2016

Risk assessment and the utility of CT coronary angiography for coronary artery disease in HIV infection

James Nadel
The University of Notre Dame Australia

Risk assessment and the utility of CT coronary angiography for coronary artery disease in HIV infection

James Nadel

Bachelor of Arts (Advanced) (BA Adv.)

Bachelor of Medicine, Bachelor of Surgery (MBBS) (Hons I)

A thesis by publication submitted for the degree of Master of Medicine / Surgery at

The University of Notre Dame, Sydney in 2016

Dedication

To the great women in my life - Electra Foley and Melinda Itzkowic - without whom I would not be living and could not survive.

Table of contents

Abstract

Background

Human immunodeficiency virus (HIV) infection is now considered a chronic, treatable disease, although treatment is associated with increased rates of coronary artery disease (CAD). Screening of this at-risk population for CAD remains contentious. The aim of this thesis is to provide some guidance into the management of cardiovascular disease in HIV and examine the utility of screening CTCA in this population group.

Methods

We set out to disseminate our generated results via publications. The first paper was a literature review that sought to provide insight into the management of this complex population, in particular focusing on the risk assessment and screening of this population group. The second paper was original research; a retrospective single centre analysis that compared the CTCA findings and clinical endpoints of a group (n=32) of HIV patients to their uninfected counterparts (n=65), in an effort to appraise the efficacy of CTCA in the screening and prediction of adverse cardiac outcomes.

Results

Regarding the literature review we provided a formulaic approach to the risk assessment and screening of CAD in HIV. In our research article, patients with HIV were shown to have higher prevalence of non-calcified, high risk plaque (0.8±1.5 versus 0.3±0.7, p=0.03), experience greater rates of non-ST elevation acute coronary syndromes (ACS) (16% (5) versus 3% (2), p<0.04), but paradoxically had lower rates of coronary intervention compared to their uninfected counterparts (mean time to event 9.9±3.3 versus 20.6±4.9 months, p<0.04).

Conclusion

Currently there are no guidelines pertaining to the screening and further management of HIV patients at risk of CAD. Our literature review outlines a proposed approach for assessing and managing CAD in HIV patients. In our clinical research we demonstrated that HIV patients screened with CTCA were susceptible to developing at-risk coronary plaques and had higher rates of adverse cardiac events despite less frequent invasive coronary intervention compared to HIV negative controls. This thesis provides early evidence for the use of CTCA in the screening of HIV patients and highlights a need for further investigation to establish appropriate screening and risk assessment protocols as well as more rigorous examination of why HIV patients may be less aggressively managed following adverse cardiac events.

List of Publications Included as Part of this Thesis

1. Nadel J, Holloway CJ. Screening and risk assessment for coronary artery disease in HIV infection: an unmet need. HIV medicine. 2016 Aug 1.

2. Nadel J, O'Dwyer E, Emmanuel S, Huang J, Cheruvu S, Sammel N, Brew B, Otton J, Holloway CJ. High-risk coronary plaque, invasive coronary procedures, and cardiac events among HIV-positive individuals and matched controls. Journal of Cardiovascular Computed Tomography. 2016 Oct 31;10(5):391-7.

Statement of Original Work

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text.

I have clearly stated the contribution of others (see below) to my thesis as a whole, including the administration, ethics approval, statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the General Award Rules of The University of Notre Dame, immediately made available for research and study in accordance with the Copyright Act 1968.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material presented.

Contributions by others to the thesis

The concept and design of this project was established in conjunction with Dr. Cameron Holloway who was also instrumental in the interpretation of the research data. Dr. James Otton and Dr. Justyn Huang were responsible for the assessment of CTCA images in the cohort. Dr. Eoin O'Dwyer, Dr. Samuel Emmanuel and Dr. Sarat Cheruvu were responsible for a portion of the collation and statistical presentation of the data. Dr. Neville Sammel and Dr. Bruce Brew provided input into the editing of one of the manuscripts presented. All other work is entirely of my own undertaking including, and not limited to the documents presented in the appendices of this thesis.

Acknowledgments

I would like to acknowledge my research supervisor Dr. Cameron Holloway for his commitment and support. This project would never have been possible without his clinical expertise and guidance.

I wish to acknowledge the work of M/Med coordinator and ancillary staff whose dedication and input have been vital in creating an academic curriculum that is both thorough and relevant to its students.

Lastly, to 97 participants who took time out of their days to be involved in this project, without whom this thesis would not have been possible. I thank them on behalf of the medical community, for without their continued commitment, advances in our clinical sciences would not ensue.

Introduction

Human immunodeficiency virus (HIV) infection and Acquired immunodeficiency syndrome (AIDS) affects approximately 35 million people globally and is responsible for almost 2 million deaths per year.[1] In Australia there are 30,000 people living with HIV, representing a prevalence of 0.15%.[2] Nationwide male-to-male sexual contact remains the major route of transmission of HIV,[3] and despite Australia having both a low incidence and prevalence of HIV compared to many other countries, concern has been raised over a recent increase in the annual number of people diagnosed with HIV.[2,4]

With the advent of antiretroviral therapy (ART) morbidity and mortality has improved to a point where HIV is now considered a chronic, treatable disease.[5] Widespread access to ART has led to non-AIDS related events surpassing AIDS related events as the primary source of HIV related disease burden.[6] ART has resulted in an improvement in life expectancy at the expense of chronic age related diseases including coronary artery disease (CAD).[7,8]

Whilst the exact incidence and impact of cardiac disease in Australian patients with HIV is still unknown; patients with HIV now have a 1.5-2 fold greater risk of developing CAD compared to non-infected individuals, with an even greater risk increase conferred to those aged over 45 years.[9] Furthermore, those with HIV typically present with symptomatic disease at a younger age and experience higher rates of post-angioplasty restenosis.[10,11] Regarding subclinical disease, coronary artery plaques have been found to be more prevalent and extensive in HIV-infected men although the significance of such findings remains unclear.[12,13]

HIV and ART's role in the development of CAD

There is a complex interplay between HIV infection, antiretroviral therapy and the development of CAD. HIV infection itself modestly contributes towards abnormalities in glucose and lipid metabolism, with chronic inflammation and immune activation underlying a proatherogenic state.[14] In addition, traditional cardiovascular risk factors are overrepresented in patients with HIV; owing to a combination of population demographics and increased metabolic abnormalities from the use of antiretroviral medications.[15] While the exact mechanism by which these factors lead to the development of CAD is not fully understood, it has been postulated that interference of macrophage and endothelial cell function as well as the induction of immunosenescence in T-cells directly by the virus acts synergistically with ART induced metabolic dyshomeostasis to lead to accelerated atherosclerosis.[16,17]

Duration of therapy and individual drug regimens are also factors thought to underlie the increased incidence of CAD and myocardial infarction in treated HIV.[18,19] It has been suggested that there is an increased risk of CAD development with the use of protease inhibitors and some nucleoside reverse transcriptase inhibitors. Data however is conflicting, with several large studies disputing this assertion

and it is likely that where an association exists, it is drug specific rather than class specific.[20-23] Irrespective, the nature of ART is one of combination therapy with a variety of differing agents and classes that change frequently, making delineation difficult in clinical practice.

Myocardial disease in HIV

Although not explicitly pertaining to CAD the interplay between myocardial disease and HIV provides a wider comprehension of the disease process and its cardiac implications. The presence of myocardial disease in the pre-ART era was widely reported, with high incidences of dilated cardiomyopathy as well as systolic and diastolic dysfunction.[24] In the contemporary setting with unrestricted access to ART there has been a reduction in the prevalence of HIV-related myocardial disease although isolated ventricular dysfunction, systolic dysfunction without dilatation and diastolic dysfunction have been described.[25,26] Whilst studies have shown that most patient with HIV have normal cardiac function, there are apparent alterations in systolic and diastolic function suggesting a high prevalence of asymptomatic dysfunction.[27,28] A nationwide French study found that following myocardial infarction HIV patients were more likely to develop symptomatic heart failure than those without HIV, suggesting that the combination of underlying cardiac dysfunction and CAD confers a greater burden of disease post-infarction in the HIV population.[29]

The precise pathogenesis of myocardial disease in HIV infection remains ill defined, but is likely to be multi-factorial. The direct effects of HIV infection resulting in increased circulating pro-inflammatory cytokines, as well as complications from ART and myocarditis from infectious and non-infectious causes have been implicated.[28]

Screening for CAD in HIV

Despite almost half of all fatal myocardial infarctions occurring in previously asymptomatic patients,[30] controversy still surrounds the role of screening and early management of CAD. With the risk facing those with HIV thought to be similar to that of the diabetic population, it has been suggested that screening high-risk patients with treated HIV is advantageous to improving outcomes.[13,31] However, to date no studies have shown a correlation between screening for CAD and an improvement in outcomes. The cardiac investigations typically used in the assessment of CAD include stress echocardiography, CT coronary angiography (CTCA) and myocardial perfusion scanning.[32]

CTCA has a sensitivity of 98%, a specificity of 88%, and a negative predictive value of 96-100% in ruling out obstructive coronary disease compared to standard invasive angiography.[33] Nevertheless, at present CTCA has no validated role in the screening of asymptomatic individuals.[32,34] CTCA has however been used with good effect to assess for CAD in patients with HIV,[35] and there is evidence that it can aid in risk stratification of asymptomatic patients via coronary artery calcium (CAC) scoring.[36] Despite this, the utility of CAC scoring alone may be equivocal in the HIV population given the differing plaque morphologies and greater rates of higher risk, noncalcified plaque seen in these

patients.[12]

Clinical outcomes of CAD

Acute Coronary Syndrome (ACS) is the most relevant clinical manifestation of CAD. The current Australian guidelines for the management of ACS were established by the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand (NHF/CSANZ) in 2006 and have since undergone two revisions in 2007 and 2011.[37,38] The guidelines are structured around the stratification of ACS into ST-elevation myocardial infarction (STEMI) or Non-ST-elevation Acute Coronary Syndrome (NSTEACS) with the latter encompassing both Non-STEMI and the angina spectrum. NSTEACS can be further stratified into risk groups: high (NSTEACS-HR), intermediate (NSTEACS-IR), and low (NSTEACS-LR) risk.

A STEMI is defined as either a persistent ST-elevation ≥1 mm in 2 contiguous limb leads; an ST elevation ≥2 mm in 2 contiguous chest leads; or a new left bundle branch block pattern. Treatment recommendations for STEMI favour Percutaneous Coronary Intervention (PCI) over thrombolysis where available within 0–12 hours of symptom onset. Treatment of NSTEACS is variable depending on troponin levels at presentation and 6 hours after presentation as well as patient risk group. Nevertheless, for all patients with NSTEACS, upgraded medical therapy and cardiac review or coronary cardiac unit (CCU) admission is advised. In all but the NSTEAC-IR with a negative stress test and NSTEAC-LR, angiography with a view to PCI or coronary artery bypass graft (CABG) is recommended in the sub-acute setting.[38]

Risk stratification plays a key role in assessing a patient with NSTEACS and has been shown to improve outcomes.[39] However, there is concern that those with HIV are overlooked in the assessment of risk in ACS.[40,41]

Given that baseline risk is what drives the treatment-outcome benefits within a population,[42] it is logical to surmise that if clinicians attune themselves to the risk profile of their patients, then cardiovascular management strategies should be more intensive for those at greater risk. However, available evidence suggests that physicians do not always tailor management appropriately to reflect the risk profiles of their patients. For example, a number of studies have shown that treatment aggressiveness in cardiovascular disease inversely correlates with factors that are markers of poorer prognosis, such as age and comorbidity.[43,44]

Currently HIV is not recognised as a risk factor in in any ACS assessment tools.[40] With the propensity to develop more at-risk plaques, evidence of greater incidence of ACS and higher rates of post angioplasty restenosis; the presence of HIV may be clinically under-recognised as an independent risk factor and poor prognostic indicator in ACS.[45-48]

There is an increased risk of CAD and its sequelae facing the contemporary HIV population. Given the lack of available clinical data it remains unclear how best to screen and treat this at-risk group. We therefore set out to; (a) perform a literature review and provide insight into the management of this complex population and (b) undertake original research seeking to compare CTCA findings and clinical endpoints in a group of HIV patients in order to appraise the utility of CTCA in the assessment of CAD and explore whether these patients are at greater risk of associated morbidity and mortality.

Paper 1: Screening and risk assessment for coronary artery disease in HIV: An unmet need

James Nadel BA, MBBS[1,2], Cameron J Holloway FRACP, D.Phil[2,3]

[1] *University of Notre Dame, Sydney, Australia*
[2] *St. Vincent's Hospital, Sydney, Australia*
[3] *Victor Chang Cardiac Research Institute, Sydney, Australia*

Word Count: 2,356

Brief title: Screening for CAD in HIV

Disclosures: None

Journal: HIV Medicine

Abstract

Human immunodeficiency virus (HIV) infection is now considered a chronic, treatable disease, although treatment is associated with increased rates of coronary artery disease (CAD). Increased risk of CAD in HIV patients has been associated with the inflammatory sequelae of the infection as well as the greater prevalence of cardiac risk factors in HIV-positive populations and the side effects of life-prolonging antiretroviral therapies. Patients with HIV now have a 1.5-2 fold greater risk of developing CAD compared to non-infected individuals, raising the independent risk of CAD in HIV to levels similar to those with diabetes. Despite this increased risk, screening and other adjuvant assessment tools are lacking.

In this paper we explore the current climate of CAD in the contemporary HIV population and look at the tools used in the assessment and management of patients as well as the limitations of these approaches for this at-risk population group.

Introduction

Human immunodeficiency virus (HIV) infection and Acquired immunodeficiency syndrome (AIDS) affects over 35 million people globally and new infections were estimated at over 2 million in 2014.[49] The number of HIV related deaths continue to decline, with 1.5 million people dying of AIDS related cause in 2013, down 35% from the peak in 2005.[50] The advent of antiretroviral therapy (ART) has improved morbidity and mortality to a point where HIV is now considered a treatable chronic disease.[5] The life expectancy among treated individuals is now comparable to the general population.[7] This extension in expected survival has resulted in the emergence of chronic diseases including an increased incidence of coronary artery disease (CAD).[8]

Mechanisms of coronary artery disease

Increased risk of CAD in patients with HIV has been associated with the inflammatory sequelae of the infection as well as the greater prevalence of cardiac risk factors in HIV-positive populations and the side effects of life-prolonging antiretroviral therapies.[10,18,51] The underlying pathophysiological mechanisms resulting in the increased risk of CAD in patients with HIV are not well understood and likely come from a combination of traditional as well as novel risk factors (Figure 1). While the exact impact of cardiovascular disease in patients with HIV is still largely unknown – data remains inconsistent due to differences in populations, treatments and study design – CAD has emerged as an important cause of mortality and morbidity in those living with HIV.[52]

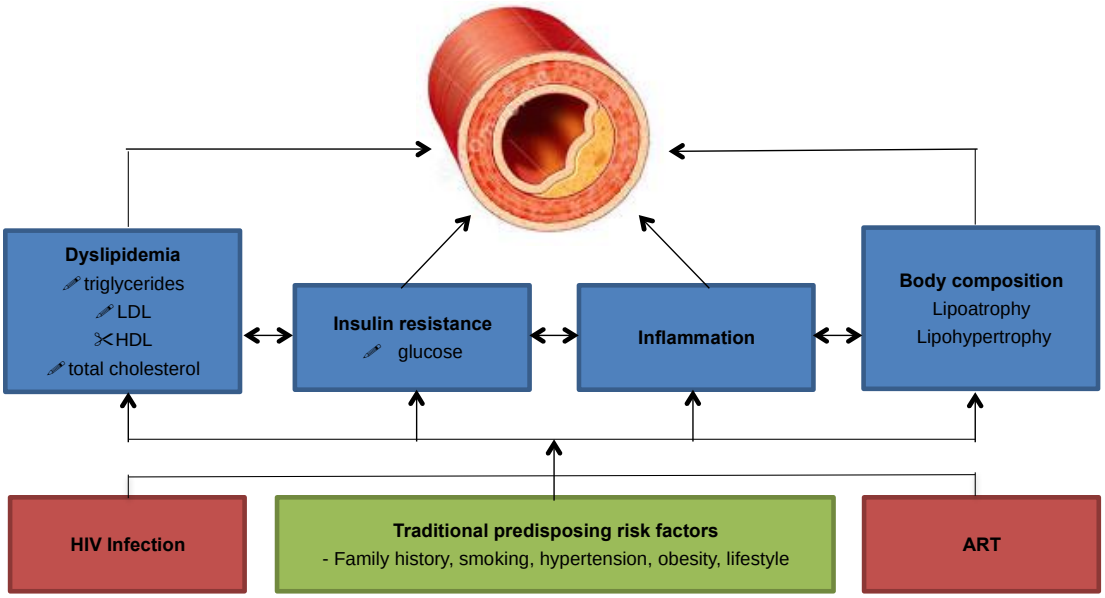


Figure 1. Multifactorial pathogenesis of increased risk of CAD in treated HIV patients

Incidence of coronary disease in patients with HIV

Patients with HIV have a 1.5-2 fold greater risk of developing CAD compared to non-infected

individuals, raising the independent risk of CAD in HIV to levels similar to those who smoke or have diabetes.[10] Those with HIV and symptomatic CAD present at a younger age and experience a higher rate of post-angioplasty restenosis.[40] Regarding subclinical disease, coronary artery plaques have been found to be more prevalent and extensive in HIV-infected men although the significance of such findings remains unclear.[12,13]

HIV infection and antiretroviral therapy's implication in cardiac risk

The duration and use of specific antiretroviral drug regimens have been implicated as factors in explaining the risk of CAD and myocardial infarction for those with HIV.[18,51] Protease inhibitors and some nucleoside reverse transcriptase inhibitor are generally thought to increase the risk of CAD development, but data has been conflicting.[22,23] Several large studies have refuted the association between ART classes and CAD.[20,21] In particular, the protease inhibitor, ritonavir, and more recently the nucleoside reverse transcriptase inhibitor, abacavir, have been implicated in conveying greater CAD risk on those with HIV,[22,23] although a recent meta-analysis has found no correlation with the latter.[53]

Despite efforts to disentangle which antiretroviral agents are responsible in the development of adverse lipid levels and CAD,[54] in clinical practice this delineation becomes difficult. The nature of ART is one of a combination of multiple agents from a variety of different classes that changes with advances in pharmacological research and individual patient circumstances. Therefore, at least from a pragmatic standpoint, considering these drugs as a whole entity is perhaps as useful as comparing individual drugs and classes. The lipid abnormalities generally seen in patients on ART are increased total cholesterol, with decreased HDL and hypertriglyceridemia.[55] Hence, it is prudent to note that relying on absolute LDL levels in treated HIV patients may underestimate their degree of cardiac risk because of concomitant lipid abnormalities.

Management of CAD risk factors in the HIV population

Irrespective of the presence of established heart disease, as a first line all patients with HIV should be given recommendations for lifestyle modifications such as smoking cessation, regular exercise, weight loss and nutritional advice.[56] As with the general population, management of traditional risk factors with lifestyle modifications and medications is imperative to slowing the progression of CAD and improving clinical outcomes.[57] Given that patients with HIV have regular contact with health care professionals, there are frequent opportunities to provide counseling and intervention strategies.

Regarding weight, diet and exercise adherence to the national guidelines is encouraged and should include a diet high in fruits, vegetables, lean meats and wholegrains along with the avoidance of foods high in sugar, saturated fat and salt. >30 minutes of moderate intensity exercise each day is recommended along with the maintenance of a healthy weight and waist circumference.[58] For patients

who smoke both, pharmacological and behavioural smoking cessation strategies should be considered.[59]

Diligent screening and management of diabetes and its complications is essential in HIV positive populations. Current recommendations include a baseline fasting glucose and oral glucose tolerance test, with additional screening before and 3-6 months after the commencement of antiretroviral therapy that includes a protease inhibitor. In those with identified impaired glucose metabolism, meticulous adherence to National Diabetes Management Guidelines is recommended. At minimum, this should include yearly (but preferably 3-6 monthly) retinal, foot and urinary albumin screening.[15] Where possible, metabolically favourable antiretroviral drug regimens should also be considered. If oral hypoglycaemic drug therapy is required, insulin sensitising agents such as metformin or thiazolidinediones are preferred[15,60]

Lipid lowering recommendations should be based on the current guidelines for lifestyle interventions. An initial trial of six weeks of lifestyle modification is appropriate as per the guidelines, prior to the consideration of pharmacological intervention.[58] At first diagnosis, an initial baseline fasting lipid panel should be performed which includes total cholesterol, LDL, HDL and triglyceride levels[56,60]

Regarding the pharmacological management of lipid profiles, consideration needs to be given to the way in which lipid lowering agents interact with anti-retroviral therapy. To varying degrees most statins are metabolised in the liver by the CYP34A system, an enzymatic system that some antiretroviral have been shown to down regulate.[61] Protease inhibitors in particular have been implicated in the down regulation of CYP34A and therefore when used in conjunction with statin therapy can lead to high serum concentrations and adverse side effects including hepatoxicity and myositis.[61]

Both atorvastatin and rosuvastatin are effective in reducing LDL and triglyceride levels and neither are entirely metabolised by CYP34A, making them more likely to be safe to use in conjunction with protease inhibitors than other statins.[61] Despite this efficacy, studies assessing the safety of rosuvastatin when taken concomitantly with protease inhibitors are conflicting.[62,63] Hence, due to its high efficacy and low interaction profile, currently atorvastatin is considered to be the first line agent for hyperlipidemia management in the HIV patient.[61]

Assessing Risk of CAD in the HIV population

The ability to provide primary and secondary health intervention has led to the development and utilisation of risk assessment tools to direct further investigations and management. These assessment tools use regression equations derived from a population sample of the Framingham heart and the Framingham offspring studies.[64] Although the Framingham risk calculators have been shown to predict risk reasonably well, the accuracy of these scores has been shown to vary across different population groups.[65-67] In patients with HIV, the Framingham risk score underestimates the

presence of subclinical atherosclerosis, as well as under-predict rates of myocardial infarction.[68,69] These findings suggest that such tools are unhelpful in this population group where the CAD disease process is purportedly complicated by ART, chronic inflammation and oxidative stress on top of pre-existing conventional risk factors.[69,70]

Consequently, HIV specific risk assessment tools have emerged. The Data collection on Adverse Effects of Anti-HIV Drug Study (DAD) was a prospective multinational cohort study that recruited 22,625 HIV infected patients.[71] The study sought to develop a model that predicted risk of CAD and its sequelae. The model includes; age, sex, systolic blood pressure, smoking status, family history of CAD, diabetes, total cholesterol, HDL cholesterol and exposure to certain ART. The DAD risk tool was found to be more accurate in predicting risk of CAD and myocardial infarction when compared to the traditional Framingham risk score in the HIV population.[71]

Methods for screening CAD in the HIV population

Despite almost half of all fatal myocardial infarctions occurring in previously asymptomatic patients,[30] controversy surrounds the role of screening and early management of CAD. Both the modality of screening and timing for when to screen at-risk asymptomatic individuals remains unclear even amongst the general population.[32] With the risk facing those with HIV thought to be similar to that of the diabetic population, where screening is appropriate, screening high-risk patients with treated HIV may be advantageous to improving outcomes.[31] However, to date no studies have shown a correlation between screening for CAD and an improvement in outcomes, making such suggestions based on expert opinion rather than being evidence based.

Regarding the modalities used to screen these high-risk patients the cardiac investigations most commonly utilised include stress echocardiography, CTCA and myocardial perfusion scanning.[32]

<u>Stress echocardiography</u>

The role of stress echocardiography in screening asymptomatic people in moderate to high-risk populations is well documented, despite no specific data pertaining to those with HIV. Nevertheless, it appears reasonable to use stress echocardiography to screen for obstructive CAD in patients with HIV.[31] This modality however does not provide evidence on mild to moderate coronary disease,[72] which is available through CTCA,[73] suggesting stress echocardiography should be used in those with optimal medical therapy, where the finding of early vascular disease won't change management (Figure 2). The finding of early atherosclerosis on CTCA enables clinicians to risk stratify and provide early intervention for their patients. CTCA allows for insight into early plaque deposition where stress echocardiography only identifies patients with established vascular disease.

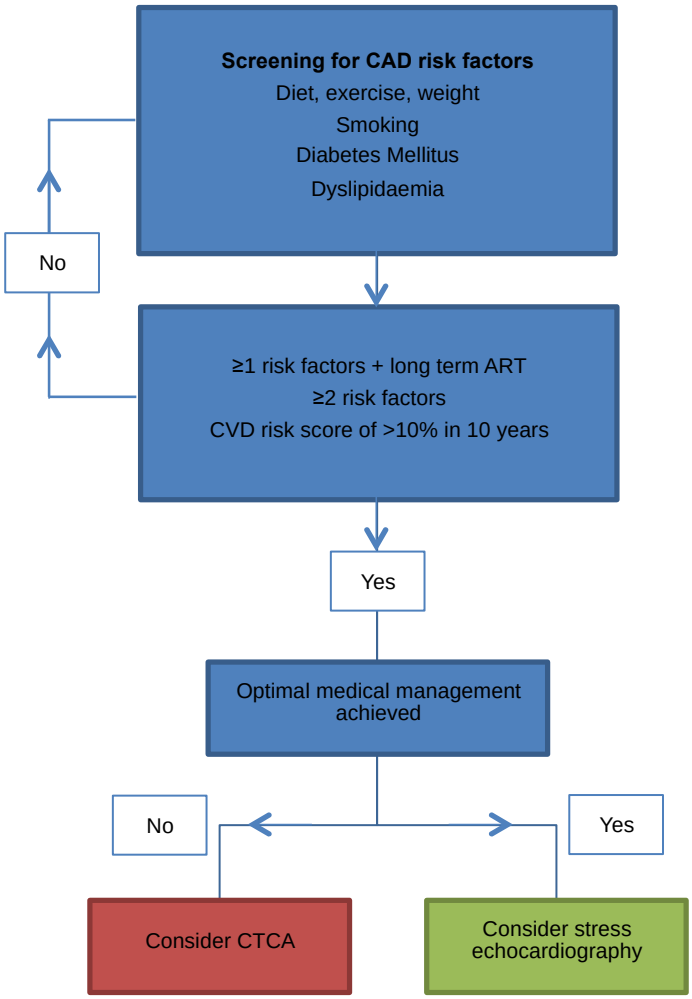


Figure 2. Screening for CAD in HIV patients

Myocardial perfusion scanning

The utility of myocardial perfusion scanning is uncertain due in part to its limited clinical availability. Moreover, the use of myocardial perfusion scanning as a first line testing modality for risk stratification is currently not recommended in any category of primary prevention subjects.[74] Despite this, some guidelines have advocated the uses of myocardial perfusion scanning in intermediate-risk or high-risk target populations.[75]

CT coronary angiography

CTCA allows for an accurate assessment of the location and perfusion of atherosclerotic plaque in the coronary artery vasculature.[76] It can also gauge the degree of stenosis affecting a coronary vessel, determine if a plaque is obstructive or non-obstructive and provide calcium scoring as a surrogate measure of calcific CAD.[73,77] Currently, 64-slice (or higher) CTCA is the non-invasive modality of choice for assessing CAD in a broad spectrum of patients.[78-80]

As a clinical tool it has a sensitivity of 98% and specificity of 88% and has been found to be as

effective as standard invasive angiography in ruling out obstructive coronary disease.[33] With an established role in the investigation of intermediate chest pain,[81,82] its utility as a screening tool in asymptomatic individuals remains contentious. Limited information on the role of CTCA for risk assessment in asymptomatic persons is available. A paucity of clinical trials has resulted in the current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines not recommending its use in asymptomatic adults (level C evidence).[83] There is however evidence that CTCA can aid in risk stratification of asymptomatic patients via coronary calcium scoring and its role in the screening of asymptomatic high-risk patients is still considered uncertain due to insufficient evidence.[36,84] Nevertheless, recent evidence has shown that CTCA may be of both clinical benefit and is cost effective in the screening of CAD in HIV-positive men.[35]

Independent of traditional cardiovascular risk factors, coronary plaque, especially noncalcified “soft” plaque, is more prevalent and extensive in those with HIV compared to their uninfected counterparts (Figure 3).[12] The presence of noncalcified plaques on CTCA is associated with greater rates of ACS when compared to mixed and calcific plaques.[85,86] Given the predominance of high-risk soft plaque development, there is growing concern that calcium score alone may not adequately assess HIV patients at risk of CAD. Subsequently, CTCA has been considered as the screening tool of choice to rule out obstructive disease in patient who have established risk factors.[31] Nevertheless, to date there are no published trials evaluating the impact of specific therapy on clinical outcomes in patients identified as having noncalcified atheroma by CTCA.[83]

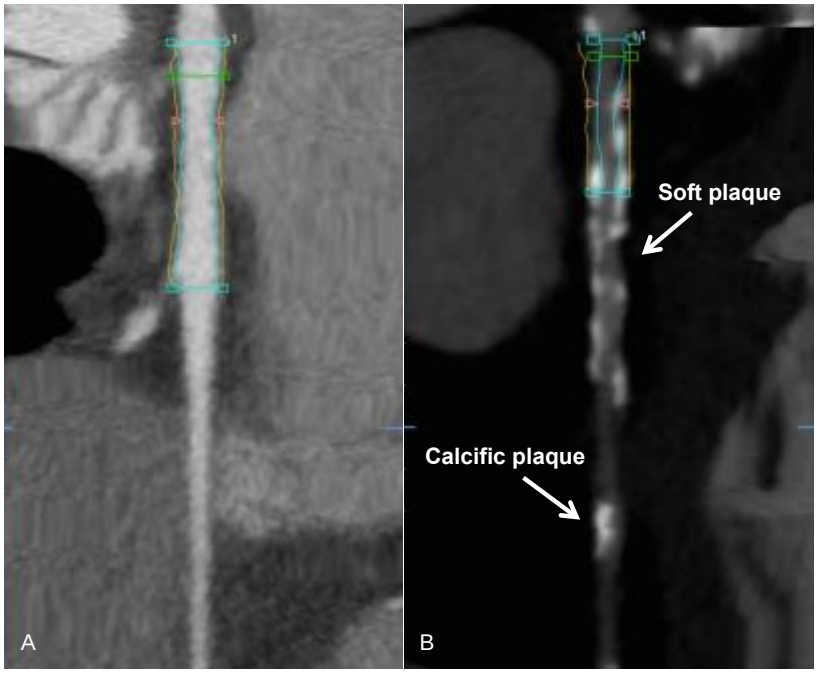


Figure 3. (A) CTCA image of a normal left anterior descending (LAD) coronary artery; (B) LAD artery with significant plaque burden and differing plaque types as labeled

Our approach to the screening of at-risk HIV patients is outlined in Figure 2. For those with optimal medical management we suggest the use of stress echocardiography to assess for life threatening

plaque. In those with suboptimal medical management, poor metabolic control or in the case of clinician uncertainty regarding management we advocate the use of CTCA in an effort to assess burden of disease and dictate the aggressiveness of pharmacological therapy or need for further intervention.

Clinical outcomes of CAD

Acute Coronary Syndrome (ACS) is the most relevant clinical manifestation of CAD. ACS encompasses either ST-elevation myocardial infarction (STEMI) or Non-ST-elevation Acute Coronary Syndrome (NSTEACS) with the latter comprising both Non-STEMI and the angina spectrum.[38]

Assessing risk in ACS has been shown to be of clinical importance. In NSTEACS risk stratification plays a key role in assessing patients and improving outcomes.[39] Similarly, recent studies have suggested, risk assessment may be used to identify those patients who require coronary care unit admission - which has historically been based on criteria for reperfusion therapy rather than absolute risk - and in turn improve both the long and short-term clinical outcomes of ACS sufferers.[87] However, there is concern that those with HIV are overlooked in the assessment of risk in ACS, with evidence suggesting that HIV patients are more likely to experience recurrent ACS and restenosis following coronary intervention than their uninfected counterparts.[40,48]

Currently the presence of HIV is not recognised in any ACS risk assessment tools.[40] With the propensity to develop more at-risk plaques and evidence of greater incidence of ACS, there is growing concern that the presence of HIV in symptomatic patients is being neglected.[46-48] Failure to recognise HIV as a significant independent risk factor in ACS may be responsible for poorer outcomes in the acute and sub-acute settings.

Conclusion

There is an increased risk of CAD facing the contemporary HIV population as well as a propensity for these patients to develop high-risk coronary plaques. Moreover, because of a lack of available clinical data it remains unclear how best to screen and treat this at-risk group. We propose the use of stress echocardiography and/or CTCA is appropriate in the screening of moderate to high-risk patients. Future studies should look to identify appropriate screening and risk assessment tools and protocols for the primary and secondary management of this unique population.

Authors contribution

Manuscript preparation: JN
Supervision, editing: CH

References

1. UNAIDS. Fast-track: Ending the AIDS epidemic by 2030. Geneva: UNAIDS; 2014 2014.
2. Weber R, Ruppik M, Rickenbach M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. HIV medicine 2013;14:195-207.
3. Clarke A. What is a chronic disease? The effects of a re-definition in HIV and AIDS. Social Science & Medicine 1994;39:591-7.
4. Antiretroviral Therapy Cohort C. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293-9.
5. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. Journal of acquired immune deficiency syndromes 2006;43:27-34.
6. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D, Database CEGftFH. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. Aids 2003;17:2479-86.
7. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of clinical endocrinology and metabolism 2007;92:2506-12.
8. Group DADS, Friis-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. The New England journal of medicine 2007;356:1723-35.
9. Boccara F, Lang S, Meuleman C, et al. HIV and coronary heart disease: time for a better understanding. Journal of the American College of Cardiology 2013;61:511-23.
10. Hsue PY, Giri K, Erickson S, et al. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. Circulation 2004;109:316-9.
11. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Annals of internal medicine 2014;160:458-67.
12. Grunfeld C, Delaney JA, Wanke C, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. Aids 2009;23:1841-9.
13. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 2002;360:1747-8.
14. Costagliola D, Lang S, Mary-Krause M, Boccara F. Abacavir and cardiovascular risk: reviewing the evidence. Current HIV/AIDS reports 2010;7:127-33.
15. Klein D, Hurley LB, Quesenberry CP, Jr., Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? Journal of acquired immune deficiency syndromes 2002;30:471-7.
16. Bergersen BM. Cardiovascular risk in patients with HIV Infection: impact of antiretroviral therapy. Drugs 2006;66:1971-87.
17. Cruciani M, Zanichelli V, Serpelloni G, et al. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. Aids 2011;25:1993-2004.
18. Fontas E, van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? The Journal of infectious diseases 2004;189:1056-74.
19. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. JAMA : the journal of the American Medical Association 2003;289:2978-82.
20. Dube MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2003;37:613-27.
21. Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). Circulation 1994;89:975-90.
22. National Heart Foundation of A, Cardiac Society of A, New Z. Lipid management guidelines--2001. National Heart Foundation of Australia, The Cardiac Society of Australia and New Zealand. The Medical journal of Australia 2001;175 Suppl:S57-85.
23. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Thorax 2000;55:987-99.
24. Samaras K. The burden of diabetes and hyperlipidemia in treated HIV infection and approaches for cardiometabolic care. Current HIV/AIDS reports 2012;9:206-17.
25. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. Journal of acquired immune deficiency syndromes 2002;31:257-75.
26. Dubé MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clinical Infectious Diseases 2003;37:613-27.
27. Calza L, Colangeli V, Manfredi R, et al. Rosuvastatin for the treatment of hyperlipidaemia in HIV-infected patients receiving protease inhibitors: a pilot study. Aids 2005;19:1103-5.
28. van der Lee M, Sankatsing R, Schippers E, et al. Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. Antiviral therapy 2007;12:1127-32.
29. Anderson KM, WOLSON P, Odell PM, Kannel WB. An updated coronary risk profile: a statement fo rhealth professionals. Circulation 1991;83:356-62.
30. Brindle P, Jonathan E, Lampe F, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. Bmj 2003;327:1267.
31. Hense H-W, Schulte H, Löwel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany—results from the MONICA Augsburg and the PROCAM cohorts. European Heart Journal 2003;24:937-45.

32. Menotti A, Puddu P, Lanti M. Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. European Heart Journal 2000;21:365-70.
33. Law M, Friis-Møller N, El-Sadr W, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D: A: D Study. HIV medicine 2006;7:218-30.
34. Parra S, Coll B, Aragones G, et al. Nonconcordance between subclinical atherosclerosis and the calculated Framingham risk score in HIV-infected patients: relationships with serum markers of oxidation and inflammation. HIV medicine 2010;11:225-31.
35. Kaplan RC, Kingsley LA, Sharrett AR, et al. Ten-year predicted coronary heart disease risk in HIV-infected men and women. Clinical Infectious Diseases 2007;45:1074-81.
36. Friis-Møller N, Thiébaut R, Reiss P, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. European journal of cardiovascular prevention & rehabilitation 2010;17:491-501.
37. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996;93:1981-92.
38. Ferket BS, Genders TS, Colkesen EB, et al. Systematic review of guidelines on imaging of asymptomatic coronary artery disease. Journal of the American College of Cardiology 2011;57:1591-600.
39. Cheruvu S, Holloway C. Cardiovascular disease in human immunodeficiency virus. Internal medicine journal 2014;44:315-24.
40. Armstrong WF, Zoghbi WA. Stress echocardiography: current methodology and clinical applications. Journal of the American College of Cardiology 2005;45:1739-47.
41. Cademartiri F, Maffei E, Palumbo A, et al. Coronary calcium score and computed tomography coronary angiography in high-risk asymptomatic subjects: assessment of diagnostic accuracy and prevalence of non-obstructive coronary artery disease. European radiology 2010;20:846-54.
42. Perrone-Filardi P, Achenbach S, Möhlenkamp S, et al. Cardiac computed tomography and myocardial perfusion scintigraphy for risk stratification in asymptomatic individuals without known cardiovascular disease: a position statement of the Working Group on Nuclear Cardiology and Cardiac CT of the European Society of Cardiology. European heart journal 2010:ehq235.
43. Hendel RC, Berman DS, Di Carli MF, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide ImagingA Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine Endorsed by the American College of Emergency Physicians. Journal of the American College of Cardiology 2009;53:2201-29.
44. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. Journal of the American College of Cardiology 2008;52:1724-32.
45. Leschka S, Scheffel H, Desbiolles L, et al. Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. Heart 2008;94:1154-61.
46. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic Accuracy of Noninvasive Coronary Angiography Using 64-Slice Spiral Computed Tomography. Journal of the American College of Cardiology 2005;46:552-7.
47. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic Performance of Coronary Angiography by 64-Row CT. New England Journal of Medicine 2008;359:2324-36.
48. Leber AW, Johnson T, Becker A, et al. Diagnostic accuracy of dual-source multi-slice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. European heart journal 2007;28:2354-60.
49. Stein PD, Yaekoub AY, Matta F, Sostman HD. 64-slice CT for diagnosis of coronary artery disease: a systematic review. The American journal of medicine 2008;121:715-25.
50. Rubinshtein R, Halon DA, Gaspar T, et al. Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. Circulation 2007;115:1762-8.
51. Hoffmann U, Truong QA, Schoenfeld DA, et al. Coronary CT angiography versus standard evaluation in acute chest pain. The New England journal of medicine 2012;367:299-308.
52. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic AdultsA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology 2010;56:e50-e103.
53. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 Appropriateness Criteria for Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging□A Report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. Journal of the American College of Cardiology 2006;48:1475-97.
54. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA : the journal of the American Medical Association 2004;291:210-5.
55. Nolte JE, Neumann T, Manne JM, et al. Cost-effectiveness analysis of coronary artery disease screening in HIV-infected men. European journal of preventive cardiology 2013.
56. Hoffmann U, Moselewski F, Nieman K, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. Journal of the American College of Cardiology 2006;47:1655-62.

57. Pundziute G, Schuijf JD, Jukema JW, et al. Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. European heart journal 2008.
58. Chew DP, FCSANZa CNA, FRACPb PEA, Kelly A-M, MClinEd F, White HD. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. clinical trials 2011;4:6.
59. Nadel J, Hewitt T, Horton D. Acute coronary syndrome in Australia: Where are we now and where are we going? The Australasian medical journal 2014;7:149.
60. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). bmj 2006;333:1091.
61. Boccara F, Mary-Krause M, Teiger E, et al. Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis. European heart journal 2011;32:41-50.
62. Freiberg MS, Chang C-CH, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA internal medicine 2013;173:614-22.
63. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. European heart journal 2012;33:875-80.

Paper 2: High-risk coronary plaque, invasive coronary procedures, and cardiac events among HIV-positive indivudals and matached controls

James Nadel BA, MBBS[1,2], Eoin O'Dwyer FRACP[2], Sam Emmanuel MBBS[1,2], Justyn Huang FRACP[2], Sarat Cheruvu MBBS[2], Neville Sammel FRACP[1,2], Bruce Brew FRACP[2,4], James Otton FRACP PhD[2,3], Cameron J Holloway FRACP, D.Phil[2,3]

[1] *University of Notre Dame, Sydney, Australia*
[2] *St. Vincent's Hospital, Sydney, Australia*
[3] *Victor Chang Cardiac Research Institute, Sydney, Australia*
[4] *Peter Duncan Neurosciences Unit St Vincent's Centre for Applied Medical Research University of New South Wales, Sydney, Australia*

Word Count: 4,728

Brief title: Outcomes for HIV patients following screening CTCA

Disclosures: This study was supported by an unrestricted grant by Gilead Sciences who had no input into the study design, data collection, analysis or manuscript preparation

Journal: Journal of Cardiovascular Computed Tomography

Abstract

Background

Human immunodeficiency virus (HIV) infection is now considered a chronic, treatable disease, although treatment is associated with increased rates of coronary artery disease (CAD). We set out to appraise the utility of CTCA in the assessment of CAD amongst HIV patients and explore whether these patients are at greater risk of associated morbidity and mortality compared to HIV-negative controls

Methods

A retrospective, single centred cohort study was undertaken. Data were assessed from 97 males without a history of previous coronary artery disease who had undergone CTCA between 2011 and 2014, including 32 HIV positive and 65 matched HIV negative controls. CTCA were assessed for plaque composition. Data on the occurrence of subsequent coronary events and coronary intervention was collected.

Results

Patients with HIV had higher rates of non-calcified plaque (0.8±1.5 versus 0.3±0.7, p=0.03) compared to negative controls. At a median follow-up of 38 months, patients with HIV were at greater risk of non-ST elevation acute coronary syndrome (16% (5) versus 3% (2), p<0.04), although there was no difference in the combined endpoint of all-acute coronary syndromes despite a threefold greater risk conferred to those with HIV (19% (6) versus 6% (4), p=0.08). Following baseline CTCA, there was a higher rate of coronary intervention in patients without HIV (mean time to event 9.9±3.3 versus 20.6±4.9 months, p<0.04).

Conclusion

Patients with HIV have high-risk non-calcified plaque and higher rates of non-ST elevation acute coronary syndromes compared to negative controls, but lower rates of coronary angiography and intervention following CTCA. Larger prospective studies are needed to confirm if CTCA has a role in predicting cardiac events in patients with HIV. The less invasive management in this cohort is also worthy of further investigation.

Introduction

Human immunodeficiency virus (HIV) infection and Acquired immunodeficiency syndrome (AIDS) affects over 33 million people globally and is responsible for almost 2 million deaths per year.[1] The advent of antiretroviral therapy (ART) has improved morbidity and mortality to a point where HIV is now considered a treatable chronic disease.[2] The life expectancy among treated individuals is now comparable to that of the general population.[3] This extension in expected survival has resulted in the emergence of chronic age related diseases including coronary artery disease (CAD).[4] Increased risk of CAD in patients with HIV has been associated with the inflammatory sequelae of the infection as well as the greater prevalence of cardiac risk factors in HIV-positive populations and the side effects of life-prolonging antiretroviral therapies.[5-7]

Despite almost half of all fatal myocardial infarctions occurring in previously asymptomatic patients,[8] controversy surrounds the role of screening and early management of CAD in patients with HIV. Both the modality of screening and timing for when to screen at-risk asymptomatic individuals remains unclear even amongst the general population.[9] Screening high-risk patients with treated HIV may be advantageous to improve outcomes, [10,11] however, no studies have shown a correlation between screening for CAD and an improvement in outcomes, making such suggestions based on expert opinion rather than evidence based.

Independent of traditional cardiovascular risk factors, coronary plaque, especially non-calcified plaque, has been found to be more prevalent and extensive in those with HIV compared to their uninfected counterparts.[12] Although CTCA provides no information regarding functional myocardial ischaemia, the presence of non-calcified plaques on CTCA in the general population is associated with greater rates of ACS when compared to mixed and calcific plaques (Figure 1).[13-15] Given the predominance of high-risk non-calcified plaque development in patients with HIV, there is growing concern that calcium score alone may not adequately assess patients at risk of CAD who have HIV.

Figure 1.
Plaque types on CTCA. Red arrow; noncalcific (soft), green arrow; calcific, blue arrow; mixed plaques

We assessed the baseline CTCA and subsequent clinical endpoints in a group of HIV patients in order to; (a) appraise the utility of CTCA in the assessment of CAD amongst HIV patients and (b) explore whether these patients are at greater risk of associated morbidity and mortality compared to HIV-negative controls.

Methods

Patient Selection

A retrospective single centre observational study at St. Vincent's Hospital in Sydney, Australia, was undertaken. All patients were asymptomatic at the time of CTCA and were screened due to either suboptimal medical management, poor metabolic control or in the case of clinician uncertainty regarding patient management. A total of 97 patients were recruited. This included 32 HIV positive patients who were matched 2:1 for age, sex, Framingham risk, absence of previous coronary artery disease and date of scan with 65 HIV negative patients (Figure 2).

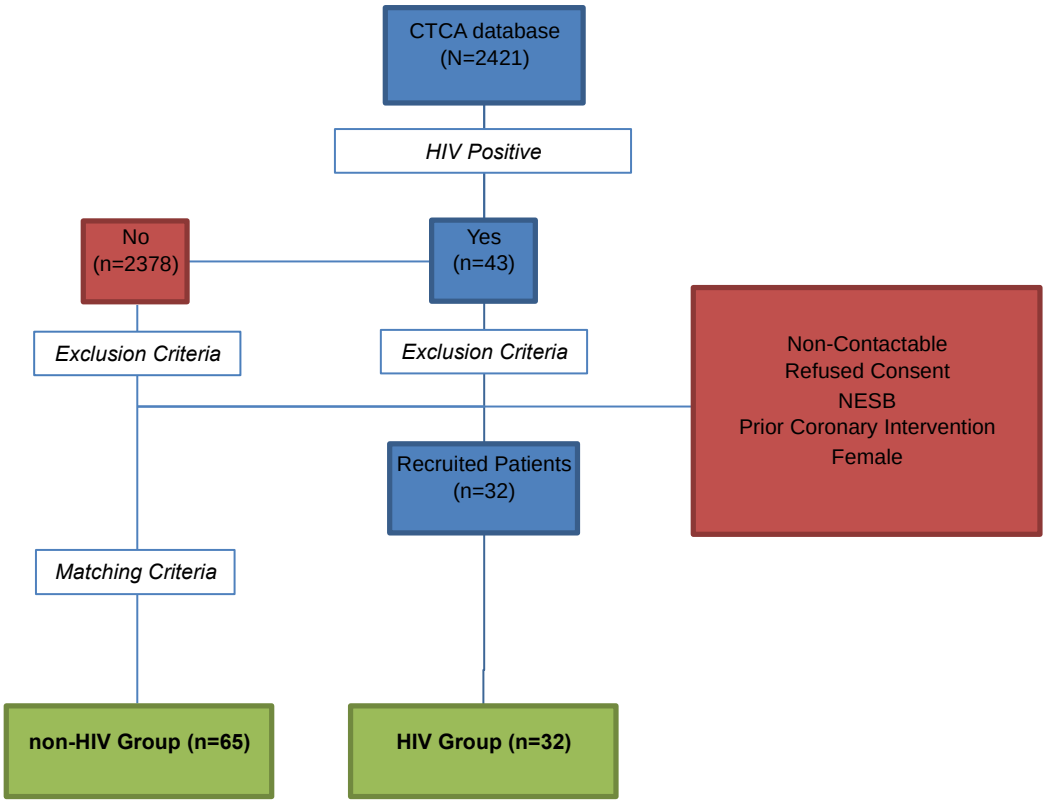


Figure 2. Patient selection

Analysis of the CTCA database between 2011 and 2014 (N=2421) identified 43 patients with HIV who had undergone CTCA with the stated inclusion criteria. Exclusion criteria included those of non-English speaking background (NESB, n=1), individuals who were non-contactable or refused consent (n=2), those who had previously undergone coronary intervention or had known ischaemic heart disease (n=5), and females (n=3; excluded to increase homogeneity of the almost all-male cohort), 32 HIV positive patients were enrolled and then matched with controls.

The Human Research and Ethics Committees (HREC) of both St. Vincent's Hospital and the University of Notre Dame approved this study and all patients gave informed consent regarding their

participation.

CTCA Analysis

A cardiologist experienced in CTCA who was blinded to all patient history including HIV status undertook analysis of the scans. The scans were performed on a Toshiba Aquillion 1,320 slice CT machine and assessed on a workstation equipped with Vitrea FX software (v.6.7.2).

As previously validated and described,[16,17] the vessels assessed on CTCA were the left main (LM), left anterior descending (LAD), left circumflex (LCX) and right coronary arteries (RCA). Arteries were assessed in a standard fashion; visually on axial, sagittal and coronal images as well as on multiplanar reformats. Each coronary tree was divided into 19 segments,[18] and then assessed for the number and degree of stenosis, plaque type and the presence of artifact. In addition, each segment was individually assessed for the volume of plaque using the Vitrea FX software. Volumes for low density non-calcified plaque, high-density non-calcified plaque and calcified plaque were attributed to -150-50, 51-150 and >150 Hounsfield's units respectively and recorded together with each segments diameter, length, diameter stenosis, area of stenosis and remodeling index. Automated plaque measurements were visually inspected in cross-section at 0.5mm intervals and manual adjustment to plaque contours was performed where necessary. Coronary artery calcium scores (CAC) were also estimated using previously validated methodology.[19]

Clinical Endpoints and Follow Up

The primary endpoint of the study was the occurrence of an acute coronary syndrome (ACS). ACS was considered as any patient who had experienced either; a ST elevation myocardial infarction (STEMI) or non-ST elevation acute coronary syndrome (NSTEACS); comprising both non-STEMI and the angina spectrum.

Secondary endpoints included mortality and a composite event pertaining to further management or investigations. The composite event consisted of invasive coronary angiogram, percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG).

A separate researcher, blinded to patient CTCA results, assessed the HIV status and clinical endpoints experienced by the cohort. This consisted of a 10-15 minute telephone survey, which was correlated with hospital medical records and the records of treating physicians. Data of deceased patients were collected from medical records and death certificates.

Statistical Analysis

All analyses were performed using SPSS statistical software (v23).

Patients were split into two discrete groups; those with HIV and a matched non-infected group (Figure 2). The specific clinical endpoints of patients with HIV versus those without were then compared.

Basic descriptive statistics were used to characterise the demographics and non-continuous variables of the cohort. For continuous variables, simple univariate statistics were used. Mann Whitney U tests were used to compare continuous variables and Fisher Exact tests for categorical variables.

Establishing dates for specific endpoints facilitated the use of Kaplan-Meier estimator plots for Survival Analyses. Log rank (Mantel-Cox) tests were used to determine mean survival times and the degree of statistical significance between groups. Logistic regression analyses were used to assess for covariates impacting outcomes.

Statistically significance was defined at $p<0.05$.

Results

Study Population

Demographic and clinical features of the cohort (N=97) are presented in Table 1. All patients were male and predominantly middle-aged Caucasians. Overall median time to follow-up was 38 months. Those without HIV had higher body mass indexes (28 versus 26, p<0.003) and exercised more frequently (p<0.005) compared to the HIV population. The HIV group had higher levels of triglycerides (2.1 mmol/L versus 1.2 mmol/L, p<0.003). There were no other statistically significant features between the two groups including Framingham risk scores. 3

Table 1. Characteristics of the cohort and their significance

Characteristic	Overall (N=97)	HIV Negative (n=65)	HIV Positive (n=32)	Significance (*p* value)
Age* (IQR), *y*	60 (56-64)	60 (56-64)	60 (56-63)	NS (0.75)
Time from CTCA to follow-up* (IQR), *m*	38 (33-44)	37 (32-44)	39 (33-43)	NS (0.86)
Framingham risk score* (IQR), *n*	13 (8-16)	13 (8-16)	13 (8-16)	NS (0.99)
Body Mass Index* (IQR), *n*	27 (24-32)	28 (25-33)	26 (23-29)	p<0.003
Hypertension (%), *n*	62 (64)	41 (63)	21 (66)	NS (1.0)
Anti-hypertensive medication (%), *n*	60 (62)	41 (63)	19 (59)	NS (0.66)
Systolic blood pressure* (IQR), *mmHg*	129 (121-140)	130 (123-141)	128 (116-140)	NS (0.65)
Diastolic blood pressure* (IQR), *mmHg*	80 (74-86)	80 (75-86)	80 (70-87)	NS (0.39)
Hypercholesterolaemia (%), *n*	70 (72)	45 (69)	25 (78)	NS (0.62)
Hypercholesterol medication (%), *n*	66 (68)	42 (65)	24 (75)	NS (0.48)
HDL* (IQR), *mmol/L*	1.1 (1.0-1.4)	1.1 (1.0-1.3)	1.2 (1.0-1.5)	NS (0.88)
LDL* (IQR), *mmol/L*	2.8 (2.2-3.4)	2.9 (2.0-3.6)	2.7 (2.2-3.4)	NS (0.88)
Triglycerides* (IQR), *mmol/L*	1.3 (0.9-2.2)	1.2 (0.9-1.7)	2.1 (1.2-2.7)	p<0.003
Total cholesterol* (IQR), *mmol/L*	4.7 (4.2-5.5)	4.7 (3.9-5.4)	4.8 (4.3-5.6)	NS (0.29)
Diabetes (%), *n*	23 (24)	14 (22)	9 (28)	NS (0.61)
Diabetic medication (%), *n*	21 (22)	13 (20)	8 (25)	NS (0.61)
Smoking* (IQR), *py*	6 (0-25)	8 (0-25)	5 (0-25)	NS (0.65)
Current smoker (%), *n*	17 (18)	9 (14)	8 (25)	NS (0.17)
Family history CAD (%), *n*	42 (43)	29 (45)	13 (41)	NS (0.67)
Exercise* (IQR), *d*	2 (1-3)	3 (1-4)	2 (0-3)	p<0.005
Ethnicity				NS (0.24)
Caucasian (%), *n*	81 (84)	56 (86)	25 (78)	
Asian (%), *n*	7 (7)	3 (5)	4 (13)	
Indian (%), *n*	2 (2)	1 (2)	1 (3)	
Arabic (%), *n*	2 (2)	2 (3)	0 (0)	
Maori (%), *n*	2 (2)	1 (2)	1 (3)	
Latino (%), *n*	1 (1)	0 (0)	1 (3)	

y = years, *n* = number, *m* = months, *py* = pack years, *d* = days/week, IQR = interquartile range, NS = not significant
* data presented as median

Specific characteristics pertaining to the HIV cohort are presented in Table 2. The HIV group mainly consisted of patients with chronic, treated HIV. 30 (94%) patients were on ART at time of follow-up with 15 (47%) prescribed ritonavir and 5 (16%) abacavir at the time of follow-up. Almost half (47%) of the population had either a previous or current diagnosis of AIDS.

Table 2. Characteristics of the HIV group

Characteristic	HIV Positive (n=32)
Years since diagnosis* (IQR), *y*	26 (16-30)
ART,	
Current ART use (%), *n*	30 (94)
Current ritonavir (%), *n*	15 (47)
Current abacavir (%), *n*	5 (16)
Time on current ART regimen* (IQR), *y*	7 (4-10)
Total time on ART* (IQR), *y*	19 (14-24)
HIV serology	
Current CD4* (IQR), *x10^6 cells /L*	649 (481-851)
Lowest recorded CD4* (IQR), *x10^6 cells /L*	286 (79-378)
Current viral load, *copies/mL*	
<20 (%), *n*	28 (88)
20-100 (%), *n*	2 (6)
101-30,000 (%), *n*	0 (0)
>30,000 (%), *n*	2 (6)
Past/Current AIDS (%), *n*	15 (47)
y = years, *n* = number	
* data presented as medians	

The findings and comparison of the CTCA scans are presented in Table 3. The average radiation dose was 7.1±5.5 mSv. Those with HIV had higher non-calcified plaque counts (p=0.03) and ratios of calcified to non-calcified plaque (p<0.03). There were no other differences between the groups on CTCA including; stenosis score, stenosis count and CAC score.

Table 3. CTCA findings and their significance

Characteristic	Overall (N=97)	HIV Negative (n=65)	HIV Positive (n=32)	Significance (*p* value)
Vessel Count* (IQR), *n*	10 (10-10)	10 (10-10)	10 (10-10)	NS (0.49)

Stenosis score* (IQR), *n*	4 (1-9)	4 (1-7)	6 (1-9)	NS (0.59)
Stenosis count* (IQR), *n*	4 (1-6)	3 (1-6)	4 (1-6)	NS (0.69)
Plaque count* (IQR), *n*				
Soft	0 (0-1)	0 (0-0)	0 (0-1)	p=0.03
Mixed	2 (0-4)	2 (0-4)	2 (0-4)	NS (0.85)
Calcific	0 (0-1)	0 (0-1)	0 (0-1)	NS (0.34)
Plaque ratio* (IQR), *n*				
Soft	0 (0-0)	0 (0-0)	0 (0-0)	p<0.03
Mixed	1 (0-1)	1 (0-1)	1 (0-1)	NS (0.99)
Calcific	0 (0-0)	0 (0-0)	0 (0-0)	NS (0.42)
Plaque Sum* (IQR), mm^3				
Plaque 1, -150-50 HU	1171 (947-1539)	1171 (994-1533)	1182 (863-1643)	NS (0.74)
Plaque 2, 51-150 HU	1543 (1289-1968)	1617 (1354-1933)	1453 (1180-2031)	NS (0.47)
Plaque 3, >150 HU	490 (262-777)	464 (245-755)	503 (381-890)	NS (0.27)
Total plaque	3340 (2684-4377)	3340 (2734-4157)	3242 (2543-4403)	NS (0.86)
Remodeling index* (IQR), *n*	1 (1-1)	1 (1-1)	1 (1-4)	NS (0.42)
CAC Agatston score* (IQR), *n*	95 (0-508)	122 (0-508)	56 (0-545)	NS (0.45)
n = number, HU = Hounsfield's units NS = not significant				
* data presented as medians				

Clinical Outcomes

At the time of follow-up 3 patients were deceased, 2 from cancer and 1 from sepsis. No deaths were from cardiac pathology. Regarding all-cause mortality, 2 patients were from the HIV positive group compared to 1 from the HIV negative group (p=0.26). 10 patients had experienced ACS; 7 having suffered NSTEACS and 3 a STEMI.

Acute Coronary Syndrome

Of the 10 ACS events, 6 occurred in the HIV group and 4 in the control group. The occurrence of NSTEACS was significantly higher in the HIV group compared to those without a diagnosis of HIV (16% versus 3%, p<0.04). There was a threefold higher incidence of ACS in the HIV group compared to the non-HIV group (19% versus 6%), although this was not significant on survival analysis (mean time to event 28.3±4.8 versus 33.2±3.9 months, p=0.18, Figure 3).

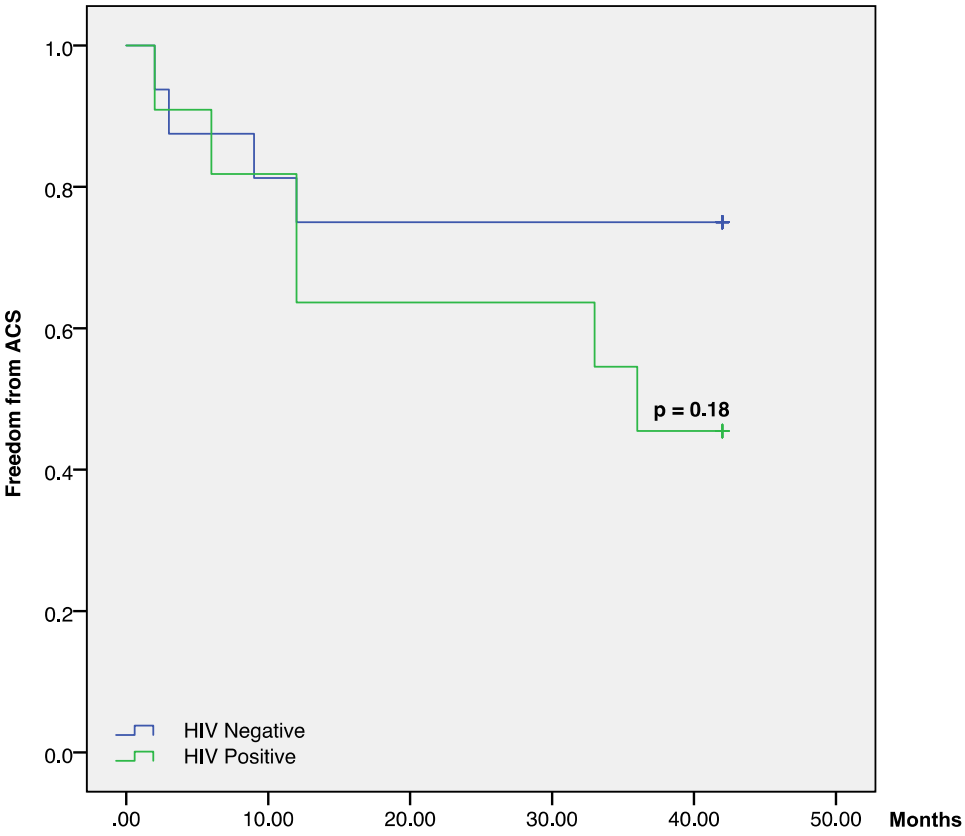


Figure 3. Kaplan-Meier plots for ACS according to HIV status. The plot demonstrates no significance between the rate of events in the HIV positive and negative groups (mean time to event 28.3±4.8 versus 33.2±3.9 months, p=0.18)

Intervention

A total of 20 patients (6 (19%) HIV positive and 14 (22%) HIV negative) had further intervention with either invasive angiography, PCI or CABG. A composite endpoint for these procedures was significant, with HIV negative patients having undergone adjuvant coronary intervention following CTCA sooner than those with HIV (mean time to event 20.6±4.9 versus 9.9±3.3 months, p<0.04, Figure 4).

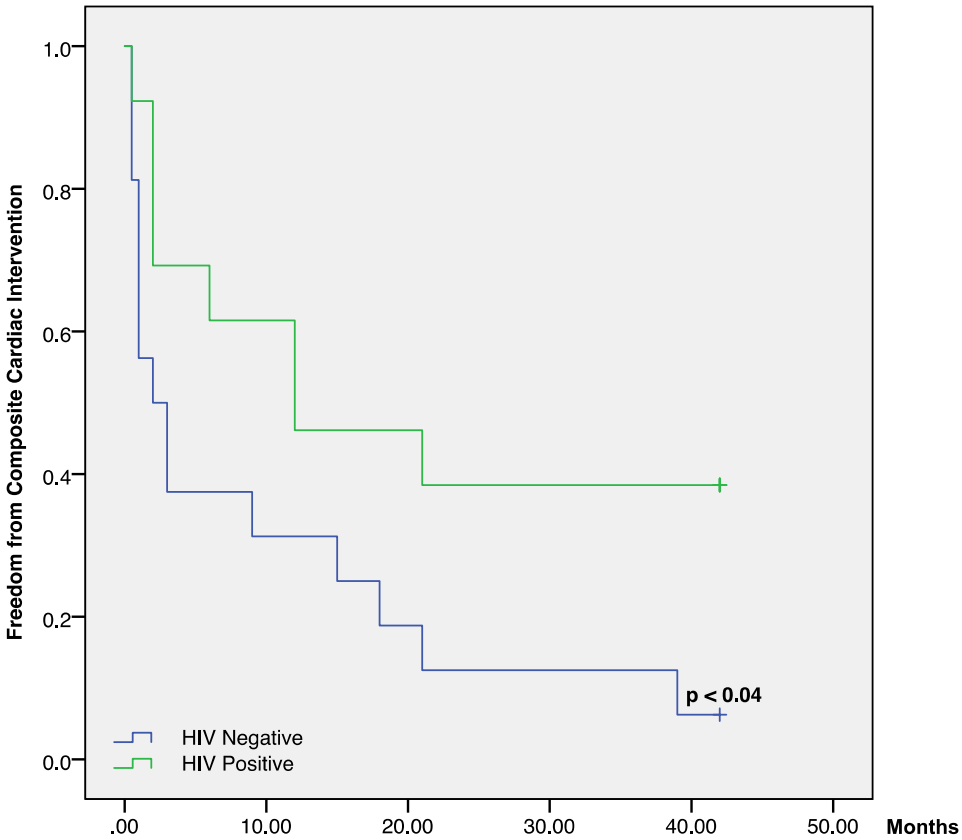


Figure 4. Kaplan-Meier plots for Composite Event (CA, PCI, CABG) according to HIV status. The plot demonstrates significance between the rate of events in the HIV positive and negative groups (mean time to event 20.6±4.9 versus 9.9±3.3 months, p<0.04)

In order to assess for compounding covariates, logistic regression analysis was performed. Statistically significant variables at baseline which included; body mass index, exercise in days per week and triglycerides, as well as other potential confounders such as the use of ritonavir or abacavir in those with HIV, age and a family history of cardiovascular disease were all entered into the model. These variables were examined and found to not be predictive for the occurrence of either ACS or the composite event for cardiac intervention. Similarly, there was no statistically significant correlation between the presence of non-calcified plaque and degree of stenosis on ACS.

Discussion

This study demonstrates that patients with HIV have greater amounts of non-calcified plaque on CTCA and higher rates of NSTEACS, although less timely management with further coronary interventions. The data suggest that patients with HIV have increased high-risk plaque which likely predicts the increased coronary events and that CTCA may be an appropriate screening tool to identify at risk individuals, though further assessment is required.

The presence of non-calcified plaque on CTCA poses a greater risk of ACS in affected individuals,[13-15] and may be a causal factor in the higher rate of NSTEACS observed among our HIV cohort. Our results are consistent with the body of evidence demonstrating the higher prevalence of at-risk plaques in the HIV population.[12,20,21] We now demonstrate this may translates to a greater risk of cardiac events in this population. Although no statistical correlation between non-calcified plaque and ACS could be found in this study; we believe this is due a lack of statistical power and our findings will need to be replicated in a larger investigation.

Recently, Post and colleagues published findings identifying that independent of cardiovascular risk factors coronary non-calcified plaque and CAC were more prevalent in an HIV population.[12] In our study we found that CAC scores were comparable between HIV infected and uninfected individuals. CAC scoring provides prognostic information in patients with CAD but its utility in the HIV population has been questioned given the higher prevalence of non-calcified plaque.[22,23] Although previous evidence has identified higher CAC scores in the HIV population,[12] a study by Fitch and colleagues suggests that higher CAC scores may be due to a greater prevalence of co-morbid metabolic syndrome.[21] The authors found that patients with HIV infection and metabolic syndrome had increased coronary artery calcification when compared to those without metabolic syndrome, and this finding was independent of HIV status.[21] Our data suggests CTCA is an effective tool in the detection of high-risk plaques and that such plaques are more prevalent in the HIV population within whom CAC scoring alone may not be of benefit.

Regarding clinical outcomes, the rate of ACS was consistent with previous studies in patients with HIV having higher rates of acute myocardial infarction than their uninfected counterparts.[24,25] The rate of ACS in our population was similar to that found by Freiberg and colleagues who in a cohort of over 80,000 patients identified that HIV infection carried a 50% increased risk of acute myocardial infarction compared to those without HIV.[25]

While the HIV cohort remains at high risk of CAD, the utility of screening tools for these patients remains unclear. Current guidelines suggest there is insufficient evidence to support the use of CTCA in any asymptomatic adults.[26] Despite this some clinicians advocate CTCA as the tool of choice for the assessment of coronary disease in the high-risk HIV population.[10,22] To our knowledge ours is the first study assessing the correlation between atherosclerosis seen on CTCA and future cardiac events

in HIV patients. Although we were unable to present a correlation between plaque type seen on CTCA and cardiac outcomes, our findings provide early evidence for the use of CTCA in asymptomatic at-risk individuals and warrants further exploration into the utility of CTCA in such a cohort. In particular, future studies are required to confirm the relationship between the deposition of plaque and ACS in order to determine whether such a correlation exists and if aggressive therapy in those with non-calcified plaque will prevent the progression of CAD and its sequelae in this population."

With regard to intervention using coronary angiography, PCI or CABG; patients with HIV were managed less aggressively compared to their uninfected counterparts following baseline CTCA. Currently there are limited data pertaining to the ongoing assessment and management of CAD in the HIV population, however our data parallels less invasive management strategies observed in the diabetic population. Alter and colleagues found in a cohort of over 25,000 patients that diabetic patients were less likely to receive coronary angiography, PCI and cardiologist follow-up than non-diabetic patients in the year following an ACS.[27] The precise reasons for the paradoxical relationship between increased baseline risk and clinician intensity of management is unclear. Evidence suggests that clinicians see differences in the efficacy of evidence based therapies and interventions when the number of chronic comorbid conditions increases.[28] Similarly, uncertainties over the expectations of prognostic benefits incurred for patients with chronic disease, coupled with a physician's aversion toward doing harm may alter decision making toward a more conservative approach.[27,29] Moreover, physicians caring for patients with more than one chronic disease are less attentive to the treatment necessities required for managing concurrent disease processes.[30]

In a multicentre study, Bocarra and colleagues compared the 1-year prognosis of HIV patients to uninfected individuals who had experienced an ACS and found HIV infected patients were more likely to experience recurrent ACS than those without HIV. Interestingly, they found that PCI in the HIV group was prompted by recurrent ACS and more likely to be urgent in nature, which contrasted with the uninfected group for whom PCI was largely non-urgent and driven by silent ischaemia.[31] Similarly, our data show less aggressive management of an at-risk population. We believe the discrepancy may be the result of a perceived lower need for invasive procedures in HIV infected patients, due in part to the unknown prognosis of the HIV disease itself and therefore less aggressive management by treating cardiologists.

There is growing concern that despite their higher risk profile the presence of HIV infection as an independent risk in symptomatic patients is being neglected.[25,31-33] This may be due to the absence of a screening tool that takes HIV infection into consideration when assessing ACS. Cardiovascular risk in HIV infected patients is not fully explained by traditional risk factors. The chronic inflammatory process of HIV infection, along with antiretroviral therapy evidently accelerates CAD risk.[34,35] It appears that routine secondary prevention may not take this into account. Nevertheless, given the small numbers in our analysis, our results should be interpreted cautiously and further research into the treatment of this at-risk population is required in order to confirm whether management and

intervention is sub-optimal.

Limitations

When interpreting our findings, a number of limitations need to be considered. Our study was retrospective in design and former exposures to risk variables prior to CTCA could not be accurately accounted for. This may have an impact on the event rate in either group and possibly skewed the presented data. However, the rate of ACS in our study was comparable to event rates in prior studies in patients at high-risk of CAD, suggesting that selection bias was not a major confounder to our results. Another limitation is that the study was performed on men and any conclusions should not be extrapolated to a unisex population. The absence of a correlation between CTCA and clinical outcomes is a further limitation of the paper. Our cohort was relatively small with few clinical events and we believe that the absence of a correlation between non-calcified plaque and degree of coronary stenosis with ACS was due to a lack of statistical power. Our findings will need to be replicated and validated in a larger, preferably multicentre investigation. Furthermore, although the time to follow up was not significantly different between those with and without HIV, the variability of the range (26-61 months) presents the potential for confounding as longer follow up times may have allowed for the manifestation of more cardiovascular complications. Finally, the significant difference in body mass indexes, rate of exercise and triglycerides between those with and without HIV could potentially interact with the outcomes. However, logistic regression modeling including these covariates was not predictive of ACS or the composite event for cardiac intervention.

Conclusion

CTCA assessed for and identified that those with HIV were susceptible to developing at-risk coronary plaques and had higher rates of adverse cardiac events despite less aggressive further coronary intervention. The data suggest that HIV patients are at greater risk of CAD independent of traditional risk factors and that CTCA is a potential screening tool that may aid early management and reduce the burden facing HIV infected patients. The less timely management of patients with HIV needs further assessment to determine if this represents suboptimal treatment for a high-risk population.

Authors Contributions

Manuscript preparation: JN
Data collection: JN, EO, SC
Statistical analysis: JN, SE
CTCA analysis: JH, JO
Editing: CH, BB
Supervisor: CH, NS

References

1. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Washington: UNAIDS: Washington; 2010.
2. Clarke A. What is a chronic disease? The effects of a re-definition in HIV and AIDS. Social Science & Medicine 1994;39:591-7.
3. Antiretroviral Therapy Cohort C. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293-9.
4. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. Journal of acquired immune deficiency syndromes 2006;43:27-34.
5. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D, Database CEGftFH. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. Aids 2003;17:2479-86.
6. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of clinical endocrinology and metabolism 2007;92:2506-12.
7. Group DADS, Friis-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. The New England journal of medicine 2007;356:1723-35.
8. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996;93:1981-92.
9. Ferket BS, Genders TS, Colkesen EB, et al. Systematic review of guidelines on imaging of asymptomatic coronary artery disease. Journal of the American College of Cardiology 2011;57:1591-600.
10. Cheruvu S, Holloway C. Cardiovascular disease in human immunodeficiency virus. Internal medicine journal 2014;44:315-24.
11. Grunfeld C, Delaney JA, Wanke C, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. Aids 2009;23:1841-9.
12. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Annals of internal medicine 2014;160:458-67.
13. Hoffmann U, Moselewski F, Nieman K, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. Journal of the American College of Cardiology 2006;47:1655-62.
14. Pundziute G, Schuijf JD, Jukema JW, et al. Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. European heart journal 2008.
15. Schuijf JD, Beck T, Burgstahler C, et al. Differences in plaque composition and distribution in stable coronary artery disease versus acute coronary syndromes; non-invasive evaluation with multi-slice computed tomography. Acute cardiac care 2007;9:48-53.
16. Fischer C, Hulten E, Belur P, Smith R, Voros S, Villines TC. Coronary CT angiography versus intravascular ultrasound for estimation of coronary stenosis and atherosclerotic plaque burden: a meta-analysis. Journal of cardiovascular computed tomography 2013;7:256-66.
17. Voros S, Rinehart S, Qian Z, et al. Prospective validation of standardized, 3-dimensional, quantitative coronary computed tomographic plaque measurements using radiofrequency backscatter intravascular ultrasound as reference standard in intermediate coronary arterial lesions: results from the ATLANTA (assessment of tissue characteristics, lesion morphology, and hemodynamics by angiography with fractional flow reserve, intravascular ultrasound and virtual histology, and noninvasive computed tomography in atherosclerotic plaques) I study. JACC: Cardiovascular Interventions 2011;4:198-208.
18. Miller JM, Dewey M, Vavere AL, et al. Coronary CT angiography using 64 detector rows: methods and design of the multi-centre trial CORE-64. European radiology 2009;19:816-28.
19. Otton JM, Lønborg JT, Boshell D, et al. A method for coronary artery calcium scoring using contrast-enhanced computed tomography. Journal of cardiovascular computed tomography 2012;6:37-44.
20. Zanni MV, Abbara S, Lo J, et al. Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. AIDS (London, England) 2013;27:1263.
21. Fitch KV, Lo J, Abbara S, et al. Increased coronary artery calcium score and noncalcified plaque among HIV-infected men: relationship to metabolic syndrome and cardiac risk parameters. Journal of acquired immune deficiency syndromes (1999) 2010;55:495.
22. Bhamra-Ariza P, Holloway C. The assessment and management of coronary artery disease in patients with HIV. Journal of AIDS and Clinical Research 2014;5.
23. Mehta V, Patel M, Venuraju S, Jeevarethinam A, Yerramasu A, Lahiri A. Prevalence of coronary atherosclerotic plaque in patients with a low coronary artery calcium score. BMC Proceedings; 2012: BioMed Central. p. P25.
24. Lang S, Mary-Krause M, Cotte L, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. Aids 2010;24:1228-30.
25. Freiberg MS, Chang C-CH, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA internal medicine 2013;173:614-22.
26. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic AdultsA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology 2010;56:e50-e103.
27. Alter DA, Khaykin Y, Austin PC, Tu JV, Hux JE. Processes and Outcomes of Care for Diabetic Acute Myocardial Infarction Patients in Ontario Do physicians undertreat? Diabetes Care 2003;26:1427-34.
28. Mottur-Pilson C, Snow V, Bartlett K. Physician explanations for failing to comply with" best practices". Effective clinical practice: ECP 2000;4:207-13.
29. Rothwell PM. Why do clinicians sometimes find it difficult to use the results of systematic reviews in routine clinical practice? Evaluation & the health professions 2002;25:200-9.

30. Redelmeier DA, Tan SH, Booth GL. The Treatment of Unrelated Disorders in Patients with Chronic Medical Diseases. New England Journal of Medicine 1998;338:1516-20.
31. Boccara F, Mary-Krause M, Teiger E, et al. Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis. European heart journal 2011;32:41-50.
32. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of Clinical Endocrinology & Metabolism 2007;92:2506-12.
33. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. European heart journal 2012;33:875-80.
34. El-Sadr W, Lundgren JD, Neaton J, et al. CD4+ count-guided interruption of antiretroviral treatment. New Engl J Med 2006;355:2283-96.
35. Oliviero U, Bonadies G, Apuzzi V, et al. Human immunodeficiency virus per se exerts atherogenic effects. Atherosclerosis 2009;204:586-9.

Conclusion

The aim of this thesis was to provide some guidance into the management of CAD in HIV and examine the utility of screening CTCA in this population group. Currently there are no guidelines pertaining to the screening and further management of this at-risk population. Our literature review outlines a proposed approach for assessing and managing HIV patients at risk of CAD.

The review advocates the use of echocardiography and/or CTCA in the screening of high-risk patients as well as pharmacological and lifestyle modifications aimed at reducing cardiovascular disease. We believe the ability of CTCA to assess plaque-type, degree of obstruction and provide coronary artery calcium scoring makes it a beneficial tool when used in the appropriate clinical setting. For HIV patients who are optimally medical managed we suggest the use of stress echocardiography to assess for life threatening atheroma. However, in those with suboptimal medical management, poor metabolic control or in the case of clinician uncertainty we advocate the use of CTCA in an effort to assess burden of disease and dictate the aggressiveness of pharmacological therapy or need for further intervention. Future studies should look to identify appropriate screening and risk assessment tools and protocols for the primary and secondary management of this unique population.

Despite the fact that approximately 50% of fatal myocardial infarctions occur in previously asymptomatic patients,[30] there remains little consensus about the appropriate screening modalities and timing of when to screen at-risk patients. There is limited data pertaining to the use of any imaging modalities in the screening of CAD; resulting in the majority of guidelines not recommending the use of any imaging modalities for the screening of CAD.[32,49,50] Coronary artery calcium scoring is one of the few imaging techniques with sufficient data to assess its utility;[36,51,52] and some international guidelines have subsequently advocated the use of CT derived coronary artery calcium scoring in intermediate-risk asymptomatic patients.[32] The pitfall with coronary calcium scoring in the HIV population is that those with HIV have been shown to have more prevalent and extensive non-calcified coronary artery plaque,[12] likely resulting in an underestimation of sub-clinical disease and under prediction of future myocardial infarction. Non-calcific CAD is best assessed via CTCA and is considered more high risk than calcific disease,[53-55] putting the already vulnerable HIV population at even greater risk.

With the recommendations of our review in mind we proceeded to examine the utility of CTCA in the screening of HIV patients. Those with HIV had been found to have greater rates of myocardial infarction compared to uninfected counterpart,[46] and coronary intervention in this population is more likely to be emergent in nature and driven by recurrent ACS. Nevertheless, given a paucity of clinical trials the current American College of Cardiology Foundation/American Heart Association guidelines do not recommend CTCA in asymptomatic adults (level C evidence).[50] In our research we present 3 year data demonstrating that HIV patients screened with CTCA were susceptible to developing at-risk coronary plaques and had higher rates of adverse cardiac events despite less aggressive further

coronary intervention compared to HIV negative controls.

To our knowledge ours is the first study to assess for a correlation between atherosclerosis seen on CTCA and future cardiac events in HIV patients. Our findings provide further support for the use of CTCA in the detection of CAD – whilst also identifying its prognostic utility in predicting clinical outcomes – therefore strengthening the argument for the use of CTCA in asymptomatic at-risk individuals. Nonetheless, further studies are required to confirm the relationship between the deposition of noncalcified plaque and ACS in order to determine if aggressive therapy will prevent the progression of cardiovascular disease and its sequelae in this population.

We believe our data make a substantial contribution to the literature in this field. It provides early evidence for the use of CTCA in the screening of HIV patients and highlights a need for further exploration into why this population is less aggressively managed. This discrepancy regarding ACS management in HIV may be the result of a perceived lower need for invasive procedures in HIV patients, due in part to the unknown prognosis of the disease itself and therefore less aggressive management by treating cardiologists. Nevertheless, given the small numbers in our analysis, our results should be interpreted cautiously and further research into the treatment of this population is needed to confirm whether management and intervention is sub-optimal.

Future research should seek to explore whether current risk assessment tools – in particular the Framingham Risk and DAD calculator predict CTCA finding in patients with HIV. A correlation between risk assessment tools and CTCA would further support the latter's use as a screening tool and help strengthen guideline recommendations for the assessment and management of CAD in HIV. Similarly, a larger prospective trial which sort to examine whether CTCA can predict risk of ACS in patients with HIV would further enhance the potential utility of this imaging modality in the assessment of asymptomatic patients.

References

1. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Washington: UNAIDS: Washington; 2010.
2. Institute TK. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2011. The Kirby Institute, the University of New South Wales, Sydney, NSW: The Kirby Institute; 2011.
3. McDonald AM, Crofts N, Blumert CE, et al. The pattern of diagnosed HIV infection in Australia, 1984-1992. Aids 1994;8:513-20.
4. Guy RJ, McDonald AM, Bartlett MJ, et al. HIV diagnoses in Australia: diverging epidemics within a low-prevalence country. Medical Journal of Australia 2007;187:437.
5. Clarke A. What is a chronic disease? The effects of a re-definition in HIV and AIDS. Social Science & Medicine 1994;39:591-7.
6. Neuhaus J, Angus B, Kowalska JD, et al. Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. Aids 2010;24:697-706.
7. Antiretroviral Therapy Cohort C. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293-9.
8. Palella FJ, Jr., Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. Journal of acquired immune deficiency syndromes 2006;43:27-34.
9. Currier JS, Lundgren JD, Carr A, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation 2008;118:e29-35.
10. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of clinical endocrinology and metabolism 2007;92:2506-12.
11. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. Journal of acquired immune deficiency syndromes 2003;33:506-12.
12. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Annals of internal medicine 2014;160:458-67.
13. Grunfeld C, Delaney JA, Wanke C, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. Aids 2009;23:1841-9.
14. Stein JH, Hsue PY. Inflammation, immune activation, and CVD risk in individuals with HIV infection. JAMA : the journal of the American Medical Association 2012;308:405-6.
15. Samaras K. The burden of diabetes and hyperlipidemia in treated HIV infection and approaches for cardiometabolic care. Current HIV/AIDS reports 2012;9:206-17.
16. Gibellini D, Borderi M, Clo A, et al. HIV-related mechanisms in atherosclerosis and cardiovascular diseases. Journal of cardiovascular medicine 2013;14:780-90.
17. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. The Journal of infectious diseases 2012;205 Suppl 3:S375-82.
18. Group DADS, Friis-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. The New England journal of medicine 2007;356:1723-35.
19. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. The New England journal of medicine 2003;349:1993-2003.
20. Bergersen BM. Cardiovascular risk in patients with HIV Infection: impact of antiretroviral therapy. Drugs 2006;66:1971-87.
21. Klein D, Hurley LB, Quesenberry CP, Jr., Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? Journal of acquired immune deficiency syndromes 2002;30:471-7.
22. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 2002;360:1747-8.
23. Costagliola D, Lang S, Mary-Krause M, Boccara F. Abacavir and cardiovascular risk: reviewing the evidence. Current HIV/AIDS reports 2010;7:127-33.
24. Ho JE, Hsue PY. Cardiovascular manifestations of HIV infection. Heart 2009;95:1193-202.
25. Hsue PY, Hunt PW, Ho JE, et al. Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail 2010;3:132-9.
26. Ntsekhe M, Mayosi BM. Cardiac manifestations of HIV infection: an African perspective. Nature clinical practice Cardiovascular medicine 2009;6:120-7.
27. Cerrato E, D'Ascenzo F, Biondi-Zoccai G, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. European heart journal 2013;34:1432-6.
28. Holloway CJ, Ntusi N, Suttie J, et al. Comprehensive Cardiac Magnetic Resonance Imaging and Spectroscopy Reveal a High Burden of Myocardial Disease in HIV Patients. Circulation 2013;128:814-22.
29. Lorgis L, Cottenet J, Molins G, et al. Outcomes After Acute Myocardial Infarction in HIV-Infected Patients Analysis of Data From a French Nationwide Hospital Medical Information Database. Circulation 2013;127:1767-74.
30. Tunstall-Pedoe H, Morrison C, Woodward M, Fitzpatrick B, Watt G. Sex differences in myocardial infarction and coronary deaths in the Scottish MONICA population of Glasgow 1985 to 1991. Presentation, diagnosis, treatment, and 28-day case fatality of 3991 events in men and 1551 events in women. Circulation 1996;93:1981-92.
31. Cheruvu S, Holloway C. Cardiovascular disease in human immunodeficiency virus. Internal medicine journal 2014;44:315-24.
32. Ferket BS, Genders TS, Colkesen EB, et al. Systematic review of guidelines on imaging of asymptomatic coronary artery disease. Journal of the American College of Cardiology 2011;57:1591-600.
33. Stein PD, Yaekoub AY, Matta F, Sostman HD. 64-slice CT for diagnosis of coronary artery disease: a systematic review. The American journal of medicine 2008;121:715-25.
34. Choi EK, Choi SI, Rivera JJ, et al. Coronary computed tomography angiography as a screening tool for the detection of occult coronary artery disease in asymptomatic individuals. Journal of the American College of Cardiology 2008;52:357-65.
35. Nolte JE, Neumann T, Manne JM, et al. Cost-effectiveness analysis of coronary artery disease screening in HIV-infected men. European journal of preventive cardiology 2013.

36. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA : the journal of the American Medical Association 2004;291:210-5.
37. Aroney CN, Aylward P, Chew DP, et al. 2007 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006. The Medical journal of Australia 2008;188:302-3.
38. Chew DP, FCSANZa CNA, FRACPb PEA, Kelly A-M, MClinEd F, White HD. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. clinical trials 2011;4:6.
39. Nadel J, Hewitt T, Horton D. Acute coronary syndrome in Australia: Where are we now and where are we going? The Australasian medical journal 2014;7:149.
40. Hsue PY, Giri K, Erickson S, et al. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. Circulation 2004;109:316-9.
41. Lang S, Mary-Krause M, Cotte L, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. Aids 2010;24:1228-30.
42. Cobbe SM. Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. The American Journal of Cardiology 1997;79:756-62.
43. Alter DA, Naylor CD, Austin PC, Tu JV. Biology or bias: practice patterns and long-term outcomes for men and women with acute myocardial infarction. Journal of the American College of Cardiology 2002;39:1909-16.
44. Alter DA, Khaykin Y, Austin PC, Tu JV, Hux JE. Processes and Outcomes of Care for Diabetic Acute Myocardial Infarction Patients in Ontario Do physicians undertreat? Diabetes Care 2003;26:1427-34.
45. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. The Journal of Clinical Endocrinology & Metabolism 2007;92:2506-12.
46. Freiberg MS, Chang C-CH, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA internal medicine 2013;173:614-22.
47. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, et al. Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy. European heart journal 2012;33:875-80.
48. Boccara F, Mary-Krause M, Teiger E, et al. Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis. European heart journal 2011;32:41-50.
49. De Backer G, Ambrosionie E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). European Journal of Cardiovascular Prevention & Rehabilitation 2003;10:S1-S78.
50. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic AdultsA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Journal of the American College of Cardiology 2010;56:e50-e103.
51. Cademartiri F, Maffei E, Palumbo A, et al. Coronary calcium score and computed tomography coronary angiography in high-risk asymptomatic subjects: assessment of diagnostic accuracy and prevalence of non-obstructive coronary artery disease. European radiology 2010;20:846-54.
52. Leschka S, Scheffel H, Desbiolles L, et al. Combining dual-source computed tomography coronary angiography and calcium scoring: added value for the assessment of coronary artery disease. Heart 2008;94:1154-61.
53. Mehta V, Patel M, Venuraju S, Jeevarethinam A, Yerramasu A, Lahiri A. Prevalence of coronary atherosclerotic plaque in patients with a low coronary artery calcium score. BMC Proceedings; 2012: BioMed Central. p. P25.
54. Pundziute G, Schuijf JD, Jukema JW, et al. Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. European heart journal 2008.
55. Schuijf JD, Beck T, Burgstahler C, et al. Differences in plaque composition and distribution in stable coronary artery disease versus acute coronary syndromes; non-invasive evaluation with multi-slice computed tomography. Acute cardiac care 2007;9:48-53.

Appendices

Appendix A: Telephone Survey

Introduction

- Good morning/afternoon/evening my name is Dr. James Nadel and I am a researcher from the St. Vincent's Hospital Darlinghurst, may I please speak with *(insert participant's name)*.

If not available ask if there is a better time to contact the participant and reschedule.

If participant is deceased, apologies for the disruption and re-assure that they will not be contacted again regarding this matter.

- I am calling to follow up on a package you were sent a couple of weeks ago asking if you were interested in partaking in a survey.

- I was wondering whether you had any questions about the documentation?

Yes ☐

No ☐

If 'No' move to next point

If 'Yes' allow the participant to voice questions and respond appropriately

- Are you happy to participate in the survey?

Yes ☐ No ☐

If 'No' state the following

- On behalf of the St. Vincent's Hospital and the University of Notre Dame we would like to thank you for taking the time to read the documentation and apologies for any inconveniences.

If 'Yes' move to next point.

- Are you willing to go through the survey with me now it will take between 3-5 minutes?

Yes ☐

No ☐

If 'Yes' state the following

- Great, the survey is made up of a number of questions most of which will require a one-word answer. I will direct you as we go through it. If at any stage you feel uncomfortable or you would like to stop for any reason please let me know. Also, at the end of the survey we ask, if you have not already done so to please mail back your consent form in the reply postage paid envelope you were sent. If you have lost the form I can mail out another one for you?

If 'No' move to the next point

- Can I arrange with you another time to complete the survey?

  Yes ☐

  No ☐

If 'Yes' arrange a time and date

- Great, I look forward to speaking with you then, if you have any questions please don't hesitate to contact me. In the meantime if you haven't already done so, may I ask you to mail back your consent form in the reply postage paid envelope. If you have lost the form I can mail out another one for you?

If 'No' state the following

- On behalf of the St. Vincent's Hospital and the University of Notre Dame we would like to thank you for taking the time to read the documentation and apologies for any inconveniences.

****

END OF SECTION

Section 1 – Cardiac Risk Factors & Demographics:

1. Have you ever been told you have high blood pressure:

   Yes ☐
   No ☐
   Unsure ☐

*If 'No' or 'Unsure' move to **Question 3***

If 'Yes' continue below

2. Do you take medication to manage this?

   Yes ☐
   No ☐
   Unsure ☐

3. Have you ever been told you have high cholesterol:

   Yes ☐
   No ☐
   Unsure ☐

*If 'No' or 'Unsure' move to **Question 5***

If 'Yes' continue below

4. Do you take medication to manage this?

   Yes ☐
   No ☐
   Unsure ☐

5. Have you ever been told you have diabetes:

   Yes ☐
   No ☐
   Unsure ☐

*If 'No' or 'Unsure' move to **Question 7***

If 'Yes' continue below

6. Do you take medication to manage this?

   Yes ☐

No ☐

Unsure ☐

7. Have you ever been diagnosed with any other of the following chronic illnesses?

Cancer ☐

Asthma ☐

Chronic obstructive airways disease ☐

Chronic kidney disease ☐

Hepatitis ☐

HIV/AIDS ☐

Cardiomyopathy/Heart Failure ☐

If 'HIV/AIDS' continue below otherwise move to ***Question 11***

8. In which year were you diagnosed with HIV?

   Year:

9. When was and do you know the results of your most recent viral load and CD4 count?

   Date:
   Viral load:
   CD4:

10. Do you know your lowest recorded CD4 count?

    Lowest CD4:

11. What is your height (cm) and weight (kg)?

    Height:
    Weight:

12. Do you have any family history of heart attacks?

Yes ☐

No ☐

Unsure ☐

If 'No' or 'Unsure' move to ***Question 13***

If 'Yes' continue below

13. Which family members?

Mother ☐

Father ☐

Brother ☐

Sister ☐

Grandparents/Uncle/Aunty/Other non-1st degree ☐

14. Are you of Caucasian decent?

Yes ☐
No ☐
Unsure ☐

*If 'Yes' move to **question 12***

If 'No' or 'Unsure' continue below

15. What is your ethnic background?

Ethnicity:

16. How many days of the week do you exercise?

0 ☐
1 ☐
2 ☐
3 ☐
4 ☐
5 ☐
6 ☐
7 ☐

17. What is your current tobacco smoking status?

Current smoker ☐
Ex-smoker ☐
Never smoked ☐

*If "Never smoked" move to **Section 2***

*If "Ex-smoker" continue below then move to **Section 2***

How many years ago did you quit?
On average how many cigarettes did you smoke per day (packets)?
How long did you smoke for (years)?

*If "Current smoker" continue below then move to **Section 2***

On average how many cigarettes do you smoke per day (packets)?
How long have you been a smoker (years)?

****

END OF SECTION

Section 2 – Chest Pain

1. Have you experienced any chest pain?

   Yes ☐
   No ☐
   Unsure ☐

*If 'No' or 'Unsure' move to **Question 5***

If 'Yes' continue below

2. Was this pain dull/crushing in nature?

   Yes ☐
   No ☐
   Unsure ☐

3. Was this pain associated with any SOB/palpitations?

   Yes ☐
   No ☐
   Unsure ☐

4. Did you seek any medical advice for this?

   Yes ☐
   No ☐

If 'Yes' please specify

   Family doctor (GP) ☐
   Specialist ☐
   Other:

5. Have you ever been admitted to hospital for investigation of chest pain?

   Yes ☐
   No ☐
   Unsure ☐

*If 'No' or 'Unsure' move to **Question 7***

If 'Yes' continue below

   On what date(s):
   Which hospital(s):

6. Did you receive any medical treatment for this?

Yes ☐

No ☐

*If 'No' or 'Unsure' move to **Question 7***

If 'Yes' please specify

Drugs ☐

Please specify which drugs:

Heart monitoring (ECG or other) ☐

Coronary stenting ☐

Balloon angioplasty ☐

Coronary bypass graft ☐

Defibrillation ☐

Other:

7. Have you ever been told you have angina?

Yes ☐

No ☐

Unsure ☐

8. Have you ever been told you have had a heart attack/myocardial infarction?

Yes ☐

No ☐

Unsure ☐

*If 'No' or 'Unsure' move to **Section 3***

If 'Yes' continue below

On what date(s):
Which hospital(s):

****

END OF SECTION

Section 3 - Medications

1. Please list the medication (if any) you take for blood pressure?

   I take:

   I don't take any medications for blood pressure ☐

   I am unsure if I take any medications for blood pressure ☐

Participant to list above and interviewer to fill below post-survey

   ACE inhibitor ☐

   ARB ☐

   CCB ☐

   B-blocker ☐

   A-blocker ☐

   Diuretic ☐

   Other ☐

2. Please list the medication (if any) you take for high cholesterol?

   I take:

   I don't take any medications for cholesterol ☐

   I am unsure if I take any medications for cholesterol ☐

Participant to list above and interviewer to fill below post-survey

   Statin ☐

   Ezetimibe ☐

   Other ☐

3. Please list the medication (if any) you take for diabetes?

   I take:

   I don't take any medications for diabetes ☐

   I am unsure if I take any medications for diabetes ☐

Participant to list above and interviewer to fill below post-survey

   Insulin ☐

   Biguanide ☐

   Sulfonylurea ☐

   Other ☐

4. Please list the medication (if any) you take for your heart? – these may include blood thinning agents (e.g. aspirin, clopidogrel) or heart rate modifying agents

I take:

I don't take any medications for my heart ☐

I am unsure if I take any medications for my heart ☐

Participant to list above and interviewer to fill below post-survey

Anti-platelet agent ☐

Chronotropic agent ☐

Inotropic agents ☐

Other ☐

5. Do you take or have you ever taken any anti-retroviral medications?

Yes ☐

No ☐

Unsure ☐

If 'No' or 'Unsure' move to ***Section 4***

If 'Yes' continue below

I take:
I have taken:

Participant to list above and interviewer to fill below post-survey

Reverse Transcriptase Inhibitors ☐

NRTI ☐

NRTI ☐

Abacavir ☐

Integrase Inhibitor ☐

Protease Inhibitor ☐

Ritonavir ☐

Entry Inhibitor ☐

Fusion Inhibitor ☐

Other ☐

6. How long have you been on your current anti-retroviral regimen?

Years:

7. When did you start anti-retroviral therapy?

Year:

****

END OF SECTION

Section 4 - Data Retrieval

1. Would you allow a researcher from this project to retrieve information about any of the topics covered in this survey from your treating doctor or hospital? All data collected will remain anonymous and you will not be identifiable in the research's data or any publications that may result from this research.

   Yes ☐

   No ☐

If 'Yes' please provide details of your (where possible gather name, contact number and address).

9a. Treating doctor:
9b. Family doctor (GP):
9c. Specialist:
9d. Treating hospital:

- That completes the survey. On behalf of the St. Vincent's Hospital and the University of Notre Dame we thank you for taking the time to participate in this survey. If you have any comments or questions please don't hesitate to get in contact with us. I would like to take this time to remind you if you haven't already done so to return your consent form via the mail as soon as possible. Thank you again. Have a nice day.

****

END OF SECTION

Appendix B: Plain Language Statement

Cardiac outcomes in patients following CT or invasive coronary angiography

Dear Sir,

You are invited to participate in the above research project that is being conducted by Dr. Cameron Holloway and Dr. James Nadel of St. Vincent's Hospital. Your name and contact details have been gathered from St. Vincent's Hospital medical records. Analysis of the computer tomography coronary angiogram (CTCA) and invasive coronary angiogram (CA) databases has nominated you as a potential participant for this study.

The aim of the project is to assess the usefulness of CTCA and CA in the investigation of at-risk populations. Your selection for this research does not necessarily mean that you are at greater risk of heart problems but that you have undergone one of the two above investigations. With the information gathered from this research we hope to help orient future health services around the prognosis and screening of patients with coronary angiography.

Participation in this research will take the form of a 3-5 minute telephone survey conducted by our researchers. We ask that you please read the forms attached and should you decide to participate in the research sign and return the consent form via the reply postage paid envelope that has been provided.

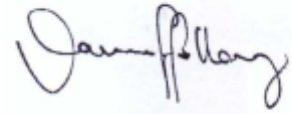
You will be telephone contacted by our researcher in approximately 2 weeks to confirm whether or not you plan to participate in the project. If you are unsure about any part of the project we ask that you withhold from signing and returning the consent form until you are contacted, at which point you will be invited to raise any questions you may have.

Your confidentiality and anonymity will be maintained throughout the entirety of the research and your participation is wholly voluntary. Furthermore, you have the right to withdraw from the study at anytime. Choosing whether or not to participate or choosing to withdraw will not affect your routine treatment, your relationship with those treating you or your relationship with the St. Vincent's Hospital.

The Human Research Ethics Committee of both St. Vincent's Hospital and the University of Notre Dame has approved this project.

Thank you for taking the time to read this documentation please don't hesitate to contact us with any queries.

Coordinating Investigator:
A/ Prof Cameron Holloway



Cardiologist, St. Vincent's Hospital
Conjoint Associate Professor of Medicine, Victor Chang Cardiac Research Faculty

Principal Investigator:
Dr. James Nadel

Resident Medical Officer, St. Vincent's Hospital
Masters Student, University of Notre Dame

Appendix C: Participant Sheet Information Sheet

PARTICIPANT INFORMATION SHEET

CLINICAL RESEARCH

Title	Cardiac outcomes in patients following CT or invasive coronary angiography
Project Sponsor	St. Vincent's Hospital/University of Notre Dame, Sydney
Coordinating Principal Investigator/ Principal Investigator	A/Prof Cameron Holloway/ Dr James Nadel
Location	St Vincent's Hospital, Sydney

Invitation

You are invited to participate in a research study assessing cardiac outcomes in those who have undergone coronary angiography.

Dr James Nadel and A/Prof Cameron Holloway of St. Vincent's Hospital, Sydney, are conducting the study.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. **'What is the purpose of this study?'**

The purpose of the study is to investigate whether coronary angiography is an effective tool in the assessment of at risk population groups. By comparing the angiograms of a group of patients to their clinical outcomes since undergoing this procedure we hope to better understand how and when these techniques should be utilised. Currently the guidelines pertaining to the treatment and screening of asymptomatic at risk individuals remains unclear, this is largely due to an absence of clinical research. We hope that this research will help orient future health services around the treatment of those individuals with cardiac risk factors including high blood pressure, high cholesterol, physical inactivity and chronic diseases such as diabetes and HIV.

2. ‘Why have I been invited to participate in this study?’

You are eligible to participate in this study because; you have had a CT coronary angiogram (CTCA) or formal coronary angiogram (CA) at St. Vincent’s Hospital and have some degree of cardiac risk.

3. ‘What if I don’t want to take part in this study, or if I want to withdraw later?’

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. However, it may not be possible to withdraw your data from the study results if these have already had your identifying details removed.

4. ‘What does this study involve?’

Participants in this research will be contacted via telephone and taken through a streamlined 3-5 minute questionnaire designed specifically for this study. These conversations will NOT be recorded. The questionnaire will seek to identify if a participant has experienced any of the outcomes associated with cardiovascular disease; their subsequent treatment and clarify their cardiac risk.

In addition to this, participants will be asked to give written consent allowing our researchers to access medical records or contact other doctors associated specifically with and limited to issues related to their cardiovascular health. This will be undertaken in an effort to attain more accurate data for the study.

There is no cost, monitoring or further commitments required of participants in this study following completion of the questionnaire.

As a participant in this study you will be asked to take the time to read the consent form in full, sign it and return it via the return postage paid envelope. If you have any questions regarding the research and your participation please withhold from signing and returning the consent form until you have been contacted by the researcher at which point you will be invited to ask any questions you may have.

This study will be conducted over an approximate 6-month period from January of 2015.

5. ‘How is this study being paid for?’

Neither the researchers nor the institutions involved are perceived to benefit financially from the study.

If required, funding will be sought from St. Vincent’s Heart and Lung Centre through Dr Cameron Holloway’s special purpose research fund. However the costs of the proposed research are anticipated to be minimal.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

6. ‘Are there risks to me in taking part in this study?’

This research does not involve any interventional treatment. As a result, there are no anticipated disadvantages of taking part in this study aside from the time lost partaking in the telephone conversation (3-5 minutes) and the returning of the consent form via mail.

If you become upset or distressed as a result of your participation in the research, the researcher will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be free of charge to participants.

7. 'Will I benefit from the study?'

This study aims to further medical knowledge and may improve future treatment of cardiovascular disease for those with chronic diseases and cardiac risk factors, however it may not directly benefit you.

8. 'Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything.

9. 'How will my confidentiality be protected?'

Of the people treating you, only Dr James Nadel and Dr Cameron Holloway will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your identifiable details and results which will be held securely at St. Vincent's Hospital. If required, only non-identifiable information will be sent off site.

10. 'What happens with the results?'

If you give us your permission by signing the consent document, we plan to compile the data for submission to a peer-reviewed journal and/or dissemination at a scientific conference.

In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

11. 'What should I do if I want to discuss this study further before I decide?'

When you have read this information, Dr James Nadel will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact him/her on 0411 415 541 or (02) 8382 1111.

12. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by St Vincent's Hospital HREC. Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on (02) 8382 2075 and quote LNR/15/SVH/45.

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.

Appendix D: Participant Consent Form

CONSENT FORM

Cardiac outcomes in patients following CT or invasive coronary angiography

1. I,…….....of..... ..... agree to participate as a participant in the study described in the Participant Information Sheet set out above (or: attached to this form).
2. I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information sheet has been explained to me to my satisfaction.
3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.
4. I understand that I can withdraw from the study at any time without prejudice to my relationship to the St. Vincent's Hospital or my treating doctors.
5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.
6. I understand that if I have any questions relating to my participation in this research, I may contact Dr James Nadel on telephone 0411 415 541 or (02) 8382 1111 who will be happy to answer them.
7. I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet.

Complaints may be directed to the St Vincent's Hospital Sydney Research Office: 02 8382 2075

Signature of participant Date

Signature of witness Date

Signature of investigator Date

Participant will be provided with a copy of the Participant Information Sheet and this Consent Form
All parties signing the Consent Form must date their own signature

Appendix E: Patient Withdrawal Form

REVOCATION OF CONSENT

Cardiac outcomes in patients following CT or invasive coronary angiography

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with the St. Vincent's Hospital or my medical attendants.

Signature of participant Date

Please PRINT name

The section for Revocation of Consent should be forwarded to

A/Prof Cameron Holloway,
Heart and Lung Clinic
Level 4,
St. Vincent's Hospital,
390 Victoria St
Darlinghurst, 2010
Ph: (02) 8382 3150
Email: cameron.holloway@svha.org.au

In the event the participant decided to withdraw verbally, please give a description of the circumstances. Coordinating Investigator to provide further information here:

Coordinating Investigator to sign the withdrawal of consent form on behalf of a participant if verbal withdrawal has been given:

Name of participant Date

Signature of investigator

Participant will be provided with a copy of this Withdrawal of Consent Form

Appendix F: St. Vincent's Hospital HREC Approval Letter

St Vincent's Hospital

A facility of St Vincent's & Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 064 038 872
390 Victoria Street
Darlinghurst NSW 2010
Australia

T + 61 2 8382 1111
F + 61 2 9332 4142
www.stvincents.com.au

4 February 2015

Dr Cameron Holloway
Cardiology Department
St Vincent's Hospital
390 Victoria Street
Darlinghurst NSW 2010

Dear Cameron,

SVH File Number: 15/003
Project Title: Cardiac outcomes in patients following CT or invasive coronary angiography
HREC Reference Number: LNR/15/SVH/45

Thank you for submitting the above project for ethical and scientific review.

Based on the information you have provided and in accordance with the NHMRC National Statement 2007 and NSW Health Policy Directive PD2010_055 'Ethical and Scientific Review of Human Research in NSW Public Health Organisations', this project has been assessed as low/negligible risk and is therefore exempt from full HREC review.

This HREC has been accredited by NSW Ministry of Health as a Lead HREC under the model for single ethical and scientific review and Certified by the NHMRC under the National model for Harmonisation of Multicentre Ethical Review (HoMER). This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

I am pleased to advise that the HREC Executive at a meeting on **27 January 2015** has granted ethical and scientific approval of the above **multi-centre** project.

The Committee noted that this project is related to the following studies, which have been approved by St Vincent's Hospital HREC:

- **SVH File No: 14/196**
  Study Title: The Characterisation of Coronary Plaque Burden in HIV patients using CTCA
  HREC Reference No: LNR/14/SVH/284

- **SVH File No: 13/272**
  Study Title: Angiographic features and burden of Coronary Artery Disease in the HIV Positive Population
  HREC Reference No: LNR/13/SVH/395

You are reminded that this letter constitutes *ETHICAL* and *SCIENTIFIC* approval only. You must not commence this research project at a site until a completed Site Specific Assessment Form and associated documentation have been submitted to the site Research Governance Officer and Authorised. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at the following sites:

- **St Vincent's Hospital, Sydney**
- **St Vincent's Private Hospital, Sydney**

If a new site(s) is to be added please inform the HREC in writing and submit a Site Specific Assessment Form (SSA) to the Research Governance Officer at the new site.

The following documents have been approved:

- Introductory Letter, dated 15 November 2014
- Survey, dated 15 November 2014
- Participant Information Sheet and Consent Form, dated 15 November 2014
- Protocol, version 1 dated 15 November 2014

The Low and Negligible Risk Research Form (LNRF) reviewed by the HREC was LNRF **AU/6/845C118.**

Please note the following conditions of approval:

- HREC approval is valid for **5 years** from the date of the HREC Executive Committee meeting and expires on **27 January 2020**. The Co-ordinating Investigator is required to notify the HREC 6 months prior to this date if the project is expected to extend beyond the original approval date at which time the HREC will advise of the requirements for ongoing approval of the study.
- The Co-ordinating Investigator will provide an Annual Progress Report beginning in **January 2016**, to the HREC as well as a Final Study Report at the completion of the project in the specified format.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by participants regarding the conduct of the project.
- Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the HREC Executive for review, in the specified format.
- The HREC Executive will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- Investigators holding an academic appointment (including conjoint appointments) and students undertaking a project as part of a University course may also be required to notify the relevant University HREC of the project. Investigators and students are advised to contact the relevant HREC to seek advice regarding their requirements.

Please note that only an electronic copy of this letter will be provided, if you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries about your project please contact the Research Office, Ph: (02) 8382-2075 or by E-mail: SVHS.Research@svha.org.au. The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office web-site to be found externally at: www.stvincents.com.au/researchoffice or at http://exwwwsvh.stvincents.com.au/researchoffice (internally).

Please quote **SVH File Number: 15/003** in all correspondence.

The HREC wishes you every success in your research.

Yours sincerely,

Dr Pamela Blaikie
Research Office Manager
St Vincent's Hospital Research Office
Level 6, de Lacy Building

cc: Dr James Nadel
TRIM REF: D/2015/6991

NB: Dr. C. Holloway is addressed as the principal researcher as per St. Vincent's Hospital requirements, Dr. J. Nadel was responsible for all ethics applications and correspondence pertaining to this research.

Appendix G: Notre Dame HREC Approval Letter

THE UNIVERSITY OF NOTRE DAME AUSTRALIA

19 Mouat Street (PO Box 1225)
Fremantle, Western Australia 6959
Telephone: +61 8 9433 0555
Facsimile: +61 8 9433 0544
Email: enquiries@nd.edu.au
Internet: www.nd.edu.au

ABN: 69 330 643 218
CRICOS PROVIDER CODE: 01032F

5 March 2015

Dr Neville Sammel
School of Medicine
The University of Notre Dame Australia
P.O Box 944
Broadway NSW 2007

Dear Neville,

Reference Number: 015020S

Project title: "Cardiac outcomes in patients following CT or invasive coronary angiography."

Thank you for submitting the above project for review. It is noted that you have ethics approval for this project from St Vincent's Hospital HREC, approval number LNR/14/SVH/146. Your application has been assessed as qualifying for a Cross-Institutional approval and is therefore exempt from HREC review. I am pleased to advise that ethical clearance has been granted for this proposed study.

The UNDA students and researchers identified as working on this project are:

Name	School	Role
Dr James Nadel	School of Medicine, Sydney	Masters Student

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

Should you have any queries about this project, please contact me at #2964 or Natalie.Giles@nd.edu.au.

Yours sincerely,

Dr Natalie Giles
Executive Officer, Human Research Ethics Committee
Research Office

cc: Prof Christine Bennett, Dean, School of Medicine Sydney;
Prof George Mandz, SRC Chair, School of Medicine Sydney.

NB: Dr. N. Sammel is listed as principal researcher as per UNDA requirements, Dr. J. Nadel was responsible for all ethics applications and correspondence pertaining to this research.

Appendix H: St. Vincent's Hospital Ethics Cover Letter

Cardiology Department

St Vincent's Hospital, Darlinghurst

NSW, Australia, 2010

Head of Committee

St Vincent's Hospital HREC

St Vincent's Hospital, Darlinghurst

NSW, Australia, 2010

RE: Ethics Proposal

Dear Sir/Madam,

My name is Dr James Nadel, I am a Masters Student at the University of Notre Dame. Together with A/Prof Cameron Holloway, A/Prof Neville Sammel and the cardiology Department at St Vincent's Hospital, I am hoping to commence research in the field of HIV-related heart disease.

Attached is my low/negligible risk ethics proposal, study protocol, PISCF, plain language statement and questionnaire.

Thank you kindly for reviewing this submission.

Please feel free to contact me if there are any queries or concerns.

Kind Regards,
Dr. James Nadel

Junior Medical Officer, St. Vincent's Hospital
Masters Student, University of Notre Dame, Sydney
Ph: 0411415541
Email: james.r.nadel@gmail.com

Appendix I: Study Protocol

Cardiac outcomes in patients following CT or invasive coronary angiography

Version Number: 1.0
Date of Protocol: 15/11/2014

1. BACKGROUND

1.1. Disease Background

Coronary plaque is the major cause of coronary artery disease (CAD). Those with HIV are thought to be at increased risk of CAD. Currently there are no clear guidelines regarding the screening of at-risk asymptomatic patients with HIV.

1.2. Rationale for Performing the Study

With the advent of anti-retroviral therapy, patients with HIV have much greater life expectancies and are less susceptible to AIDS related illness. These days, one of the leading causes of death in patients with HIV is heart disease, which results from a combination of HIV infection, lifestyle factors and the drugs used to treat the virus. The aim of this study is to examine whether those with HIV are at greater risk of CAD and its sequelae (compared to risk factor matched controls) and if so; does coronary angiography predict this risk. The results of the proposed study may help optimize treatment and screening of this specific subgroup.

2. STUDY OBJECTIVES

2.1. Primary Objective

Compare the type and distribution of coronary plaque in patients with HIV to risk factor matched controls and assess their clinical outcomes.

3. STUDY DESIGN

3.1. Design

- Retrospective study

3.2. Study Groups

1. Patients with HIV who have had either CT coronary angiograms (CTCA) or formal angiograms (CA).
2. Patients without HIV who have had CTCA or CA and have similar risk profiles in terms of traditional risk factors (smoking, diabetes, hypertension, hypercholesterolemia etc.)

3.3. Number of participants

- Approximately 200

3.4. Number of centres

- St Vincent’s Public and Private Hospital

3.5. Duration

- Approximately 6 months

4. PARTICIPANT SELECTION

4.1. Inclusion Criteria

- Males who have undergone CTCA or CA at St Vincent's Public and Private Hospital

4.2. Exclusion Criteria

- Follow up <6 months
- Female
- <18 years old
- Non-English speaking background
- Non-contactable
- Refused consent

5. STUDY OUTLINE

5.1. Investigation plan

1. Search CTCA and CA database for patients with HIV
2. Match up patients with risk factor matched controls (2:1)
3. Blind all study participants from investigators
4. Analyse and interpret CTCA and CA scans
5. Follow-up patients for clinical outcomes since angiography (via telephone survey & medical records)
6. Compare clinical outcomes and angiograms between the two groups

5.2. Recruitment and Screening

- Search of CTCA and CA databases
- Mail out of plain language statement & participant information sheet and consent form
- Participant consent obtained

5.3. Informed Consent Process

- All patients who participate will provide written consent and can withdraw this consent at any stage of the research

6. APPENDIX

6.1. Plain Language Statement

- See attached PLS

6.2. Participant Information Sheet and Consent Form

- See attached PISCCF

6.3. Telephone Questionnaire

- See attached questionnaire

Appendix J: St. Vincent's Hospital Honorary Appointment

ST VINCENT'S HOSPITAL
SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

ST VINCENT'S PRIVATE HOSPITAL
SYDNEY
CONDUCTED BY THE SISTERS OF CHARITY OF AUSTRALIA

St Vincent's Hospital Sydney Limited
ABN 77 054 038 872
390 Victoria Street
Darlinghurst NSW 2010
Telephone 02 8382 1111
Facsimile 02 9332 4142
www.stvincents.com.au

18 February 2015

Dr James Nadel
4/81 O'Brien Street
Bondi Beach NSW 2026

Dear James

HONORARY APPOINTMENT

Project 15/003
Title Cardiac outcomes in patients following CT or invasive coronary angiography.
HREC Reference No: (LNR/15/SVH/45) (LNRSSA/15/SVH/56)

I refer to your application to undertake research on the above-mentioned projects, which has successfully received both Ethics & Science, and Site Specific Assessment approval at St Vincent's Public & Private Hospital Sydney.

I am pleased to offer you an Honorary Appointment with the Hospital for the purpose of undertaking the Agreed Activities listed in the Schedule under the supervision of Doctor Cameron Holloway.

This appointment is for **a period of 12 months** and is dependent upon you continuing at St Vincent's Public Hospital.

May I take this opportunity to wish you every success in your association with St Vincent's Hospital and with your research endeavours.

Yours sincerely

Carolyn Marsh
Executive Manager – Medical Workforce
St Vincent's Hospital

CC: Dr Cameron Holloway, St Vincent's Hospital

Appendix K: HIV Medicine Publication Acceptance Letter

Decision Letter (HIV-V-11-2015-3279.R1)

From: HIVedoffice@wiley.com

To: james.r.nadel@gmail.com

CC:

Subject: HIV Medicine - Decision on Manuscript ID HIV-V-11-2015-3279.R1

Body: 28-Apr-2016

Dear Dr Nadel,

It is a pleasure to accept your manuscript entitled "Screening and risk assessment for coronary artery disease in HIV: An unmet need" in its current form for publication in HIV Medicine. The comments of the reviewer(s) who reviewed your manuscript are included at the foot of this letter.

Thank you for your fine contribution. On behalf of the Editors of HIV Medicine, we look forward to your continued contributions to the Journal.

Now that your manuscript has been accepted for publication may we point out, please, that a 'snappy' title and better keywords can often make a very significant difference to the number of article citations achieved. If you feel that there is the possibility to improve either or both of these features before publication then we would ask you, please, to communicate this to the publisher (Wiley-Blackwell) when they send you the proofs for approval.

As your paper has been accepted, the author identified as the formal corresponding author for the paper will receive an email prompting them to login into Author Services; where via the Wiley Author Licensing Service (WALS) they will be able to complete the license agreement on behalf of all authors on the paper. Please see the author guidelines for more information under the COPYRIGHT ASSIGNMENT section.

Sincerely,

Professor Brian Gazzard
Professor Jens Lundgren
Editors, HIV Medicine
HIVedoffice@wiley.com, HIVedoffice@gmail.com

Editorial Board Member Comments to Author:

Editorial Board Member
Comments to the Author:
(There are no comments.)

Appendix L: Journal of Cardiovascular Computed Tomography Publication Acceptance Letter

Date: Jul 28, 2016
To: "James Nadel" jr_nadel@hotmail.com
From: "The Journal of Cardiovascular CT" jcct@elsevier.com
Subject: Your Submission

Ms. Ref. No.: JCCT-D-16-00138
Title: High-risk coronary plaque, invasive coronary procedures, and cardiac events among HIV-positive individuals and matched controls
Journal of Cardiovascular Computed Tomography

Dear Dr. Nadel,

I am pleased to inform you that your paper "High-risk coronary plaque, invasive coronary procedures, and cardiac events among HIV-positive individuals and matched controls" has been accepted for publication in Journal of Cardiovascular Computed Tomography. Please note I have edited the paper, including the title before acceptance.

Your edited manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication

Thank you for submitting your work to Journal of Cardiovascular Computed Tomography.

Yours sincerely,

Stephan Achenbach, MD
Editor-in-Chief
Journal of Cardiovascular Computed Tomography