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CASE REPORT

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# Severe Triple Vessel Disease Presenting As a Negative Electrocardiogram Stress Test: Temptations and Pitfalls in the Management of HIV-Associated Cardiometabolic Disease

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## ABSTRACT

A 61-year-old male with human immunodeficiency virus was admitted for non-ST elevation myocardial infarction. He reported a three-year history of stable angina and was previously evaluated one year prior with an electrocardiogram exercise stress test, during which he was able to reach greater than 10 metabolic equivalents. Coronary angiography one year after this benign stress test revealed severe triple vessel disease. Here we describe unique considerations for the diagnosis of ischemic heart disease in patients with HIV-associated cardiometabolic disease.

## ARTICLE HISTORY

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## KEYWORDS

HIV, Cardiometabolic Disease, Stable Angina

### Introduction

Individuals with human immunodeficiency virus (HIV) are at high risk of cardiovascular adverse events and mortality [1]. This is due to the aggressive and unpredictable nature of HIV-associated cardiometabolic disease. We report a case of a patient with chronic HIV compliant on combined antiretroviral therapy (cART) having a negative exercise electrocardiogram (ECG) stress test one year prior to the discovery of severe triple vessel atherosclerotic coronary artery disease on coronary angiogram. This case highlights the need for comprehensive risk assessment of cardiometabolic disease in the setting of HIV infection.

### Case Description

### Patient Presentation

A 61-year-old African-American male with a history of non-insulin dependent diabetes mellitus, HIV controlled on cART (Emtricitabine/Rilpivirine/Tenofovir), hypertension, and stable angina arrived via emergency medical services with severe chest pain. He reported right-sided chest pain radiating to his back and right upper extremity that started earlier in the morning while shoveling snow. He had experienced exertional chest pain for the past three years, however, this time the pain persisted despite rest. He denied use of alcohol, tobacco, and illicit drugs. Of note, the patient had underwent an electrocardiogram (ECG) stress test one year prior to presentation, for further evaluation of his ongoing stable angina. The ECG at rest showed sinus rhythm with no other pertinent findings (figure 1). During this stress test, the patient had exercised for 7 minutes and 11 seconds completing Bruce Protocol Stage 2 and 1 min and 11 seconds into Stage 3, achieving a total of 10.1 metabolic equivalents (METS). Furthermore, he had achieved 94% of his maximum predicted heart rate, normal blood pressure response, with no ST-T changes or arrhythmias noted. The test had been terminated one minute into Stage 3 of the Bruce Protocol due to mild fatigue.

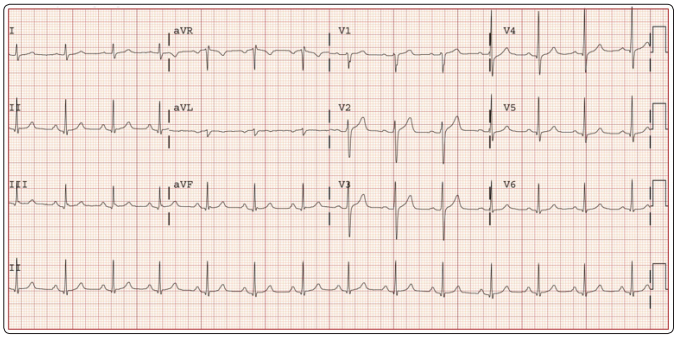


**Figure 1:** Resting electrocardiogram prior to exercise stress test

### Clinical Findings

Physical examination during the current presentation was unremarkable. Vitals on admission included a blood pressure of 101/66 mm Hg, heart rate of 70 beats/min, temperature of 98.1 F, and respiratory rate of 17 breaths/ min with an oxygen saturation of 98% on room air, and a body-mass index of 24.9 kg/m$^2$. A 12-lead electrocardiogram showed non-specific ST changes. Chest radiography showed no acute cardiopulmonary findings. Laboratory investigations were notable for an initial troponin-I of 8.82 (< 0.15 ng/mL), brain natriuretic peptide of 345 (< 100 pg/mL), creatinine of 1.00 (0.7 - 1.3 mg/dL), and hemoglobin of 11.1 (14 - 18 g/dL). The hemoglobin A1c was measured to be 6.5%. The lipid panel showed a total cholesterol was 175 mg/dl (0 - 199 mg/dL), triglycerides 74 (0 - 150mg/dL), high density

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cholesterol 39 mg/dL (≥ 55 mg/dL), and low density cholesterol 121 mg/dL (< 100mg/dL). The repeat Troponin-I was 29.77 ng/mL. Transthoracic echocardiography showed a preserved ejection fraction (EF) of 55% with mild inferolateral and mid-inferobasal wall motion abnormalities.

### Timeline

One year prior to presenting to the hospital, the patient was evaluated for his ongoing stable angina. At this visit, his blood pressure was 132/70, heart rate 77. The lipid panel drawn at this time showed a total cholesterol was 192 mg/dl (0 - 199 mg/dL), triglycerides 44 (0 - 150mg/dL), high density cholesterol 52.2 mg/dL (≥ 55 mg/dL), and low density cholesterol 131 mg/dL (< 100mg/dL). He was started on aspirin and high-intensity statin therapy at this time and was referred for an exercise ECG stress test, which was negative. On presentation to our hospital, he was admitted to the coronary care service for an admission diagnosis of non-ST elevation myocardial infarction (NSTEMI) and subsequently taken for cardiac catheterization. He was optimized on goal directed medical therapy for severe ischemic heart disease. On day four of admission, he was safely discharged home with outpatient follow-up.

### Therapeutic Intervention

In the ED, the patient was started on dual antiplatelet therapy, high-intensity statin, low-dose beta blocker, and heparin drip. Invasive coronary angiogram was completed and revealed severe three vessel atherosclerotic coronary artery disease with an EF of 60% calculated by contrast ventriculography. Significant lesions included 100% stenosis of the distal left anterior descending artery, 100% occlusion of the first diagonal artery, 95% stenosis of the distal circumflex artery, and severe atherosclerosis of the first and second obtuse marginal arteries, as well as the ramus intermedius (figures 2 and 3). Diffuse severe disease was noted in the posterior descending artery. No clear culprit lesion was identified. The diffuse distal vessel disease was severe and as such, no amenable targets were identified for stent or bypass graft placement.

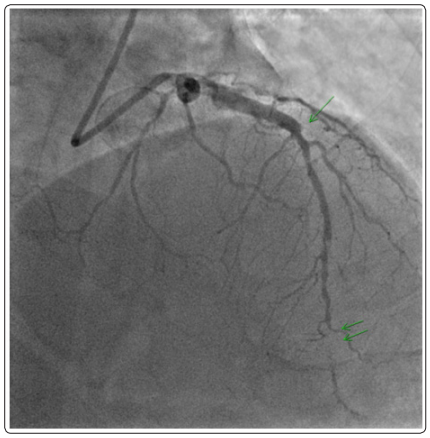

**Figure 2:** Coronary angiography demonstrating total, likely chronic, occlusion at the ostium of the first diagonal branch (single arrow) and the distal left anterior descending artery (double arrow).

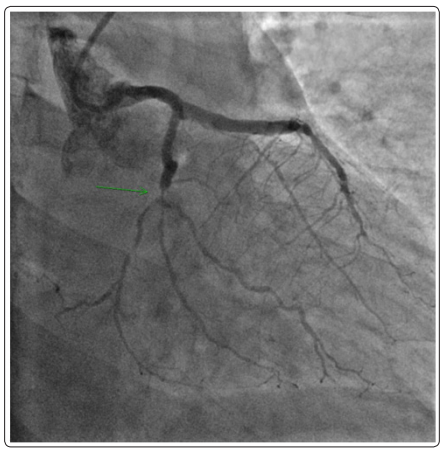

**Figure 3:** Coronary angiography demonstrating severe (95%) occlusion of the distal left circumflex artery, at the origin of the first obtuse marginal branch. The lesion was trifurcating from which the first and second obtuse marginal branches, as well as the distal circumflex artery, arise

Given the severity of the atherosclerotic burden, aggressive medical therapy and risk factor modifications were recommended. The patient was optimized with dual antiplatelet therapy (aspirin, clopidogrel), beta-blocker (metoprolol succinate), high-intensity statin (rosuvastatin), proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor (evolocumab), and brush border cholesterol inhibitor (ezetimibe). The patient was safely discharged from the coronary care service with outpatient cardiology follow-up.

### Discussion

HIV-associated cardiometabolic disease may be considered a separate phenotype of cardiometabolic disease with a unique presentation and pathogenesis. Individuals with HIV have a 50% greater risk of acute myocardial infarction as compared to those without HIV [1]. The pathogenesis of coronary artery disease (CAD) in this context is multifactorial. HIV is independently associated with increased atherogenesis, likely secondary to chronic inflammation, endothelial injury, and dyslipidemia [2, 3]. HIV induces visceral lipohypertrophy which produces insulin resistance and consequently, diabetes mellitus [4]. While multiple modes of endothelial injury have been proposed, the overall remodeling culminates in arterial stiffness, resulting in hypertension [5]. The use of antiretroviral therapy (ART) in the treatment of HIV may further substantiate risk. The role of ART remains unclear but has been postulated to further enhance atherogenesis by independently stimulating chronic inflammation and dyslipidemia [3]. It has been speculated that these patients may experience silent ischemia in a similar fashion to patients with diabetes mellitus [6]. The synergy of these pathogenic pathways produces an enhanced phenotype of cardiometabolic disease, which has not been fully considered in current guidelines on stable ischemic heart disease (SIHD).

The most appropriate initial diagnostic modality for the evaluation of CAD in HIV patients is unclear. Electrocardiogram (ECG) exercise stress testing is a common first step in diagnosing CAD and has remained a fundamental noninvasive tool. However, it yields moderate diagnostic value, with a sensitivity of 68% and specificity of 77% [7]. The sensitivity of this test may be further augmented by total METs achieved during the test; found that patients who achieved ≥ 10 METs without ST-depression during an

exercise stress test had a low risk of ischemia [8]. That said, ECG exercise stress testing is most useful in the evaluation of patients with intermediate pretest probability of CAD [7]. High pretest probability of CAD is associated with a high false-negative rate [7]. Likewise, exercise capacity may not truly reflect the extent of vessel disease and may lead clinicians to falsely exclude severe vessel disease. This is highlighted in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, in which the majority of cardiovascular deaths or nonfatal myocardial infarctions were sustained in individuals with normal stress test results [9].

The choice of invasive testing in HIV patients presenting with stable angina may be considered for those with a high pretest probability of disease [7]. Guidelines on SIHD from the American College of Cardiology (ACC) remain vague in their approach to delineating patients for invasive testing, with no universally accepted approach [10]. In the 2014 update of these guidelines, a class IIb recommendation is proposed to consider coronary angiography when high clinical suspicion for CAD remains despite benign stress test results [11]. This presents a conundrum in decision-making as clinical suspicion is driven by accurate risk stratification, for which there is no validated model available that considers comorbid HIV infection [1,3,7]. Despite a lack of validation in HIV patients, multiple models do exist that may be considered. Common models used include the Diamond Forrester Score (DFS), the Framingham Risk Score (FRS), and the CAD consortium score [12,13]. The DFS score for this patient based on their initial presentation was 94%. The CAD consortium score was 69% placing this patient at intermediate-high risk, with a common cut-off for intermediate risk of 70% [12]. The FRS score for this patient was 21.6%, placing them at high-risk using a cut-off of 20% [12].

In evaluating the initial management of this patient one year prior to presentation, the patient was incorrectly categorized as intermediate risk. The patient's risk of CAD was at minimum, intermediate-high, based on the DFS score; this risk estimation may only be amplified by the presence of HIV infection treated with cART therapy. There is significant temptation for healthcare professionals to obtain ECG stress testing to evaluate and verify the presence of anginal symptoms, however this is unlikely to affect management and does not evaluate the extent of CAD [14]. As noted in the PROMISE trial, reliance on stress test results leads to missed opportunities in more aggressive prevention strategies [14]. The true value of exercise stress testing in patients with cardiometabolic disease should be reconsidered.

This case highlights the importance of comprehensive risk management and accurate use of diagnostic modalities in the management of HIV-associated cardiometabolic disease. Given the current lack of validated risk stratification tools for patients with HIV, we may recommend the use of multiple models that include cardiometabolic risk factors, such as the FRS and CAD consortium models, to estimate risk. Current guidelines recommend the use of computed tomographic coronary angiography (CTCA) for intermediate risk patients while invasive coronary angiography remains the best diagnostic modality for high risk patients. Further research is required on the clinical utility of CTCA in high risk patients. Aggressive mitigation of cardiometabolic risk factors upon the diagnosis of HIV-associated cardiometabolic disease is crucial. In addition to dual antiplatelet and beta-blocker therapy, the patient was continued on high intensity statin therapy, in addition to starting ezetimibe and evolucumab. The choice to start two additional lipid agents was based on the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International) trial, which demonstrated that an low density cholesterol (LDL-C) level near 50 mg/dL was associated with improved outcomes [15]. Furthermore, ezetimibe may be associated with a net LDL-C change of -26.7% when used in conjunction with statin therapy; this expected change would not meet the goal of 50 mg/dL therefore evolucumab was added for added benefit [16].

## Conclusion

Patients with chronic HIV, irrespective of viral load, are susceptible to the development of ischemic heart disease. This case presents an argument for more aggressive diagnostic strategies in patients who present with stable angina and HIV-associated cardiometabolic disease. These patients should be carefully delineated into an appropriate risk category before the choice of diagnostic modality is made. CTCA may be the more appropriate modality for intermediate risk patients while invasive angiography remains first-line for high risk patients. Further research is required to validate a risk stratification model for patients with HIV.

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