70% stenosis) whilst it was of mild degree (<40% stenosis) in 35% and in 5% of patients the total plaque burden was severe (>70% stenosis). Severe degree of total plaque burden was more commonly found in the culprit vessel (30%) as compared to the non-culprit vessels (5%). Furthermore, the plaque burden was found to be located predominantly in the proximal portion of the coronary arteries. The predominant plaque morphology consisted of fibrous plaque (55.4%) and fibro-fatty plaque (26.6%), while necrotic core was present in 13.3%. Dense calcium was present in only 4.7% of the cohort.

Conclusions: ST-segment elevation myocardial infarction was found to be the most common mode of presentation in HIV-positive patients with ACS. IVUS and VH demonstrated a high burden of atherosclerosis in the left anterior descending artery and proximal vasculature. The atherosclerotic plaque in HIV-positive patients was predominantly comprised of non-calcified fibrous and fibro-fatty plaque.

Keywords

Atherosclerosis
HIV
Acute coronary syndromes
Intravascular ultrasound
Virtual histology

Abbreviations

HIV	Human immunodeficiency virus
IHD	Ischemic heart disease
IVUS	Intravascular ultrasound
VH	Virtual histology
VH-IVUS	Virtual histology intravascular ultrasound
ART	Antiretroviral therapy
STEMI	ST-segment elevation myocardial infarction

INTRODUCTION

There are approximately 37 million people living with the human immunodeficiency virus (HIV) infection worldwide of whom 70% live in sub-Saharan Africa [1,2]. Studies suggest that HIV infection confers an overall 1.5-2.0 fold increased risk of developing ischemic heart disease (IHD).[3-6] Combination antiretroviral therapies (ART), particularly protease inhibitors and high levels of traditional cardiovascular disease risk factors have increased the prevalence of IHD in this population.[7,8]

Based upon spectral analysis of ultrasound backscatter, intravascular ultrasound (IVUS) facilitates the characterization of coronary plaque morphology by transforming the coronary vascular ultrasound images into a color-coded representation, thereby creating a virtual histological (VH) assessment of the plaque. Virtual histological intravascular ultrasound (VH-IVUS) imaging uses four color-coded spectral parameters (dark-green, yellow-green, red and white) representing fibrous and fibro-fatty lesions, necrotic core and calcium respectively.[9] This spectral analysis of coronary plaque has been well correlated with histopathology with a predicative accuracy of 87.1%, 87.1%, 88.3% and 96.5% for fibrous, fibro-fatty, necrotic core and dense calcium, respectively.[10]

The characteristics of the atherosclerotic plaque in HIV-negative patients with IHD are well defined. In a study of HIV-negative patients with stable angina or troponin positive acute coronary syndrome (ACS), VH-IVUS of non-culprit lesions has shown that fibrous and fibro-fatty plaque was present in 43.7 % of patients and calcific plaque was present in the remaining 56.3 % of patients.[11] On the other hand, coronary plaque characteristics in HIV-positive patients have not been well studied

and are poorly elucidated. Autopsy studies in HIV-positive patients have described coronary lesions as eccentric atherosclerotic plaques with 80-90% reduction of the vascular lumen and histopathological findings as hyperplastic endothelial cells lining a thickened intima, characterized by the proliferation of smooth muscle cells and monocyte macrophages.[12,13] Using coronary computed tomography, asymptomatic HIV-positive patients have been found to have a higher prevalence of coronary atherosclerosis and greater degree of coronary plaque volume and greater number of coronary segments with plaque as compared to HIV-negative patients with similar Framingham 10year risk for myocardial infarction.[14] To date there are no published data describing plaque characteristics and plaque burden by direct visualization using IVUS in HIV-positive patients with ACS.

AIM

The primary objective of this study was to characterize the atherosclerotic plaque and plaque burden in HIV-positive patients presenting with ACS using IVUS and VH.

METHODS

Design and study population: The study was a cross sectional prospective study of HIV-positive patients with ACS conducted at a large, urban public hospital in Johannesburg, South Africa, over 3 years (July 2012-July 2015). All HIV-positive patients with ACS at the time of admission were included in the study. Exclusion

criteria included patients <18 years, patients with previous ACS or known atherosclerotic vascular disease. Approval for the conduct of the study was obtained from the local institutional review board (Ethics clearance number M111143).

All patients underwent coronary angiography performed via the femoral route. Following left ventriculography, a 7F guiding catheter was engaged in the culprit vessel. A coronary (balanced middle weight) guide-wire was introduced through the guiding catheter and tracked into the distal portion of the coronary vessel. Intravascular ultrasound imaging was initially performed in the culprit vessel prior to coronary intervention. Culprit lesions were defined by electrocardiographic criteria such as ST-segment shift or T wave inversion and angiographic appearances such as filling defects consistent with thrombus, plaque irregularity suggestive of ulceration or point of maximal stenosis. In patients who had complete vessel occlusion, flow was first restored and then IVUS imaging was performed. The non-culprit vessels were then assessed using IVUS. Fractional flow reserve (Volcano Corporation, Rancho, California) assessment was used for intermediate lesions.

A 20Mhz Eagle Eye (Volcano Corporation, Rancho, California) intravascular ultrasound catheter with a motorized pull-back device at 0.5mm/s from the distal safe position to the guide-catheter was used to acquire IVUS images. Data was captured and analyzed offline using the image analysis software version 3.1 (Volcano Corporation). This was done independently by an experienced reader (JD), blinded to the clinical data. Each artery was divided into proximal, mid and distal segments. The plaque burden was classified into mild disease (<40% plaque), moderate disease (40-70% plaque) and severe disease (>70% plaque). Atherosclerotic plaque

characteristics as well as the total plaque burden in both the culprit and non-culprit arteries were measured. The plaque burden in each of the three coronary arteries was measured using the difference between the vessel area and the minimum lumen area. The software of the IVUS system automatically analyzed the coronary vessel area and narrowest lumen area. Plaque characterization in our patient cohort was performed using VH assessment of the IVUS images in all three major coronary arteries.

Statistical Analysis

Results are presented using descriptive statistics. Results are presented as mean ± standard deviation, median ± interquartile range (IQR) or percentages as appropriate. Mean total plaque burden at different locations was compared using the paired t-test. Data analysis was carried out using SAS version 9.4 for Windows. A 5% significance level was used.

RESULTS

Demographics and clinical presentation

The mean age of the study population was 51.1 (± 8.1) years (Table 1). Thirteen (65%) patients were males and 17 (85%) were black patients. None of the patients had known prior cardiac history. The median CD4 count of our study group was 301 cells/mm^3 (IQR 205-417). At the time of admission half of the patient cohort was on ART. The average use of ART in these patients was 24 months (IQR 5-51 months). None of the patients were on protease inhibitors. Seven (35%) patients in this group were newly diagnosed with HIV at the time of presentation with ACS. Fifteen (75%) patients presented with ST-segment elevation myocardial infarction (STEMI) (8 anterior and 7 inferior myocardial infarctions), three (15%) with non ST-segment elevation myocardial infarction and 2 (10%) patients presented with unstable angina. Only 3 (21%) of the 15 STEMI patients received thrombolysis within 6 hours of presentation. No patient had a known prior ACS event. Risk factors for IHD included smoking in 11 (55%), hypertension in 6 (30%), diabetes in 2 (10%), dyslipidemia in 2 (10%) patients and 1 (5%) patient had a family history of early IHD. The average BMI was 24.4 (± 5.5) kg/m^2 with a mean waist circumference of 83.0 (± 9.6) cm.

A typical presentation in our cohort was of a young patient with STEMI involving the left anterior descending artery which was the most common artery involved (60%), followed by the right coronary artery (35%) and the left circumflex artery (20%). Fractional flow reserve assessment was used in only 3 patients to assess

significance of the proximal left anterior descending coronary artery lesions and these were all found to be non-significant. Six 2nd generation drug eluting stents were implanted with an average length of 22mm (18-26mm). A high thrombus burden visualized angiographically, was present in 8 patients (40%) and one patient was given an intracoronary thrombolytic which resulted in improved perfusion. Four patients had complete occlusion of the infarct related artery. There were no peri-procedural complications following percutaneous coronary intervention. No patients required coronary artery bypass grafting. At 6 months follow up, one patient had in-stent restenosis and another patient died due to sudden cardiac death at home two weeks after intervention.

Intravascular ultrasound and virtual histology

In 60% of our patients, the total plaque burden in the coronary vasculature was of moderate degree, whilst in 35% the total plaque burden was mild and in a minority (5%) it was severe (Figure 1). The atherosclerotic disease was significantly higher in the proximal coronary vasculature as compared to the mid and distal segments of the coronary arteries (p=0.010). Furthermore, it was significantly higher in the mid segments than in the distal segments of the coronary arteries (p=0.0006). There was more severe plaque burden (30%) in the culprit vessel as compared to non-culprit vessels (5%).

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 2). 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 2). 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.

DISCUSSION

This is the first prospective study which has characterized the coronary plaque morphology in HIV-positive patients presenting with ACS using VH-IVUS. Firstly, we demonstrate that some form of atherosclerosis is present in all HIV-positive patients presenting with ACS without any prior cardiac history. Even normal vessels by angiography were found to have atherosclerosis and in 5% of these vessels the plaque burden was surprisingly severe. Our findings help explain the discrepancy of lower plaque volumes that have been reported in HIV-positive patients studied angiographically, as coronary angiograms are not accurate in defining minor plaque volumes.[15] Secondly, our study has shown that the predominant plaque morphology in the coronary arteries of HIV-positive patients presenting with ACS consisted of fibrous tissue in just over half of all patients and fibro-fatty tissue in a further quarter

of HIV-positive patients with ACS. Necrotic core lesions were found to be uncommon and dense calcified lesions were rare. Hence the plaque morphology in HIV-positive patients can be described as predominantly one of non-calcified fibrous and fibro-fatty disease.

Our findings are supported by non-invasive imaging such as coronary computer tomography angiography (CCTA) which has shown an increased prevalence of subclinical atherosclerosis in HIV-positive patients compared with HIV-negative patients.[16,17] A recent meta-analysis of 1229 asymptomatic HIV-positive patients on ART demonstrated a 3–fold higher prevalence of non-calcific coronary artery plaques at CCTA, as compared with HIV-negative controls.[16] Even in HIV-infected women, a significantly higher percentage of non-calcified plaque has been found on CCTA as compared to HIV-negative women.[18]

Using dual-source CCTA, features of non-calcified plaque have also been found in early atherosclerosis of healthy HIV-negative populations with a family history of early onset of coronary artery disease.[19] Thus, the plaque morphology of atherosclerosis in HIV-positive populations, as found in our study, is very similar to that found in early atherosclerosis of HIV-negative populations. Our findings suggest that the difference in plaque characteristics of atherosclerosis in HIV-positive as compared with HIV-negative populations is that the atherosclerosis is more extensive in HIV-positive patients and with less calcification. The reasons for these differences are unclear but are probably related to the link between HIV infection and atherosclerosis, independent of traditional cardiovascular risk factors. Data from the Strategies for Management of Antiretroviral Therapy (SMART) study suggest that

immune, inflammatory and viral factors contribute to higher prevalence of coronary artery disease in HIV-positive patients.[20] Undetectable viral loads do not equate to amelioration of ongoing inflammation and whilst inflammation and immune activation are diminished with ART, they are not abolished. HIV infection, even in the presence of ART, not only initiates endothelial dysfunction and immune cell activation but activates a number of cellular pathways.[21] As HIV predominantly infects T cells and macrophages there is induction of oxidative and endoplasmic reticulum stress, dysregulation of autophagy and inflammasome formation, all of which may contribute to HIV-associated atherosclerosis.[21] In addition, HIV-positive patients presenting with ACS have been found to have a 'thrombo-inflammatory' state caused by heightened platelet function, hypercoagulability and inflammation.[22] Mechanisms which promote thrombosis such as increased levels of soluble p-selectin, CD-40L and microparticles have been demonstrated in HIV-positive patients with ACS.[22] This inflammatory and thrombotic mileu may well be involved in the pathogenesis of the "athero-thrombotic plaque" as was found in 40% of our patients.

Disease severity may also contribute to atherosclerosis. An association between reduced CD4 cell count and non-calcified coronary artery plaque as well as the presence of coronary stenosis >50% in HIV-positive patients compared to HIV-negative patients have been reported.[16,23] The average CD4 count in our cohort was low (301 cells/mm^3), despite 50% being on ART at the time of presentation with ACS.

Higher rates of ACS in the general population have been reported in a number of studies to be associated with fibrous and fibro-fatty plaque as compared to mixed or calcified plaques.[14 16 23] Non-calcified plaques, as found in our cohort, represents an

earlier stage of atherosclerosis and is more prone to rupture, leading to ACS.[24] Furthermore, HIV-positive patients have a larger burden of coronary atherosclerosis, particularly non-calcified plaque as compared to HIV-negative patients with similar cardiovascular risk factors.[14] Thus, the presence of more extensive non-calcific fibrous and fibro-fatty plaque and its vulnerability to plaque rupture could explain the higher prevalence of ACS and earlier onset of ACS in HIV-positive patients as compared with HIV negative patients.

Ischemic heart disease in HIV-positive patients most commonly manifests with an acute episode of ACS. Studies to date suggest distinct demographic characteristics of ACS presentation in HIV-positive patients.[25-28] The mean age at presentation of ACS in HIV-positive patients is a decade younger (mean age 50 years) than the general population, with patients more likely to be male, current smokers and to have lower HDL levels. This is similar to our cohort where the mean age was 51.1 ($\pm$ 8.1) years, the majority being males (65%) and more than half (55%) current smokers. It is also recognized that ACS in HIV-positive patients presents with different risk factor profiles in developing as compared to developed regions.[25] Traditional risk factors such as hypertension, diabetes and dyslipidemia are more common in developed regions, whereas in the developing regions, smoking is the predominant risk factor.[25,29] Similarly, in our study few patients had hypertension, diabetes, dyslipidemia or family history of IHD but had a high prevalence of smoking (55%).

The most common mode of presentation of ACS in our cohort was STEMI, a low TIMI score (TIMI 2) and single vessel disease angiographically. These findings are consistent with other studies in HIV-positive patients.[26-28] In some regions, HIV-

positive patients with ACS may present without classic atheromatous plaques but with a large burden of thrombus in the infarct related artery.[25] In our cohort, a high thrombotic burden was present in 40% of ACS patients. Of interest is that the profile of ACS in developed countries is changing. In a recent study from 6 United States centers, half (50.4%) of all HIV-positive patients presenting with an ACS had type 2 MI, which occurs in the setting of supply and demand mismatch.[30]

In many studies, including the current study, only half of HIV-positive patients presenting with ACS were on ART. However, the expectation is that in future many more patients will be on ART based on the findings of the SMART study which found that patients who deferred or interrupted ART had a 70% increased hazard of CVD events.[20] The widespread adoption of ART will hopefully translate not only to better long-term outcomes but also lead to substantially fewer cardiac events.

Limitations

This was a single centre study with a small sample size. There were clinical limitations such as repeat coronary angiography was not performed on all patients to determine in-stent restenosis but the focus of this study was not long-term outcomes but the coronary artery plaque characteristics at ACS presentation.

Conclusion

HIV-positive patients present at a young age with STEMI being the most common mode of presentation. In these patients, atherosclerosis as determined by VH-IVUS is extensive. The left anterior coronary artery had the largest burden of disease and this disease burden was predominantly located in the proximal coronary arteries. Imaging using VH-IVUS has demonstrated that atherosclerosis in young HIV-positive patients comprises predominantly of non-calcified fibrous and fibro-fatty plaque.

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Competing interests None declared.

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Table 1 : Baseline characteristics of HIV positive patients presenting with acute coronary syndromes

	HIV-positive patients with ACS (n=20)
Age	51.1 (±8.1)
Race (Black) (%)	17 (75)
Male (%)	13 (65)
Risk Factors n (%)	
Smoking	11 (55)
Hypertension	6 (30)
Diabetes	2 (10)
Dyslipidaemia	2 (10)
Family history	1 (5)
Laboratory **(normal reference ranges)**	
Haemoglobin *(14.3-18.3g/dl)*	12,9
Creatinine *(64-104umol/l)*	80
Total cholesterol *(<4.5mmol/l)*	4,1
Triglycerides *(<1.7mmol/l)*	1,2
HDL *(>1.0mmol/l male >1.3mmol/l female)*	1,0
LDL *(<2.5mmol/l)*	2,4
CD4 *(cells/mm^3)*	313

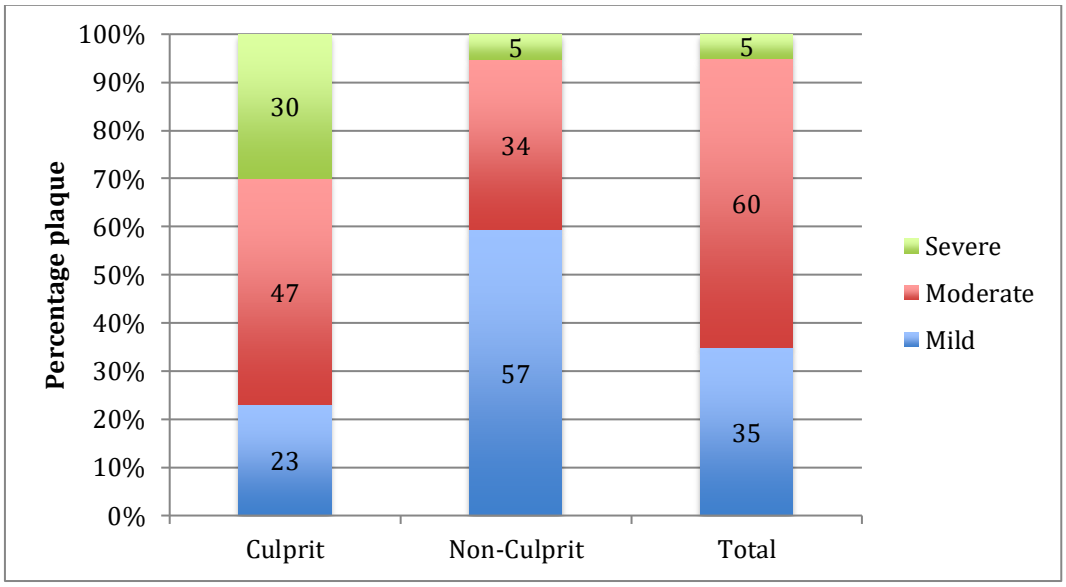


Fig. 1 : Plaque burden in HIV-positive patients with acute coronary syndromes

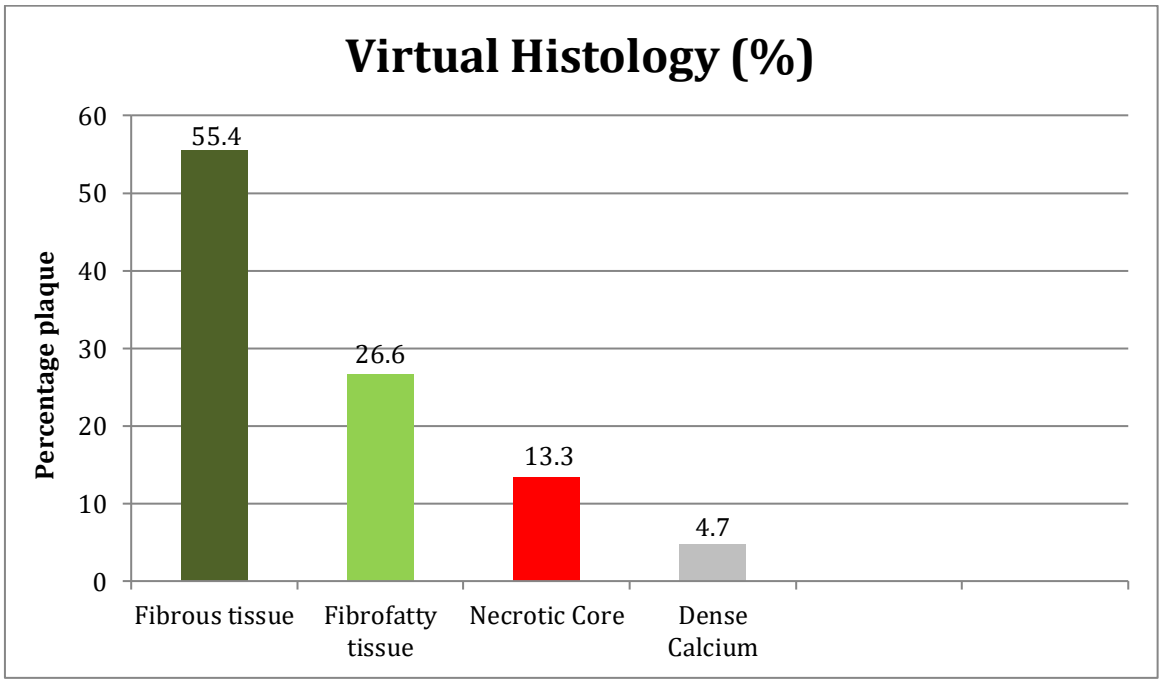


Fig. 2 : Virtual histology in HIV-positive patients with acute coronary syndromes. The mean fibrous plaque volume was significantly greater than the mean fibro-fatty plaque volume, which in turn was significantly greater than the mean necrotic core volume, which in turn was significantly greater than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

Endothelial dysfunction in HIV-positive patients with acute coronary syndromes

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Abstract

Aim: This study investigated endothelial function in HIV-positive patients with acute coronary syndrome (ACS). Flow-mediated dilatation, pulse wave velocity, carotid intima media thickness and endothelial biomarkers were used to non-invasively investigate endothelial dysfunction.

Methods: Twenty HIV positive patients with ACS (HIV+/ACS) were compared to 20 HIV negative patients with ACS (HIV-/ACS) and 20 HIV positive patients with no ACS (HIV+/no ACS).

Results: Endothelial function measured by flow mediated dilatation (FMD) was similar in both HIV+/ACS group (5.2; IQR 1.4-13.4%) and HIV-/ACS group (3.7; IQR 2.3-4.4%) (p=0.78). Arterial stiffness, measured by pulse wave velocity (PWV) was low in all three cohorts. Carotid intima media thickness (CIMT) was also low in all three cohorts. The vascular cellular adhesion molecule-1 (VCAM-1) levels in HIV-positive patients with and without ACS were significantly higher than the HIV-/ACS cohort (p=0.033 and p=0.024, respectively).

Conclusion: Non-invasive investigations like FMD, CIMT and PWV do not identify patients with HIV who are at high risk of ACS. Endothelial biomarkers such as VCAM-1 may be a useful marker to identify HIV patients who have endothelial dysfunction and increased risk of ACS.

Keywords

HIV
Acute coronary syndromes
Endothelial dysfunction
Flow mediated dilatation
Pulse wave velocity
Carotid intima media thickness

Abbreviations

cART	Combination antiretroviral therapy
CIMT	Carotid intima media thickness
FMD	Flow mediated dilatation
HIV	Human immunodeficiency virus
IHD	Ischaemic heart disease
IL	Interleukin
ICAM-1	Intercellular adhesion molecule - 1
MCP-1	Monocyte chemotactic protein - 1
PWV	Pulse wave velocity
PAI-1	Plasminogen activator inhibitor -1
TNFα	Tumour necrosis factor-alpha
VCAM-1	Vascular cellular adhesion molecule – 1

Introduction

There are approximately 37 million people living with HIV worldwide, of whom 70% live in sub-Saharan Africa (1, 2). Increased life expectancy globally as a result of better access to combination antiretroviral therapy (cART) and high levels of traditional cardiovascular disease risk factors have increased the prevalence of ischaemic heart disease (IHD) in this population (3, 4). Developed countries generally have an older HIV-positive population with a higher IHD risk profile compared to a younger HIV-positive population in the developing world with a lower IHD risk profile (5). Developed nations have substantial data on IHD in HIV-positive populations while there is a paucity of data from developing regions.

The endothelium lines the internal surface of blood vessels and is responsible for vascular homeostasis, such as maintenance of vascular tone, non-thrombotic vascular surfaces as well as immunomodulation. With the onset of endothelial dysfunction, the vasculature is predisposed to vasoconstriction, leukocyte adherence, platelet activation, pro-oxidation, thrombosis, impaired coagulation and vascular inflammation (6). Endothelial dysfunction has thus been identified as a key step in promoting atherogenesis, and is well described to be an early predictor of future cardiovascular events both in patients with established or without established cardiovascular disease (7-9).

Endothelial function can be measured in many different ways. The more common technique and one that is well validated, is the non-invasive measurement of endothelial function, which relies on high resolution ultrasound of the brachial artery (6). Another approach to study endothelial function is by measuring endothelial biomarkers. Endothelial biomarkers, such as cellular adhesion molecules are either present on the surface of endothelial cells or are expressed on endothelial cells in

response to certain stimuli. The endothelial biomarkers include the selectins (E-selectin, P-selectin, L-selectin) and vascular adhesion molecules (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) which are involved in leukocyte rolling, adhesion and transendothelial migration into sub-intimal spaces (6). There is evidence that these cellular adhesion molecules can be considered reliable biomarkers for the development and severity of atherosclerosis and could add to the predictive value of the classical risk factors for IHD in HIV-negative populations (6, 10). There is insufficient data that this can be applied in HIV-positive patients, particularly those with ACS.

Endothelial function has been studied in HIV-positive patients since the onset of the epidemic (11). There appears to be an intricate interplay between endothelial function and inflammation as markers such as VCAM-1 and ICAM-1 and are elevated in patients early after HIV infection (12). The mechanism of endothelial dysfunction and promotion of atherosclerosis in HIV infected individuals is complex but is thought to be related to a number of factors including direct involvement of HIV, endothelial activation and vascular inflammation (13-15). Endothelial dysfunction is regarded as a link between infection, inflammation and atherosclerosis and there is recent data suggesting the presence of endothelial dysfunction in untreated HIV-positive patients (16). Furthermore, following cART, it has been shown that there is a fall in markers of endothelial activation such as monocyte chemo-attractant protein, P-selectin and VCAM-1 (12). Although endothelial function has been studied in numerous studies in the past there is a paucity of data on endothelial function in HIV-positive patients presenting with acute coronary syndromes (17). Thus, we aimed firstly to assess the presence and degree of endothelial dysfunction in HIV-positive patients presenting with ACS by using flow mediated dilatation (FMD) and endothelial biomarkers. Our secondary aim was to assess carotid intima media thickness (CIMT) in these patients as a surrogate marker of atherosclerosis.

Methods

This was a prospective study of 60 patients at a large urban public hospital in Johannesburg, South Africa recruited over a 3 year period (July 2012- July 2015). Twenty HIV-positive patients presenting with ACS (HIV+/ACS) were compared to 20 HIV-negative patients with ACS (HIV-/ACS) and 20 HIV positive patients with no ACS (HIV+/no ACS). “Inclusion criteria included age ≥ 18 years and HIV-positive patients presenting with ACS**.** Risk factors for CAD that was studied included age, smoking, hypertension, diabetes and family history of premature CAD (men ≥ 55 years; women ≥ 65 years of age). Exclusion criteria included prior myocardial infarction, life-threatening disease that prevented a 2-year follow up and known carotid artery disease.” Ethical approval for the study was obtained from the local institutional body (M111143). “ACS included ST elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI) and unstable angina. STEMI included those patients presenting with ST elevation 1mm or more in at least two contiguous leads for most leads except lead V2,3 where the criteria was >2mm in a male patient <40 years or >2.5mm in a male patient >40 years and 1.5mm in a female patient. NSTEMI includes those patients presenting with angina without ST elevation but with positive cardiac enzymes. Unstable angina includes those patients hospitalized with worsening angina or new onset angina at rest without troponin elevations.”

The HIV+/ACS and HIV-/ACS patients were matched for age and gender. The HIV+/no ACS patients could only be matched for gender as cART-naïve patients presenting at our HIV clinic were found to be much younger patients. Carotid intima media thickness was measured in all three groups using a 11Mhz transducer (Phillips iE33 ultrasound machine) with the patient in the supine position with the head tilted 30 degrees to the left for the right carotid artery assessment and then 30 degrees to the right for the left carotid artery. The carotid artery bifurcation was visualized and the software automatically measured carotid artery intima thickness of the distal wall 10 mm from the bifurcation bulb.

Endothelial function was measured non-invasively using brachial FMD according to standardized guidelines (18). The maximum diameter of the brachial artery was measured at rest. A blood pressure cuff was then inflated to at least 50mmHg above the systolic pressure to occlude arterial inflow for five minutes. The brachial artery diameter was again measured two minutes after cuff release when the maximum dilation of the vessel usually occurs.

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.

Endothelial biomarkers were measured in all 60 patients and included; Interleukin (IL) 1B, IL1ra, IL-6, tumour necrosis factor alpha (TNF-α), monocyte chemotactic protein -1 (MCP-1), plasminogen activator inhibitor -1 (PAI-1), E-selectin, P-selectin, ICAM-1 and VCAM-1. Following blood collection in EDTA tubes, specimens were centrifuged for 20min at 4˚C at 1000 X G. The plasma was decanted into 1,5ml microcentrifuge tubes and stored at -70^{o}C for later analysis. IL-1β; IL-ra and IL-6, MCP1, TNFα concentrations were quantified using the Bio-Plex Pro™ Human Cytokine Standard 27-Plex Bio-Rad Laboratories, Hercules, CA) as per manufacturer's instructions. The plasma was diluted 4-fold for these assays. E-selectin and P-selectin plasma levels were measured using the Human Magnetic Luminex assay (R&D Systems, Minneapolis, MN) as per manufacturer's recommendations. Plasma was diluted 2-fold to measure E-selectin and P-selectin levels. The serum concentrations for VCAM-1, ICAM-1, and PAI-1 were analyzed in sera diluted 40-fold using the Milliplex human Sepsis Magnetic Panel 1 (Merck Millipore, Billerica, MA) as per manufacturer's instructions. Samples were analyzed using the Bio-Plex 200 system

(Bio-Rad) and concentrations were determined using the 5-pl method using Bio-Plex Manager 5.0 software.

Data analysis

The X^2 test was used to assess the relationship between categorical variables and groups. The Fisher's exact test was used where the requirements for the X^2 test could not be met. The relationship between continuous variables and groups was assessed by one-way Analysis of Variance (ANOVA) for the three groups and the unpaired t-test for two groups. Post-hoc tests for ANOVA were conducted using the Tukey-Kramer adjustment for multiple comparisons. Where the data did not meet the assumptions of these tests, a non-parametric alternative, the Kruskal-Wallis test was used for three groups, and the Wilcoxon rank sum test for two groups. Paired comparisons between continuous variables were carried out with the paired t-test or the Wilcoxon matched pairs test. Data analyses were carried out using SAS version 9.4 for Windows. A 5% level of significance was used.

Results

Demographics and clinical presentation

The HIV+/ACS patients had a mean age of 51.1 (sd=8.1) years with 13 males (65%). The mean age of 36.0 (sd=6.8) years in the HIV+/no ACS group was significantly lower than that of the HIV+/ACS group 51.1(sd=8.1) years and the HIV-/ACS group 52.3 (sd=9.0) years ($p<0.0001$). The proportion of males in each group ranged between 50 and 80%, but the differences were not statistically significant ($p=0.14$) (Table 1).

Ten (50%) of the HIV+/ACS group were on cART and none were on protease inhibitors. Seven (35%) of the patients in the HIV+/ACS group were newly diagnosed with HIV. There were 15 (75%) hospital admissions with ST-segment elevation myocardial infarction (STEMI) (8 anterior, 7 inferior), 3 (15%) with non-ST elevation segment elevation myocardial infarction and 2 patients with unstable angina (10%). The typical presentation in the HIV+/ACS group was a young patient with STEMI involving the left anterior descending artery, which was the most common artery involved (60%), followed by the right coronary artery (35%) and the left circumflex artery (20%).

Risk factors in the HIV+/ACS group included smoking in 11 (55%), hypertension in 6 (30%), diabetes in 2 (10%), dyslipidaemia in 2 (10%) patients and 1 (5%) patient had a family history of IHD (Figure 1). The prevalence of diabetes and dyslipidaemia was higher in the HIV-/ACS group compared to the HIV+/ACS and the HIV+/no ACS groups (p=0.0006 and p=0.0002, respectively). The prevalence of smoking and hypertension was lower in the HIV+/no ACS group compared to the other HIV+/ACS and the HIV-/ACS groups (p=0.0012 and p=0.0006, respectively) (Figure 1). LDL levels were no different in ACS patients whether they were HIV-positive or negative. HIV-positive patients without ACS had significantly low LDL levels.

Endothelial function

Endothelial function was measured using FMD in all three groups. The median percentage difference in FMD between baseline (before BP cuff inflation) and post BP cuff deflation 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 2). Patients without ACS had the most vasoreactivity compared to the patients with ACS.

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 with no significant differences between the 3 groups (p=0.12) (Table 1). Carotid intima media thickness was measured in all three groups. The mean CIMT of the two groups with ACS was no different. The CIMT in the group without ACS (0.50; sd=0.08 mm) was marginally but significantly lower than the CIMT of both the HIV+/ACS group (0.66; sd=0.16 mm) and the HIV-/ACS group (0.70; sd=0.06 mm), (p=0.0005 and p<0.0001, respectively) (Table 1).

There were significant differences in the endothelial biomarkers VCAM-1, ICAM-1, IL-6 and E-selectin in the 3 groups (Table 2). The median VCAM-1 levels in HIV-positive patients with and without ACS were significantly higher than in the HIV-/ACS cohort (402 and 503 vs 287 ng/ml) (p=0.033 and p=0.024, respectively). Median ICAM-1 levels on the other hand, were significantly higher only in HIV-positive patients without ACS as compared to the other two cohorts (p=0.0079 and p=0.0010, respectively). The HIV+/no ACS group had significantly lower median levels of IL-6 than the both the HIV+/ACS and the HIV-/ACS groups (p=0.033 and p=0.0050, respectively). The median E-selectin levels in HIV+/ACS patients and HIV-/ACS patients were significantly lower than that of the HIV+/no ACS group (p=0.0007 and p=0.012, respectively). There was no significant difference in median IL1 β, IL1ra, MCP-1, TNFα, P-selectin and PAI-1 levels between the groups.

Discussion

Studies suggest that an overall 1.5-2.0 fold increased risk of acute myocardial infarction is conferred by HIV infection (19, 20). Common to most studies is that the mean age at presentation of ACS in HIV-infected patients is a decade younger than the general population with a mean age of 50 years (5, 21, 22). This is similar to our cohort where the mean age was 51 years. Ischaemic heart disease in HIV-positive patients presenting with ACS have different risk factor profiles in developing and developed regions. Traditional risk factors such as hypertension, diabetes and dyslipidaemia are more common in developed regions. The current study had fewer patients with hypertension, diabetes, dyslipidaemia and family history of IHD in HIV-positive patients with ACS. In developing countries smoking appears to be the dominant risk factor with prevalence rates of 24.4% in HIV-positive males (5, 13, 23). More than half of the HIV+/ACS patients in our cohort were smokers with fewer other traditional risk factors. Furthermore, there is evidence that smoking contributes to endothelial dysfunction (24). These findings make smoking cessation an important modifiable risk factor for the prevention of IHD in HIV-positive patients.

The mechanisms for the development of atherosclerosis in HIV are multifactorial and include chronic inflammation and immune activation. These in turn may also lead to endothelial dysfunction further contributing to the pathogenesis of atherosclerosis (13, 19, 25). Endothelial dysfunction is associated with increased levels of reactive oxygen species and decreased nitric oxide levels and hence decreased vascular reactivity (6). HIV itself has been linked to endothelial dysfunction (13, 26). This is supported by findings of a significant improvement in FMD in patients in the first 24 weeks after initiation of cART, suggesting that suppression of HIV viraemia leads to improved endothelial function (27). The impact of viral components (gp120, TAT) on the endothelium, via adhesion molecules (ICAM-1, E-selectin), a prothrombotic state (increase of von Willebrand factor, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA) has been implicated in the pathogenesis of

atherosclerosis in HIV positive patients (28). Telomere length and CDKN2A expression were both consistent with increased biological ageing in HIV-infected individuals (29). Anti-retroviral therapies may be linked to coronary artery disease, specifically protease inhibitors, however the risk of CAD associated with anti-retroviral therapy is small compared with the impressive reductions in all-cause mortality with cART (30)."

Endothelial dysfunction is well known to be associated with atherosclerosis in HIV-negative populations (31, 32). It has also been described in HIV-positive patients without ACS (26, 33, 34). In our study, HIV+/ACS patients had almost the same degree of endothelial dysfunction as the control group of ACS patients without HIV. Although it would appear that endothelial dysfunction was not more prevalent in the HIV-positive group with ACS it must be borne in mind that the latter group had significantly fewer coronary risk factors such as hypertension, diabetes, dyslipidaemia and family history of IHD compared to the HIV negative patients with ACS, suggesting that HIV infection itself contributed to endothelial dysfunction. HIV-positive patients without ACS had the highest brachial artery vasoreactivity compared to the patients with ACS. This is an interesting finding but is most likely a reflection of the much younger age of this group as compared to the other two groups.

In HIV-positive patients endothelial activation may lead to structural and functional vascular changes. Exposure to long-term subclinical inflammation is related to accelerated stiffening of large arteries. Peripheral waveform analysis using PWV has been shown to provide a noninvasive method of measuring 'global' endothelial function (35). Increasing levels of arterial stiffness are correlated with higher pulse wave velocities. The value for stiff vessels is a PWV >10m/s and this value has been found to be an independent marker of end organ damage (36, 37). In our study we found uniformly low values (<5) for PWV. This finding, we believe, is largely an age related effect. This is supported by Fourie et al who recently reported increasing PWV velocities only after age of 50 years in HIV-positive, cART naïve patients (16).

By studying ACS patients who were HIV-positive and comparing them to ACS patients who were HIV-negative we were able to assess endothelial activation in both groups of patients. In developing countries high levels of endothelial markers such as IL-6, TNF-α, PAI-1, sCD14 have been reported in HIV-positive patients compared with HIV-negative patients (38-41). Studies of endothelial function from developing nations have demonstrated that in recently seroconverted Kenyan women endothelial biomarkers (VCAM-1 and ICAM-1) were significantly elevated in these patients early after HIV infection (12). In a recent study from South Africa, HIV-positive patients were found to have higher levels of adhesion molecules compared to HIV-negative patients with an odds ratio of 3.9 (2.2-7.0) for ICAM-1 and 16.2 (7.5-35) for VCAM-1 (42). Furthermore, the same investigators reported that ICAM-1 and VCAM-1 were elevated in both treated and cART naïve patients with odds being greater for the never treated group (36). Another study from South Africa which assessed endothelial biomarkers in ACS patients who were HIV positive, also found significantly elevated VCAM-1 levels in HIV-positive patients with ACS as compared to control patients who were either HIV negative or HIV-positive without ACS (5). Similarly, in our cohort of HIV+/ACS patients we found significantly higher levels of VCAM-1 as compared to HIV negative patients, findings that are in concert with previous reported results. VCAM-1 is a member of the immunoglobulin super-family and is involved in cellular adhesion and transmigration of leucocytes through endothelial cells and is thought to a play a role in the development of atherosclerosis (34). With the stimulation of endothelial cells by inflammatory cytokines there is increased expression of VCAM-1 and this is associated with an increased predictive value for future cardiovascular events (43). Thus VCAM-1 may be an informative biomarker for predicting the risk of HIV disease progression, morbidity and mortality (12).

The proinflammatory cytokine, IL-6, induces expression of adhesion molecules such as VCAM-1 and ICAM -1 and may be seen as an early modulator of leukocyte trafficking in the vascular wall (44). However, we did not find significantly elevated levels of IL-6 in HIV-positive and HIV-negative patients with ACS. Lack of significant

difference in IL-6 and other markers of endothelial dysfunction in HIV infected and non-infected controls have also been previously reported (5,36).

Non-invasive surrogate tools such as CIMT and coronary computer tomography angiography indicate an increased prevalence of subclinical atherosclerosis in HIV-positive compared to HIV-negative patients (45-47). A meta-analysis of 13 observational studies suggests a trend towards increased CIMT in HIV-infected patients (45). As early as childhood, HIV-infected children receiving cART were found to have increased CIMT, suggesting that IHD risk may already be heightened in HIV-infected patients at a young age (48). Carotid intima media thickness has been shown to decrease with cART and less CIMT progression was associated with suppressed viral load at baseline (49). In our cohort, CIMT measurements were unexpectedly lower in the HIV+/ACS compared to the HIV-/ACS patients. The HIV+/no ACS patients also had low CIMT measurements. One possible explanation for the finding of lower CIMT in HIV+/ACS patients is the relative lack of traditional risk factors for atherosclerosis, such as hypertension, diabetes and low LDL levels in the HIV+/ACS group. It has been shown that presence of high cardiovascular risk factor profiles in HIV-positive patients is associated with increased CIMT (50).

This study has the following limitations. Firstly, the study is a single centre study with a small sample size. Given the nature of the study it took almost 3 years to recruit 20 HIV-positive patients presenting with ACS to our centre. With the small sample size we were not able to perform multivariate analyses. Secondly, given the type of the clinical presentation of patients in the study we were unable to completely match case control patients for age, gender and cardiovascular risk factors. Although the HIV+/no ACS group were gender matched, they could not be matched for age as the majority of HIV+/no ACS patients, who were cART-naïve, presenting at the HIV clinic were young. Lastly, HIV+/no ACS patients in the study were newly diagnosed and therefore duration of infection was not known.

Conclusion

Endothelial dysfunction as assessed by brachial FMD was similar in HIV-positive patients with ACS as compared to HIV-negative patients with ACS. The only endothelial biomarker that was significantly raised in the HIV+/ACS patients and HIV+/no ACS patients was VCAM-1. Our cohort of HIV-positive patients with ACS had impaired FMD but near normal CIMT and PWV measurements. Given that FMD, CIMT and PWV were similar in HIV+ and HIV- patients with ACS, the use of endothelial biomarkers (like VCAM-1) may provide a more promising modality to investigate endothelial dysfunction.

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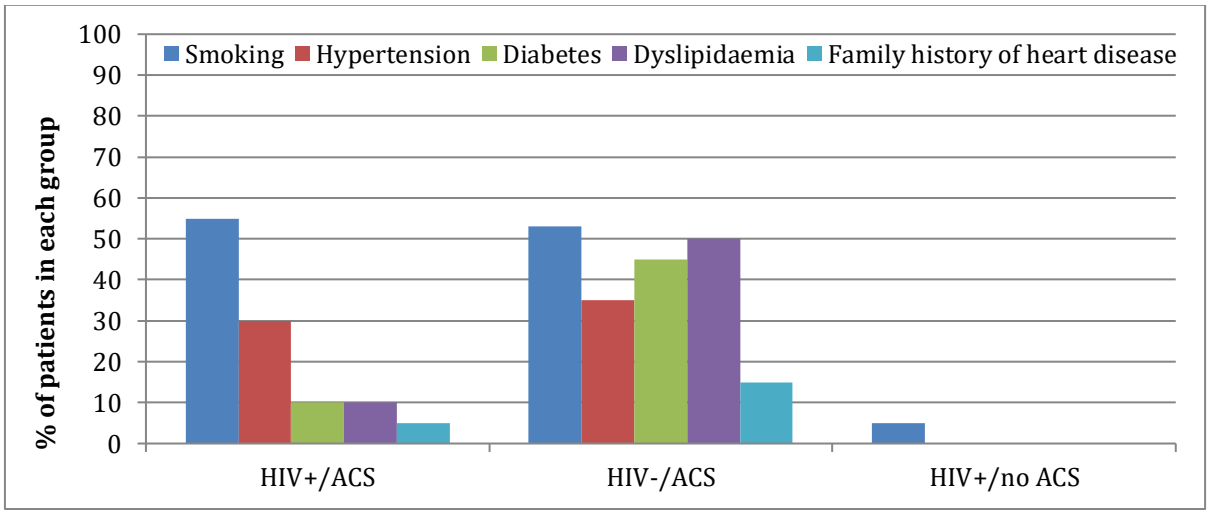


Figure 5 Risk factor profile

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.

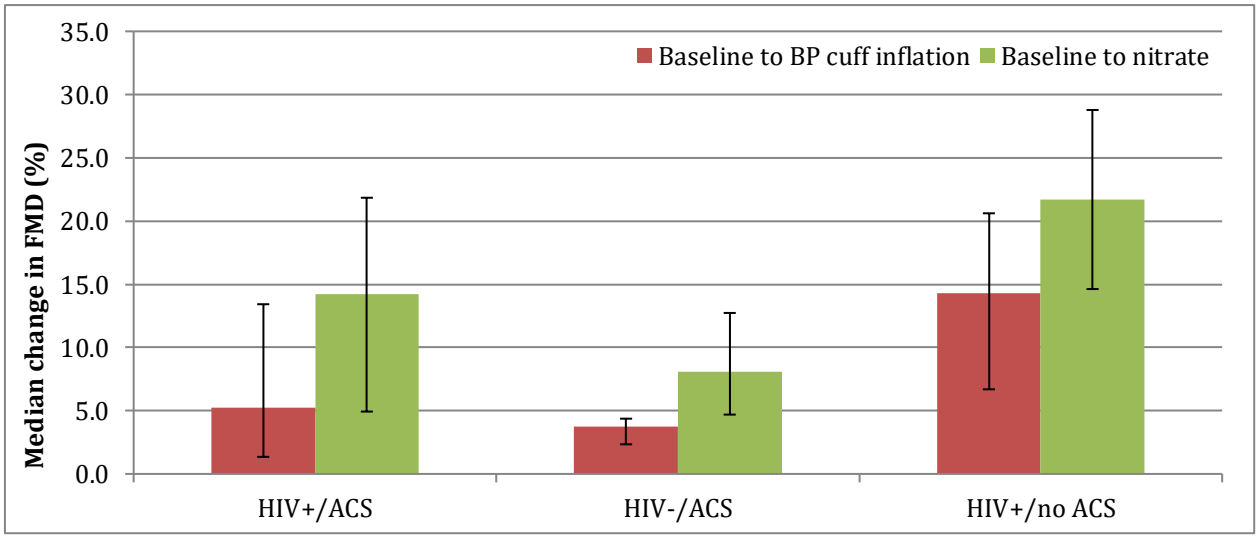


Figure 2: Mean change in FMD post BP cuff inflation. HIV+/ACS patients had similar change from baseline of brachial flow mediated dilatation compared to the HIV-/ACS patients (p=0.78). The HIV+/no ACS group had the most vasoreactivity but they were significantly younger (p=0.0001)

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/mm³)	*(cells/mm³)*	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*	

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Regular Article

Prognostic Indicators for Recurrent Thrombotic Events in HIV-infected Patients with Acute Coronary Syndromes: Use of Registry Data From 12 sites in Europe, South Africa and the United States

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ABSTRACT

Aims: Limited data are available on prognostic indicators for HIV patients presenting with ACS.
Methods and results: Data on consecutive patients with HIV infection receiving standard highly active antiretroviral therapy (HAART) presenting with ACS between January 2001 and September 2012 were collected. Cardiac death and myocardial infarction (MI) were the primary end-points. 10,050 patients with ACS were screened, and among them a total of 201 patients (179 [89%] males and a median age of 53 [47-62] years) were included, 48% of them admitted for ST-elevation myocardial infarction and 14% having left ventricular systolic dysfunction (LVSD) at discharge. CD4+ counts less than 200 cells/mm^3 were reported in 18 patients (9%), and 136 patients (67%) were treated with nucleoside-reverse transcriptase inhibitors (NRTI). After a median of 24 months (10–41), 30 patients (15%) died, 12 (6%) for cardiac reasons, 20 (10%) suffered a MI, 29 (15%) a subsequent revascularization, and 7 (3%) a stent thrombosis. 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 NRTI (hazard ratio = 9.9 [95%

Abbreviations: ACS, Acute coronary syndromes; CABG, Coronary artery bypass grafting; CV, Cardiovascular; HAART, Highly active antiretroviral therapy; HIV, Human immunodeficiency virus; LVSD, Left ventricular systolic dysfunction; MI, Myocardial infarction; NRTI, Nucleoside-reverse transcriptase inhibitors; NSTEMI, Non-ST-elevation myocardial infarction; PCI, Percutaneous coronary intervention; PHD, Percutaneous coronary intervention and surgical revascularization in HIV Database; STEMI, ST-elevation myocardial infarction; TLR, Target lesion revascularization; TVR, Target vessel revascularization; UA, Unstable angina.

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CI: 2.1-46: p = 0.03); a CD4 cell count <200 cells/mm^3 was the only predictor of MI (hazard ratio = 5.9 [95% CI: 1.4-25: p = 0.016]).
Conclusions: HIV patients presenting with ACS are at significantly increased risk for cardiac death if not treated with NRTI, and at significantly increased risk of MI if their CD4 cell count is <200 cells/mm^3, suggesting that the stage of HIV disease (and lack of NRTI treatment) may contribute to cardiovascular instability.
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Introduction

Antiretroviral therapy (ART) dramatically increases life expectancy for patients with human immunodeficiency virus (HIV) [1], such that their long term outlook appears to be similar to that of general population in the highly active antiretroviral therapy (HAART) era [2]. The shift from an acute to a chronic condition leads subjects with HIV to exposition to the long-term detrimental effects of both disease progression and antiretroviral therapy [3,4].

Heart disease represents one of the most important causes of morbidity and mortality for these patients [4,5]. Before the introduction of HAART, clinically significant cardiomyopathy mainly related to myocarditis was already reported in up to 10% of patients [6–9]. In the HAART era, increased and persistent arterial inflammation leading to aggressive atherosclerosis [10] was demonstrated, most likely related to a complex (and not yet thoroughly clarified) relationship between coronary HIV infection, immune-mediated response and adverse risk factor profile [11].

The high risk of cerebro- and cardiovascular events (CV) [12,13] and especially acute coronary syndromes (ACS) represents the clinical consequence of these pathological processes. Most of the evidence on HIV and ACS, however, derives from small studies [13–22], not performed in the contemporary era, and with a subspecialty focus, thus limiting a comprehensive clinical evaluation of these patients.

We thus designed the Percutaneous coronary intervention and surgical revascularization in HIV Database (PHD) study whose aim was to investigate the outcome of HIV-positive patients treated as in contemporary practice.

Methods

Design, Patients and Treatments

The PHD study was a retrospective registry conducted at 12 sites in Europe and USA. All consecutive HIV-positive patients presenting with ACS between January 2001 and September 2012 were enrolled, irrespectively of their management by percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or medical therapy. International guidelines on ACS were used to diagnose and classify ACS [23,24], distinguishing ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). All patients had been diagnosed with HIV infection by means of enzyme-linked immunosorbent assay [ELISA] confirmed by Western blot [25]. The paper was written according to the Strobe Statement [26].

Data Collection

Four cardiologists and two infectious disease specialists developed the dedicated database, choosing variables, outcomes, and definitions. Data regarding cardiac history and HIV treatment, as well as details and complications [27] of the coronary revascularization, were systematically sought for and recorded. Details pertaining to antiretroviral treatment and HIV infection were obtained by a local specialist in each center.

Outcomes and Definitions

The incidence and predictors of cardiac death or MI (both STEMI and NSTEMI) were the main outcomes of interest. Secondary outcomes were target lesion revascularization (TLR), target vessel revascularization (TVR), and stent thrombosis. Cardiac death was also distinguished as sudden and non-sudden. MI was defined according to international guidelines [23,24]. TLR was defined as repeat PCI or CABG for significant restenosis or disease progression after PCI in the previously stented segment or in the adjacent 5 mm segments, while TVR was defined as repeat revascularization on the same coronary vessel. Stent thrombosis was adjudicated according to the Academic Research Consortium definition [27]. Major and minor bleeding were described in accordance with the Thrombolysis in Myocardial Infarction (TIMI) definitions [27]. Left ventricular systolic dysfunction (LVSD) was defined as an ejection fraction <35%. Data were obtained by direct visits, telephone interviews, queries of institutional electronic databases, referring physicians, or municipal civil registries.

Analysis

Continuous variables were reported as mean (standard deviation) or median (first-third quartile) and were compared with unpaired t-test or analysis of variance. Categorical variables are presented as counts and percentages, and were compared with the Fisher exact test. Survival analysis was performed with the Kaplan-Meier method and log-rank test. Multivariable adjusted survival analysis was conducted with Cox proportional hazard analysis, including in the model as covariates all baseline variables significantly ($p < 0.05$) associated to the dependent variable of interest at unadjusted analysis, as well as recruitment center (United States of America vs. Europe) [3,28–30]. P-values unadjusted for multiplicity are reported throughout, with statistical significance set at the two-tailed 0.05 level. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA).

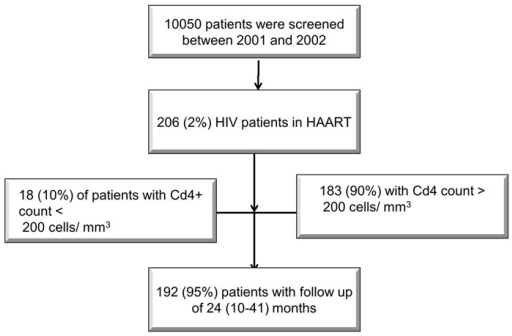


Fig. 1. Flow chart of patients.

Table 1
Baseline clinical features.

	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
Age (years)	54 ± 10	54 ± 11	54 ± 10	0.86
Male gender	180 (88)	25 (89%)	155 (89)	0.67
Diabetes mellitus	36 (18)	5 (18%)	31 (17.8)	0.58
Diabetes Mellitus Insulin Dependent	18 (8.8)	2 (7.1)	16 (9.2)	0.53
Glycosylated hemoglobin (%)	6.1 ± 0.5	7.2 ± 0.1	6.0 ± 0.3	0.023
Hypertension	98 (48)	11 (39)	87 (50)	0.85
Hyperlipidemia	107 (53)	15 853)	92 (53)	0.9
Smoker:				0.9
–former	93 (45)	13 (48)	80 (46)	
–current	52 (23)	7 (25)	45 (26)	
Familiarity for Cardiovascular disease	46 (23)	6 (22)	40 (23)	0.56
Chronic renal failure*	18 (9)	7 (25)	11 (6.3)	**0.005**
Chronic heart failure	24 (12)	2 (7.1)	22 (12.6)	0.32
Peripheral artery disease	17 (8)	2 (7.1)	15 (10)	0.48
Previous coronary revascularization:				**0.049**
-percutaneous	40 (20)	9 (32)	31 (18)	
-surgical	11 (5.4)	4 (14.3)	7 (4)	
Drug abuser				0.32
–: previous story of injection drug	26 (13)	4 (14)	22 (13)	
–previous or current story of non-injection cocaine use	7 (3.4)	2 (7)	5 (3)	
Positive toxicological exam at admission	4 (2)	1 (4.5)	3 (2.3)	0.46
Hepatitis C virus positive	49 (24)	10 (36)	39 (26)	0.21
Hepatitis B virus positive	23 (11)	4 (15)	19 (13)	0.49
Time from HIV diagnosis	3.9 ± 4.05	3.2 ± 4.04	4.1 ± 4.1	0.422
Time from begin of HAART therapy	1.4 ± 1.5	1.4 ± 0.9	0.8 ± 1.3	0.073
CD4+ count (cell/mm$^{3)}$	651 ± 510	716 ± 996	623 ± 356	0.49
CD4+ nadir count (cell/mm$^{3)}$	212 ± 172	179 ± 182	219 ± 129	0.29
CD4+ cell/mm^3 < 200	20 (9)	7 (25)	13 (9.5)	**0.04**
Viral load:				0.29
not fully suppressed	35 (17)	3 (13)	32 (25)	
fully suppressed < 50 copies/mm3	96 (47)	18 (78)	78 (61.4	
fully suppressed < 200 copies/mm	19 (9.3)	2 (8.7)	17 (13)	
HAART at admission:				0.63
–nucleoside reverse transcriptasis	136 (67)	21 (84)	115 (84)	
–non nucleoside reverse transcripatasis	54 (51)	10 (40)	44 (33)	
–protease inhibitors	87 (43)	12 (48)	75 (56)	

* dyalisis or serum creatinine more than 2 mg/dl.

Table 2
Admission diagnosis, and interventional procedures.

	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
Admission diagnosis:				0.93
–STEMI	71 (35)	10 (36)	61 (37)	
–NSTEMI	61 (31)	10 (35)	51 (32.3)	
–UA	58 (28)	8 (28)	50 (30.5)	
Primary PCI	74 (36)	9 (32)	65 (37)	0.79
Grace score	106 ± 30	123 ± 39	101 ± 76	**0.006**
Grace Score more than 140	14 (6.9)	3 (19)	11 (16)	0.51
Management:				0.79
–PTCA	154 (76)	22 (84)	132 (79)	
–CABG	11 (5.4)	1 (3.8)	10 (6)	
–Medical therapy	28 (14)	3 (12)	25 (15)	
Multivessel or left main disease	101 (49)	20 (71)	81 (47)	**0.013**
Revascularized vessel:				
Unprotected left main disease	11 (8)	3 (12)	8 (5)	0.19
Proximal descending anterior	78 (38.2)	11 (42)	67 (42)	0.19
Proximal circumflex	42 (23)	12 (46)	40 (25)	0.01
Proximal right coronary artery	61 (28)	10 (37)	51 (33)	0.07
Chronic total occlusion	20 (10)	3 (11)	17 (11)	0.56
Use of Drug Eluting Stent	91 (45)	18 (72)	73 (48)	**0.021**
Use of Intra-aortic balloon pump	4 (2)	1 (3.6)	3 (1.8)	0.45
Use of Glycoprotein IIb/IIIa inhibitors	18 (8.8)	1 (3.6)	17 (10)	0.23
TIMI major bleeding	9 (4.5)	1 (3.8)	8 (5.6)	0.58
Ejection fraction less than 35% at discharge	28 (13)	8 (28)	20 (12)	**0.023**
Double antiaggregant therapy (DAT) at discharge	149 (78)	23 (82)	126 (83)	0.55
Lenght of DAT (months)	9.4 ± 8	7.5 ± 1.5	8.2 ± 0.8	0.8
Statin at discharge	156 (78)	21 (75)	135 (82)	0.25

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

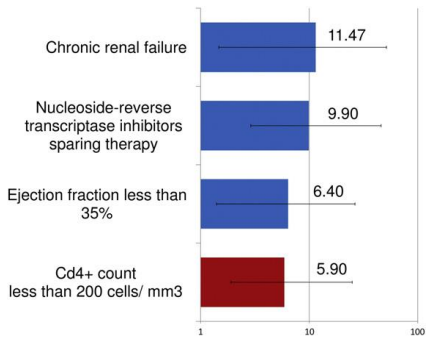


Fig. 2. Independent predictors of cardiac death (blue) and of myocardial infarction (red).

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

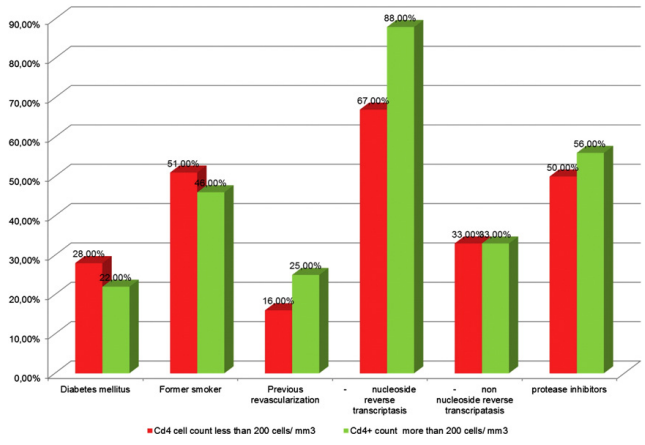


Fig. 3. Main baseline features according to number of CD4 cell count (p 0.03 for nucleoside reverse transciptasis).

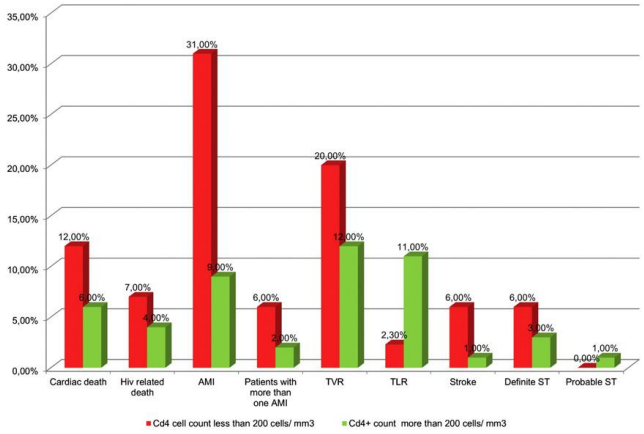


Fig. 4. Outcomes according to number of CD4 cell count (p 0.024 for cardiac death and p 0.024 for myocardial infarction.

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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Evaluation of Coronary featUres Of HIV patients pREsenting with ACS: the CUORE a multicenter study

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ABSTRACT.

Background. The risk of recurrence of myocardial infarction (MI) of HIV patients presenting with acute coronary syndrome (ACS) is well known, but there are limited evidence about potential differences in coronary plaques compared to non-HIV patients.

Methods. In this multicenter case-control study, HIV patients presenting with ACS with intravascular-ultrasound (IVUS) data, enrolled between February 2015 and June 2017 and undergoing highly active antiretroviral therapy (HAART), were retrospectively compared to non-HIV patients presenting with ACS, before and after propensity score with matching, randomly selected from included centers. Primary end-point was the prevalence of multivessel disease. Secondary end-points were the prevalence of abnormal features at IVUS, the incidence of major-acute-cardiovascular-events (MACE), a composite end point of cardiovascular death, MI, target lesion revascularization (TLR), stent thrombosis (ST), non-cardiac death and target vessel revascularization (TVR). For each end-point a subgroup analysis was conducted in HIV patients with CD4 cell count <200/mm^3.

Results. Before propensity score, 66 HIV patients and 120 non-HIV patients were selected, resulting in 20 and 40 after propensity score. Patients with multivessel disease were 11 and 17 respectively (p=0.56). IVUS showed a lower plaque burden (71% vs. 75%, p<0.001) and a higher prevalence of hyperechoic non-calcified plaques (100% vs. 35%, p<0.05) in HIV patients; a higher prevalence of hypoechoic plaques (7% vs 0%, p<0.05), a higher incidence of MACE (17.4% vs 9.1% vs l'8.0%, p<0.05), of MI recurrence (17.2% vs 0.0% vs 2.3%, p<0.05), and ST (6.7% vs 0.3% vs 03%, p<0.05) in HIV patients with CD4<200/mm^3.

Conclusions. Our study may provide a part of the pathophysiological basis of the differences in coronary arteries between HIV-positive and HIV-negative patients, suggesting that the former present with peculiar morphological features at IVUS, even after adjustment for clinical variables. Furthermore, we confirmed that an advanced HIV infection is associated with a high risk of non calcific plaques and with a worse prognosis, including cardiovascular events and ACS recurrence.

INTRODUCTION.

HIV patients are exposed to a major risk of adverse cardiovascular events and coronary artery disease than general population. The high cardiovascular risk in HIV patients was known earlier before highly active antiretroviral therapy (HAART) introduction[i,ii,iii], when cardiovascular mortality and morbidity were mainly related to underlying problems of immune dysfunction and opportunistic infections.[iv] The acronym HAART, identifies the current standard therapy for HIV-positive patients; represent a combination of different types of drugs belonging to different drug categories: Six classes of antiretroviral agents currently exist, as follows: Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), Integrase inhibitors (INSTIs), Fusion inhibitors (FIs), Chemokine receptor antagonists (CCR5 antagonists).

HAART introduction drastically changed HIV infection course, causing the increase in life expectation, so that morbidity non-historically related to HIV take on greater significance, particularly the cardiovascular one.[v] Moreover a shift of the cardiovascular disease spectrum to a higher incidence of coronary disease was noted.[vi,vii,viii] In the last decade the risk of ischemic heart disease in HIV patients has further increased and it results to be higher than in the general population.[ix]

Pathogenesis of cardiovascular disease in HIV patients is related to the interactions occurring between traditional risk factors[1,x,xi,xii], HIV infection itself[xiii,xiv], and HAART, which role is still controversial, with some studies claiming the association between antiretroviral therapy and acute coronary syndrome (ACS)[xv,xvi,xvii], and others denying it.[xviii,xix,xx]

This population is particularly exposed to the risk of ACS, secondly to the development of atherosclerosis, to which these patients are a peculiar subset, due to the factors described above and to others interactions, which cause inflammation and immune dysfunction [xxi , xxii] , coagulopathy [xxiii , xxiv , xxv] and endothelial dysfunction (ED)[xxvi,xxvii,xxviii,xxix], leading to atherosclerosis.[xxx]

Recently, a role of the gut microbiota has been highlighted, [xxxi,xxxii,xxxiii] while it is still not clear if a lower CD4+ cell count is associated with a higher cardiovascular risk. or not [xxxiv xxxv xxxvi xxxvii]

In the setting of ACS, HIV patients are usually younger, smokers, predominantly males, with an age of onset <50 years[xxxviii], but with a higher risk of cardiovascular complications and sudden cardiac death.[xxxix]

In this setting, there is lack of data about coronary disease features of HIV patients presenting with acute coronary syndrome, and their potential impact on prognosis.

The aim of our study is to assess morphological and volumetric features of coronary lesions with intravascular-ultrasound (IVUS) and to evaluate the major cardiovascular adverse events (MACEs) in HIV patients presenting with ACS.

METHODS.

Patients

In these multicenter case-control prospective study, we enrolled:

- HIV patients, already undergoing HAART, presenting with ACS (defined according to ESC guidelines as Unstable Angina [UA], Non ST Segment Elevation Myocardial Infarction [NSTEMI] and STEMI [ST Segment Elevation Myocardial Infarction]) enrolled between February 2015 and June 2017 at our Institutions: Division of Cardiology, Città della Salute e Della Scienza, University of Turin; Division of Cardiology, "Sapienza" University of Rome. These patients were retrospectively compared to
- Non HIV patients with ACS diagnosis, randomly selected from consecutive patients enrolled in 30 days in both Institutions in the same time period.

Enrolled population has been divided into:

1) cases including 66 HIV patients, among which 32 with available IVUS data

2) controls including 120 non HIV patients, among which 73 with available IVUS data.

Clinical features

Baseline clinical features, HIV infection-related features, angiographic features of coronary lesions, IVUS data when available and follow up were collected for each patient enrolled in the study. Any patient data, about risk factors and previous cardiovascular events, HIV infection, ongoing HAART and previous therapy, ACS episode and last available follow up, has been collected in each centre using the data collection networks of the reference hospital.

IVUS imaging

IVUS imaging was performed during index angiography using a commercially available Volcano Eagle Eye IVUS-catheter (20-MHz, electronic transducer, Volcano Inc., Rancho Cordova, California): the tip of the IVUS catheter was placed in the coronary vessel unless a diameter <2.5 mm was present. The pullback was performed automatically with 0.5 mm/s (Volcano Track Back II), accordin to the technical requirements for IVUS systems recommended by the American College of Cardiology. Quantitative analysis of IVUS have been reported in table 1 (see appendix, web only) while the following were the definition for morphological analysis:

- calcium: bright echoes that obstruct the penetration of ultrasound, “acoustic shadowing
- hypoechoic (soft): echolucent atheroma
- hyperechoic non-calcified (fibrous): an intermediate echogenicity between soft (echolucent) atheromas and highly echogenic calcific plaque
- hyperechoic calcified (fibrous): bright echoes that obstruct the penetration of ultrasound, “acoustic shadowing
- mixed: plaques frequently contain more than one acoustical subtype

- thombus: an intraluminal mass, often with a layered, lobulated, or pedunculated appearance

End Point

Number of patients with multivessel disease is the primary end-point.

Secondary end-points were:

- the prevalence of abnormal features at IVUS (morphological and volumetric)
- the incidence of MACEs (composite end point of cardiovascular death, myocardial infarction, target lesion revascularization and ST), non cardiac death and target vessel revascularization.

For each end-point the subgroup analysis was conducted for HIV patients with $CD4^+$ cell count <200/mm^3.

Cardiovascular death has been defined as death for cardiac cause (acute myocardial infarction, heart failure with low ejection fraction, fatal arrhythmias), invasive procedure related death and death for unknown cause.

MI has been defined as myocardial infarction recurrence in at least 6 months, thus including STEMI and NSTEMI, and excluding unstable angina.

Stent thrombosis (ST) has been defined according to ARC classification in:

- Definite or confirmed event (symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis)
- Probable event (any unexplained death after 30 days)
- Possible event (any unexplained death after 30 days)

Statistical analysis

Categorical variables were compared with the use of Fisher' exact test. Parametric distribution of continuous variables (presented as means±SD) was tested graphically and with Kolmorogov Smirnov and appropriate analysis were used according to the results. For propensity score, first logistic regression analysis for all baseline features which were different for those with and without HIV and finally

matching was compute after division in quintiles and methods of nearest neighbor on the estimate propensity score. Calibration was tested with Hosmer-Lermeshow and accuracy with Area Under the Curve. Standardized differences were evaluated before and after matching to evaluate performance of the model. All statistical analyses were performed with SPSS 21 and differences were considered significant at $\alpha=0.05$.

RESULTS.

Before propensity score with matching, 66 patients with HIV and 120 without were selected, resulting in 20 and 40 after propensity score with matching **(see Table 1**).

Before matching.

Clinical and angiographic characteristic

Before matching, patients with HIV were younger, with a lower burden of cardiovascular risk factor and presenting more often with STEMI (58% vs 14%, p<0.001, **see Table 1**). They presented more often with a multivessel disease (54% vs 34%, p=0.04), but with lower rates of severe calcification (10% vs 30%, p<0.001). 36% of them reported a Cd4 cell count lower than 500 cc/m3, with a time from HIV diagnosis of 8 (5-13) years **(see appendix, web only Table 2).**

IVUS characteristic

Regarding IVUS analysis, (**see appendix, web only Table 3**) HIV patients reported a lower plaque burden (65% vs. 73%, p<0.05), and with higher rates of hyperechoic non-calcified plaques (96% vs. 34%, p <0.05) and thrombus (20% vs. 11%, p=0.02). While, in the HIV negative patients, was found higher rates of hypoechoic plaques (4% vs. 12%), without reaching a statistically significant difference.

After matching.

Clinical and angiographic characteristics

Similar features between HIV and non HIV patients were reported, with comparable profile of cardiovascular risk factors and clinical presentation (STEMI ad clinical presentation in 38% vs. 30% p=0.07**, see Table 1).** Angiographic features were the following **(see Table 2)**: in both group left anterior descending was the more frequent diseased vessel (33% vs 40%), followed by circumflex (31% vs 24%), right coronary artery (30% vs 27%) and left main (9% vs 9%). No differences in multivessel disease were reported (11,51% and 17,44% respectively, p=0.56, **see appendix, web only Figure 1**).

IVUS characteristics

IVUS evaluation showed a lower plaque burden (71% vs. 75%, p<0.001) and a higher prevalence of hyperechoic non-calcified plaques (100% vs. 35%, p<0.05) in HIV patients **(see Figures 1 and 2)**.

Instead, a higher prevalence of hypoechoic plaques and a longer atherosclerotic lesion in HIV patients with CD_4<200/mm^3 compared to those with CD_4>200/mm^3 **(see Figure 3).**

Outcomes

HIV patients with aggressive disease presented a higher incidence of MACE (17.4% vs 9,1% vs l'8%, p<0.05), as well as of MI (myocardial infarction) recurrence (17,2% vs 0.0% vs 2.3%, p<0.05), TVR (target vessel revascularization), i.e. the revascularization of the vessel previously treated but on a different lesion, (13,6% vs 1% vs 2%, p<0.05), TLR (target lesion revascularization), i.e. the revascularization of the same lesion previously treated (4,5% vs 0,5% vs 0,3%, p<0.05) and stent thrombosis (6,7% vs 0,3% both in HIV patients with CD_4 >200/mm^3 and in non HIV patients, p<0.05) **(see Appendix, web only Figure 2)**.

HIV infection related characteristics

Regarding HIV infection **(see Appendix, web only Table 1)** years elapsed since diagnosis were a median of 8 (5-13), patients have been treated for a median of 6 (4-9) years with at least two antiretroviral drugs of HAART, 9 (20%) patients received PI (protease inhibitors), 19 (42%) received NNRTI (non-nucleoside reverse transcriptase inhibitors) and 17 (38%) received NRTI (nucleoside reverse transcriptase inhibitors)-sparing regimens. 16 (36%) patients reported a CD_4 cell count less than 500 cells/mm^3. For these patients, sensitivity analysis was performed according to CD_4 cell count. Those with advanced HIV disease did not show peculiar differences when compared to those with CD_4 more than 500 cells/mm^3, apart from high rates of hypo echoic plaques (7% vs. 0%, $p<0.05$).

DISCUSSION.

The major findings of the present study are:

1) HIV patients present with a lower burden of traditional cardiovascular risk factors
2) IVUS evaluation showed a lower plaque burden in HIV patients and a higher prevalence of hypoechoic plaques in patients with aggressive disease ($CD_4<200/mm^3$).
3) HIV patients present a higher incidence of the MACEs.

In the present study, a high prevalence of smokers, was found, consistently with the observed by several international groups. Moreover, cardiovascular risk factors were less prevalent in HIV patients than in non HIV **(see Table 1)**. In interpreting this result it is necessary to consider that HIV patients were more than a decade younger than non HIV, with a statistically significant difference ($p<0.001$). Results of the previous study are only partially similar to those of the present study: *Boccara et al.* [38] prospective observational study, showed that hypertriglyceridemia was more frequent in HIV patients ($p<0.0001$), while other risk factors were balanced in the two groups.

On the contrary, *Hsue et al.*[xl] showed in their prospective study that hyperlipidemia was more frequent in non HIV patients (p=0.045); this result is consistent with that of the present study.

As far as the angiographic features are concerned, the present study showed that after matching features of the two groups were similar and are superimposable for diseased vessels and anatomic features **(see Table 2)**.

On the contrary, IVUS analysis showed that coronary plaques features, as described in results section, were significant different between the two groups **(see Figures 1 and 2)**. These results were confirmed after matching **(see Figure 1 and 2 and Appendix web only Figure 2)**.

Results published by *Boccara et al.*[38] are similar to those of the present study, with no differences found in angiographic features between HIV and non HIV patients, but partially disagree with those of the other two studies: *Hsue et al.*[40] observed a more extensive disease in non HIV (p=0.007); Similarly *Knudsen et al.*[41] revealed less complex angiographic lesions in HIV patients (p<0.0001), with a lower rate of calcified lesions; this last finding is similar to that of the present study.

A further significant result of the present study concerns the follow up of enrolled HIV patients: in patients presenting with advanced disease, defined as a CD_4 cell count <200/mm^3 at admission, MACE occurrence was significant higher both than HIV patients with non aggressive disease and than non HIV ones. ST, MI, TLR and TVR incidence was likewise higher in HIV patients. None of the previous studies considered the follow up of a sufficiently high number of patients subjected to coronary intervention to ascertain if long-term results of PCI were good, except for *Boccara et al.*[38] and *Badr et al.*[xli] studies. Independent events predictors found were initial AMI diagnosis (p=0.005), and chronic renal insufficiency history (p=0.044).

Calcification of vessels reduces their elasticity, affecting hemodynamic parameters of the cardiovascular system. Stage of advancement and the extent of accumulation of calcium deposits in vessel walls are key risk factors of ischemic events [42]. It has been shown that very low levels of 25(OH) vitamin D are associated with increased all-cause mortality in patients with and without kidney disease [43]. In

patients with 25(OH) vitamin D levels <75 nmol/l (or < 30 ng/dl), treatment with calcidiol causes significant reduction in parathormone (PTH) levels [44]. Clinical guidelines suggest stringent control of PTH, calcium and phosphate in an attempt to lower the risk of vascular calcification. Infact, is known that physiological concentrations of vitamin D3 have a myorelaxation effect, reduce endothelial thrombogenicity, increase fibrinolysis and inhibit inflammatory response [45-47]. On the other hand excessive supply of vitamin D3 inflicts intense accumulation of calcium deposits in tunica intima and media, elastin degradation, increased stiffness of vessel walls and left ventricular hypertrophy [48]. Restoration of physiological concentrations of calcitriol results in rapid regression of vascular calcification [49]. Increased concentration of calcitriol, through the suppression of parathormone-like proteins, lead to intensified activation of alkaline phosphatase, which inflicts degradation of pyrophosphates – inhibitors of calcium phosphate precipitation [50,51]; it also results in increased concentration of calcium and phosphate ions, which are important stimulators of matrix vesicle production [52]. Several studies have demonstrated low vitamin D levels among HIV-infected patients [53,54]. Certain lifestyle and hormonal factors, which increase the risk of bone loss, are prevalent in HIV-infected patients. These include physical inactivity, suboptimal intake of calcium and vitamin D, cigarette smoking, alcohol and opiate use, and low testosterone levels. ART itself may be associated with decreased bone mineral density. In our HIV positive patients, we found that more than 78% had a vitamin D deficiency (< 30 ng/dl), while only 4.5% had hypocalcemia. About patints with vitamin D deficency, only 11.5% were subjected to calcium and vitamina D supplementation (for more information see appendix table 4).

Low rates of calcified plaques for HIV patients presenting with ACS reflect the lower burden of traditional cardiovascular risk factors. Actually, the degenerative process of coronary sclerosis has been related to aging, which exposes coronary arteries to dilation, tortuosity, medial calcification, and ED. [55,56,57,58,59,60] Diabetes mellitus, hyperlipidemia and hypertension increase these mechanisms and the extent of coronary calcification has been found to add incremental prognostic significance to conventional risk factors for CAD.[61]

Furthermore, HIV patients present with hypoechoic non calcified plaques, reflecting the enhanced and persistent inflammation burden. Cytokine's expression and vascular damage are higher in HIV patients, as well as ED, which is closely connected to development of early atherosclerosis. For example, ED was reported even in young patients under treatment when compared with non-infected ones [61]. Moreover, different trials have been conducted to assess HAART impact on ED, most of which with neutral or negative results. [62,63]

Eventually, ED has been described related to vulnerable plaques at IVUS evaluation. Particularly, during the plaque development, ED is associated with a thin cap, increased inflammation, and difference of elasticity between the cap and lipid pool in plaque.[64,65] Finally, the increase of stress eases, through inflammation, plaque rupture, which is responsible for 75% of ACS.[66-70].

HIV patients with a highly replicating virus are exposed, moreover, to a high risk of more unstable plaques. Low rates of CD_4 cell counts reflect a poorly controlled disease, increasing the previously described mechanisms of plaque instability, and it may be related to immune-dysfunction (immune activation and immune senescence) or to the prevalence of other infection potentially affecting endothelial cells (cytomegalovirus, HHV-8, and others). [66,67] From a clinical point of view, this finding has been largely depicted as related to increased risk of myocardial infarction in primary prevention, and of recurrent events in secondary prevention. The present study provides a potential explanation, describing the presence of instable plaques in these patients, prone to rupture, due to the increased presence of apoptotic cells like macrophages and lymphocytes. [68] Moreover, our results stress even more usefulness of statins in primary prevention for these patients, and raise the question of effectiveness-risk of use of aspirin, especially for those at high risk of recurrent ischemic events, despite lack of randomized controlled trial. [69,70]

Limitations

The present study shares many limitations. First of all, it has all the limits of the observational studies. The low number of patients represents the most important one, although this represents, to the best of our knowledge, the largest sample size

of HIV patients presenting with ACS. Propensity score matching, though performed on a low number of patients, proved a satisfying overall performance, with good calibration (non significant Hosmer-Lermeshow test) and accuracy (AUC of 0.83 [0.78-0.89]. Lack of data about statin therapy, with their well known effect on coronary plaque, were not present, although their impact may be more evident on follow up. In this study very relevant determinants and co-morbidities were not analyzed, such as chronic kidney disease and peripheral vasculopathies. Furthermore, we have not performed an intra-/inter- observer variability analysis for this study and for the IVUS analysis we used only the visual inspection.

CONCLUSIONS.

Our study may provide a part of the pathophysiological basis of the differences in coronary arteries between HIV-positive and HIV-negative patients, suggesting that the former presents with peculiar morphological features at IVUS, even after adjustment for clinical variables. In fact, it has been demonstrated that low rates of calcified plaques in HIV patients are related to the low burden of traditional cardiovascular risk factors and to increased inflammation.

Furthermore, we confirmed that an advanced HIV infection is associated with a high risk of soft plaques and with a worse prognosis, including cardiovascular events and ACS recurrence. An additional positive aspect of our study is that it represents a real world multicentric experience.

Thanks to these observations it would be interesting to identify a subgroup of population with particularly advanced HIV infection, in which to intensify the prevention of ischemic heart disease, both in primary and in secondary prevention, and to define dedicated therapeutic approaches (specific stents or specific pharmacological protocols).

Table 1. Baseline features before and after matching.

	Before matching			After matching		
	HIV patients n 66	Non HIV patients n 120	P value	HIV patients n 20	Non HIV patients n 40	P value
Age (years)	52±7	68±10	**<0.001**	57±5	64±8	0.56
Female patients (%)	12 (24)	26 (22)	0.59	5 (25)	5 (25)	0.67
Hypertension (%)	19 (32)	93 (78)	**<0.001**	8 (47)	11 (55)	0.31
Hyperlipidemia (%)	8 (14)	22(52)	**<0.001**	4 (24)	7 (29)	0.32
Smoker habit (both previous and current%)	37 (52)	34 (37)	0.67	9 (45)	9 (45)	0.43
Diabetes mellitus (%)	6 (10)	26 (30)	**<0.001**	3 (22)	5 (25)	0.34
Previous myocardial infarction (%)	5 (7)	28 (34)	**0.01**	2 (10)	4 (17)	0.32
Previous percutaneous coronary intervention (PCI %)	4 (1)	58(44)	**<0.001**	2 (10)	4 (17)	0.32
Indication for PCI			**<0.001**			0.07
Unstable Angina (%)	14 (10)	47 (44)		3 (23)	4 (24)	
NSTEMI						
STEMI	18 (31)	43(42)		9 (45)	10 (46)	
	34 (58)	30 (14)		7 (38)	6 (30)	

Table 2. Angiographic features before and after matching.

	Before matching			After matching		
	HIV patients n 66	Non HIV patients n 120	P value	HIV patients n 20	Non HIV patients n 40	P value
Radial access (%)	58 (92)	103 (91)	0.67	20 (100)	38 (99)	0.56
Multivessel disease (%)	33 (54)	38 (34)	**0.04**	11 (51)	17 (44)	0.56
Vessel involved (%)			0.61			0.45
LM						
DA	6 (9)	11 (9)		4 (20)	7 (18)	
CX	22 (33)	48 (40)		6 (29)	13 (37)	
RCA	20 (31)	29 (24)		5 (26)	11 (25)	
	18 (30)	32 (27)		5 (25)	9 (20)	
Localization (%):			0.67			0.91
Ostial	1 (2)	2 (4)		1 (1)	2 (3)	
Proximal	23 (34)	47 (39)		7 (34)	12 (34)	
Medium	17 (34)	35 (28)		6 (37)	12 (33)	
Distal	15 (30)	36 (29)		6 (27)	14 (29)	
Type C lesion (%)	15 (52)	15 (37)	0.67	9 (45)	9 (45)	0.43
Severe calcification (%)	3 (10)	12 (30)	<0.001	3 (22)	5 (25)	0.34
Bifurcation (%)	20 (31)	30 (36)	0.56	11 (33)	14 (35)	0.45
Predilatation (%)	45 (75)	95 (80)	0.81	14 (71)	32 (76)	0.98
Diameter of stent (mm)	3.0±0.45	2.8±0.33	0.78	3.1±0.41	2.9±0.34	0.91
Length of stent (mm)	18±3	17±2	0.67	21±3	20±4	0.78
Predilatation (%)	51 (82)	101 (83)	0.89	18 (83)	26 (84)	0.67

FIGURES

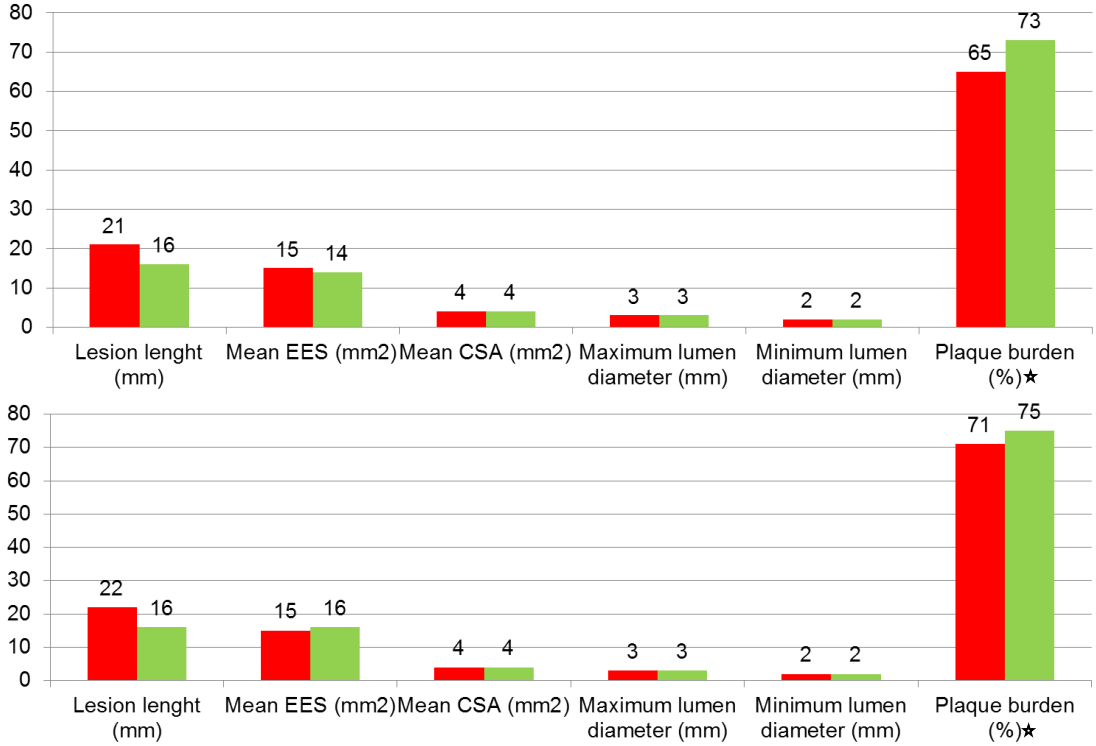


Figure 1: Volumetric analysis before (above) and after (below) propensity score matching between HIV (red) and non HIV (green) patients.

★ p<0.05

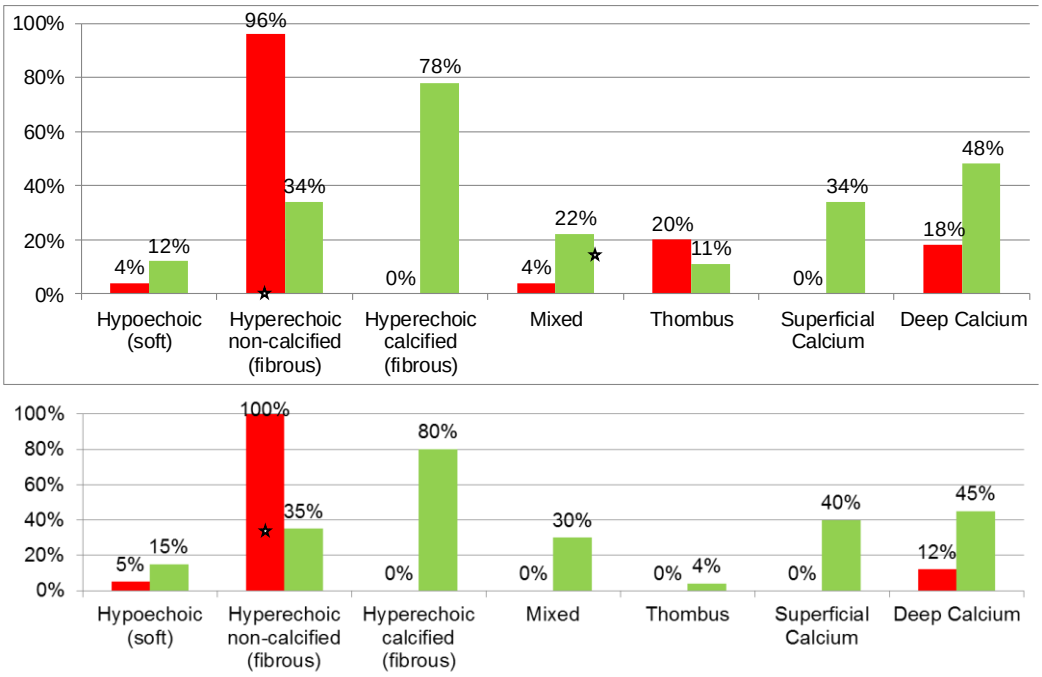


Figure 2: Morphological analysis before (above) and after (below) propensity score matching between HIV (red) and non HIV (green).

⋆p<0.05

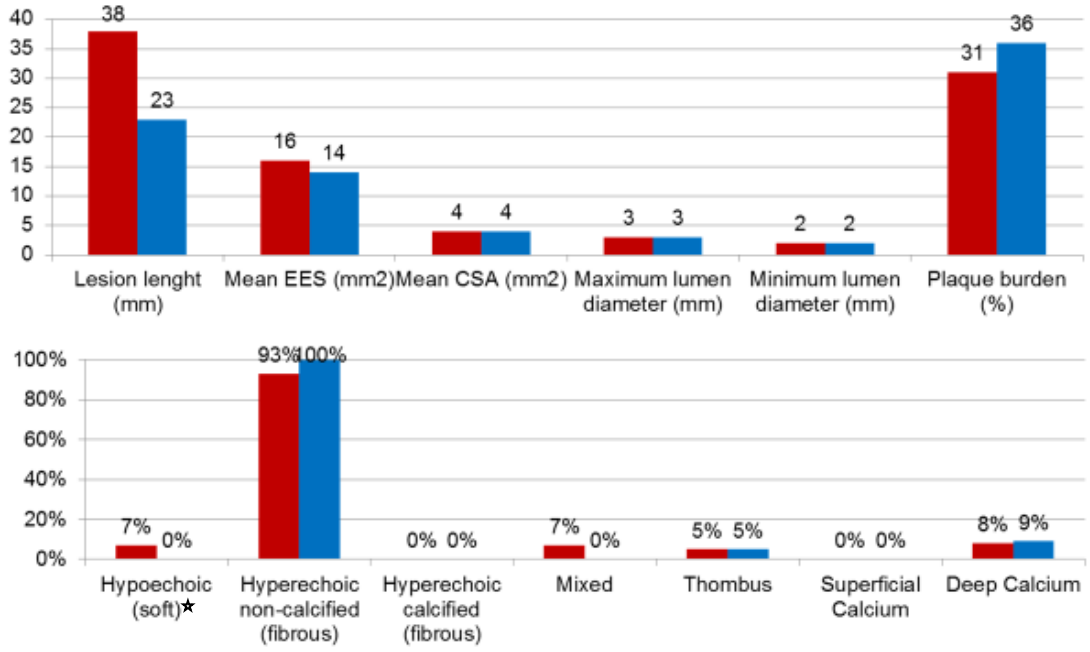


Figure 3: Volumetric (above) and morphological (below) examination between HIV patients with Cd4 cell count less than 200 cells/mm^3 (red) and more than 200 cells/mm^3 (blue).

⋆P<0.05.

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Declaration
Student's contribution to articles and agreement of co-authors

I, Ahmed Vachiat, student number 9901325H, declare that this Thesis is my own work and that I contributed adequately towards research findings published in the articles stated below which are included in my Thesis.

Signature of Student.....**Date**.....27/3/18.....
Name of Primary Supervisor Prof Pravin Manga
Signature of Primary Supervisor.....
Date.....27/3/18.....

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of his Thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his degree purposes.

Article 1: HIV and Ischemic Heart Disease

JACC Vol 69. No.1 2017

Authors	Name	Signature	Date
1st Author	Ahmed Vachiat		27/3/18
2nd Author	Keir McCutcheon		28/3/18
3rd Author	Nqoba Tsabedze		27/03/2018
4th Author	Pravin Manga		27/3/2018

Comments by primary supervisor

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Article 2: New face of Cardiac emergencies Human Immunodeficiency Virus-Related cardiac Disease

Cardiol Clin. 2018 Feb;36 (1):161-170.

Authors	Name	Signature	Date
1st Author	Nqoba Tsabedze		28/03/2018
2nd Author	Ahmed Vachiat		27/3/2018
3rd Author	Don Zachariah		27/3/18
4th Author	Pravin Manga		27/3/18

Comments by primary supervisor

Dr Vachiat's major contribution to this paper was related to ischaemic heart disease, particularly acute coronary syndrome presentation to emergency room. This he is entitled to use for degree purposes

Article 3: Atherosclerotic plaque in HIV-positive patients presenting with acute coronary syndromes

Submitted Open Heart

Authors	Name	Signature	Date
1st Author	Ahmed Vachiat		27/3/18
2nd Author	Keir McCutcheon		28/3/18
3rd Author	Nqoba Tsabedze		28/03/2018
4th Author	Don Zachariah		27/3/18
5th Author	Pravin Manga		27/3/18

Comments by primary supervisor

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Article 4: Endothelial dysfunction in HIV patients presenting with acute coronary syndromes

Submitted Cardiovascular Journal of Africa

Authors	Name	Signature	Date
1st Author	Ahmed Vachiat		27/3/18
2nd Author	Therese Dix-Peek		28/03/18
3rd Author	Raquel Duarte		28/03/18
5th Author	Pravin Manga		27/3/18

Comments by primary supervisor

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Article 5: Prognostic indicators for recurrent thrombotic events in HIV-infected Patients with acute coronary syndromes: Use of registry data from 12 sites in Europe, South Africa and the United States.

Thrombosis Research 134 (2014) 558-564

Fabrizio D'Ascenzo , Enrico Cerrato, Darryn Appleton, Moretti C, Calcagno A, Abouzaki N, Vetrovec G, Lhermusier T, Carrie D, Das Neves B, Escaned J, Casese S, Kastrati A, Chinaglia A, Belli R, Capodanno D, Tamburino C, Santilli F, Parodi G, ***Vachiat A****, Manga P, Vignali L, Mancone M, Sardella G, Fedele F, DiNicolantonio JJ, Omede P, Bonora S, Gaita F, Abbate A, Zoccai GB; Percutaneous coronary intervention and surgical revascularization in HIV Database (PHD) Study Investigators.et al.*

Comments by primary supervisor

Dr Vachiat's findings from this thesis were used to publish the above data which use registry data from 12 different sites in the world.

Article 6: Evaluation *of Coronary featUres of HIV patients pREsenting with ACS : the CUORE a multicenter study*

Accepted Atherosclerosis

Mattia Peyracchia MD, Giulia De Lio MD, Chiara Montrucchio MD, Pierluigi Omedè MD, Gabriella d'Ettore MD, Andrea Calcagno MD, Vincenzo Vullo Prof, Enrico Cerrato MD, Mauro Pennacchi MD, Gennaro Sardella Prof, Pravin Manga Prof, Walter GrossoMarra MD, Francesco Vullo MD, Francesco Fedele Prof, Giuseppe Biondi Zoccai MD MStat, Claudio Moretti MD, ***Ahmed Vachiat MD****, Stefano Bonora Prof and Massimo Mancone MD PhD and Fabrizio D'Ascenzo MD.*

Comments by primary supervisor

Dr Vachiat's findings from this thesis were used to publish this collaborative paper assessing coronary features of HIV patients presenting with ACS

9901325h:PhD_Thesis_Ahmed_Vachiat_26_March_2018_08h..

ORIGINALITY REPORT

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