

Outcomes of coronary artery bypass grafting in patients with human immunodeficiency virus infection

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Abstract

Background: With early and effective antiretroviral therapy and improved survival for persons living with human immunodeficiency virus infection (PLHIV), this patient population now faces an increasingly elevated risk of cardiovascular disease. However, the data on outcomes after coronary artery bypass grafting (CABG) for revascularization of coronary artery disease (CAD) in HIV+ patients is limited.

Methods: We conducted a retrospective analysis of 16 patients undergoing isolated CABG at the Medical University of Vienna from 2005 to 2018, who were HIV+ on admission. The primary endpoint of the study was survival. Secondary endpoints included the components of major adverse cardiac and cerebrovascular events (MACCE): cardiovascular death, stroke, myocardial infarction (MI), and repeat revascularization.

Results: Patients were followed for a median of 49 months (range, 7-142 months). Survival was 100% and 90% at 1 and 3 years after CABG, respectively. There were no strokes. MI and subsequent repeat revascularization were observed in two patients.

Conclusion: CABG provides excellent short- and midterm survival and freedom from MACCE in HIV+ patients with CAD requiring revascularization.

KEYWORDS

coronary artery bypass grafting, coronary artery disease, highly active antiretroviral therapy, human immunodeficiency virus infection

1 | INTRODUCTION

Improved survival for persons living with human immunodeficiency virus infection (PLHIV) has shifted the focus of health care towards older individuals who are at greater risk for comorbidities such as cardiovascular disease. Several factors contribute to HIV-associated coronary artery disease (CAD), among them chronic inflammation and immune activation.¹ In addition, PLHIV have a greater prevalence of traditional cardiovascular risk factors including dyslipidemia, hypertension, insulin resistance, and smoking than uninfected persons.² Furthermore,

antiretroviral therapies (ARTs) have been associated with an elevated risk of atherosclerotic cardiovascular disease-related events.²

Coronary artery bypass grafting (CABG) is the treatment of choice for patients with complex CAD.³⁻⁵ However, the outcomes of CABG in HIV+ patients are not well described. Only a few reports exist, and these include noncontemporary patient populations undergoing CABG surgery nearly two decades ago, with short durations of follow-up.⁶⁻¹⁰

As of 2018, there were 8055 PLHIV in Austria, with the majority of PLHIV currently on ART in care at the Allgemeines Krankenhaus/Medical University of Vienna.¹¹ Here, we report the

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clinical outcomes of a contemporary population of HIV+ patients with CAD requiring revascularization undergoing CABG at the Medical University of Vienna.

2 | MATERIALS AND METHODS

Between 1 January 2005, and 31 December 2018, 3962 patients underwent isolated CABG at the Medical University of Vienna. Of these, 16 patients (0.4%) were HIV+ at the time of admission for CABG surgery. We conducted a retrospective observational analysis to evaluate clinical outcomes after isolated CABG surgery in these HIV+ patients. The primary endpoint of the study was survival. Secondary endpoints included the components of major adverse cardiac and cerebrovascular events (MACCE): cardiovascular death, stroke, myocardial infarction (MI), and repeat revascularization.

Patients' cardiovascular demographic and perioperative data from admission until the time of discharge were obtained from a national, prospectively maintained and audited registry (Cardiac Registry). HIV infection-associated patient data were obtained from the electronic health records of the Austrian HIV Cohort Study, the HIV Patient Management System. Patients were followed for the occurrence of events up to 1 April 2019 for a median of 49 months (range, 7-142 months). Follow-up included review of digital in-hospital and outpatient clinic patient records and cross reference with the Austrian national death registry for determination of survival status. The study was approved by the Ethics Committee of the Medical University of Vienna (EK# 2263/2018) and complies with the guidelines of the Declaration of Helsinki.

2.1 | Statistical analysis

The mean, median, and standard deviation were calculated for all continuous variables, and frequency counts and percentages for categorical variables. Actuarial freedom from events (death) was calculated using the Kaplan-Meier method. Data were analyzed using SPSS 22.0 software (SPSS Inc, Chicago, IL).

3 | RESULTS

3.1 | Demographic and cardiovascular patient characteristics

The baseline demographic and cardiovascular patient characteristics are shown in Table 1. Patients' average age was 56.4 ± 9.8 years, and all patients were male. The patients had a high incidence of cardiovascular risk factors such as diabetes (37.5%) and smoking (50%), and also a high incidence of prior MI (56.3%). The majority of patients presented with stable angina (81.3%) and three-vessel disease (75%).

TABLE 1 Baseline demographic and cardiovascular patient characteristics

Variables	
Age, y, mean (\pm SD)	56.4 \pm 9.8
Male, n (%)	16 (100)
Body mass index, kg/m ² , mean (\pm SD)	25.2 \pm 4.7
Diabetes mellitus, n (%)	6 (37.5)
Smoker, n (%)	8 (50)
Hypertension, n (%)	14 (87.5)
Stable angina, n (%)	13 (81.3)
Previous myocardial infarction, n (%)	9 (56.3)
Cerebrovascular disease, n (%)	3 (18.8)
Ejection fraction, %, mean (\pm SD)	56.3 \pm 8.6
Three vessel disease, n (%)	12 (75)
Left main disease, n (%)	5 (31.3)
Preoperative medication use, n (%)	
Aspirin	12 (75.0)
P2Y ₁₂ inhibitor	8 (50.0)
Statin	10 (62.5)
β -Blocker	5 (31.3)
Angiotensin-converting-enzyme inhibitor	10 (62.5)

3.2 | CABG operation and postoperative course

CABG was performed via median sternotomy with the use of extracorporeal circulation and cross-clamping of the aorta in all patients (Table 2). The number of bypass grafts performed per patient was 3.1 ± 0.9 . Multiarterial revascularization, that is, revascularization with use of greater than or equal to two arterial grafts, was performed in seven patients (43.8%). The left internal thoracic artery (LITA) was used in all patients; the second arterial graft was the right internal thoracic artery (RITA) in four patients, the radial artery (RA) in two patients, and both a RITA and RA graft were used in one patient. A sequential LITA graft was used in one patient. Complete arterial revascularization using only arterial grafts was performed in four patients (25%); 12 patients (75%) received supplemental vein grafts. Only two patients (12.5%) required intraoperative transfusion of packed red blood cells; platelet transfusion was required in five patients (31.3%).

The patients' average hospital length of stay after CABG was 10.5 days. All patients were prescribed aspirin at discharge, and 81.2% received statins. There were no severe postoperative infectious complications (Table 2). One patient developed postoperative cholecystitis and concomitant bacteremia with *Serratia marcescens*, without signs of sepsis, and recovered on targeted antibiotic therapy. One patient developed urinary tract infection that was also adequately treated with antibiotic therapy. New postoperative atrial fibrillation was recorded in three patients; all patients were subsequently discharged in sinus rhythm.

TABLE 2 Surgical details and postoperative course

Variables	
No. of grafts per patients, mean (\pm SD)	3.1 \pm 0.9
Use of \geq 2 arterial grafts, <i>n</i> (%)	7 (43.8)
Off-pump CABG, <i>n</i> (%)	0
Extracorporeal circulation time, min, mean (\pm SD)	125.7 \pm 38.7
Aortic cross-clamp time, min, mean (\pm SD)	74.4 \pm 22.2
Blood products used during surgery	
PRBC, <i>n</i> (%)	2 (12.5)
Platelets, <i>n</i> (%)	5 (31.3)
Hospital length of stay after CABG, d, mean (\pm SD)	10.5 \pm 8.5
Discharge medications, %	
Aspirin	16 (100)
P2Y ₁₂ inhibitor	9 (56.2)
Statin	13 (81.2)
β -Blocker	14 (87.5)
Angiotensin-converting-enzyme inhibitor	9 (56.2)
Pneumonia	0
Mediastinitis	0
Sternal wound infection	0
Any infectious episode	2
Reoperation for bleeding/tamponade	0
Renal failure requiring renal replacement therapy	0

Abbreviations: CABG, coronary artery bypass graft; PRBC, packed red blood cells.

Two patients developed organic psychosyndrome; both cases resolved until discharge.

3.3 | HIV infection-associated parameters

HIV infection-associated patient characteristics are shown in Table 3. The duration of HIV infection at the time of admission for CABG was 206.0 \pm 81.5 months. Twelve patients (75%) were on protease

inhibitors with a mean duration of 103.6 \pm 79.8 months of protease inhibitor therapy at the time of CABG. Eight patients (50%) were on abacavir with a mean duration of 79.0 \pm 50.7 months of abacavir therapy at the time of CABG. Patients' HIV-1 viral load was low at 1.55 \pm 0.59 log copies/mL. The preoperative CD4+ T cell count was 580.0 \pm 300.0 cells/mm³. The CD4+ T cell count dropped in the perioperative period with an average decrease of less than 10%, but returned to preoperative levels within 1 year after CABG (Figure 1).

3.4 | Survival and MACCE

Follow-up data on survival and MACCE beyond hospital discharge were available for 15 of 16 patients. Survival was 100% and 90% at 1 and 3 years after CABG, respectively (Figure 2). MACCE is shown in Table 4. There were no in-hospital deaths. The operative mortality, defined as mortality within 30 days after CABG surgery, was also 0%. There were two late deaths: one late death occurred at 1.6 years and the other at 4.6 years after CABG. The causes of late death were multiorgan failure and streptococcal sepsis causing multiorgan failure, respectively.

The stroke rate in the HIV+ CABG population was 0% in the perioperative period as well as in the follow-up period. There were two MIs; both patients that experienced an MI underwent percutaneous coronary intervention (PCI) for repeat revascularization. One periprocedural MI (Type 5 MI) occurred within 24 hours after CABG. The patient had presented with non-ST-elevation acute coronary syndrome and underwent revascularization of the left anterior descending artery (LAD) and distal circumflex artery (CX) with a LITA and a saphenous vein graft (SVG), respectively. Intraoperative transit time flow measurement showed adequate flow in the LITA graft, but insufficient flow in the SVG, and the SVG to CX anastomosis was revised. The patient postoperatively developed asystole that did not respond to external pacing and required cardiopulmonary resuscitation. Occlusion of both bypass grafts was found on subsequent coronary angiography, and the patient underwent emergency PCI of the LAD. There was one spontaneous MI (type 1 MI, non-ST elevation acute coronary syndrome) during

TABLE 3 HIV infection-associated patient characteristics

Variables	
HIV infection duration before CABG, mo, mean (\pm SD)	206.0 \pm 81.5
CD4+ T-cell count, cells/mm ³ , mean (\pm SD)	580.0 \pm 300.0
Viral load, HIV-1 RNS, log c/mL	1.55 \pm 0.59
Patients on PI, <i>n</i> (%)	12 (75)
Duration of PI therapy before CABG, mo, mean (\pm SD)	103.6 \pm 79.8
Patients on Abacavir, <i>n</i> (%)	8 (50)
Duration of Abacavir therapy before CABG, mo, mean (\pm SD)	79.0 \pm 50.7
Coinfection, <i>n</i> (%)	
Hepatitis B	5 (31.2)
Hepatitis C	1 (6.2)

Abbreviations: CABG, coronary artery bypass grafting; HIV, human immunodeficiency virus; PI, protease inhibitors.

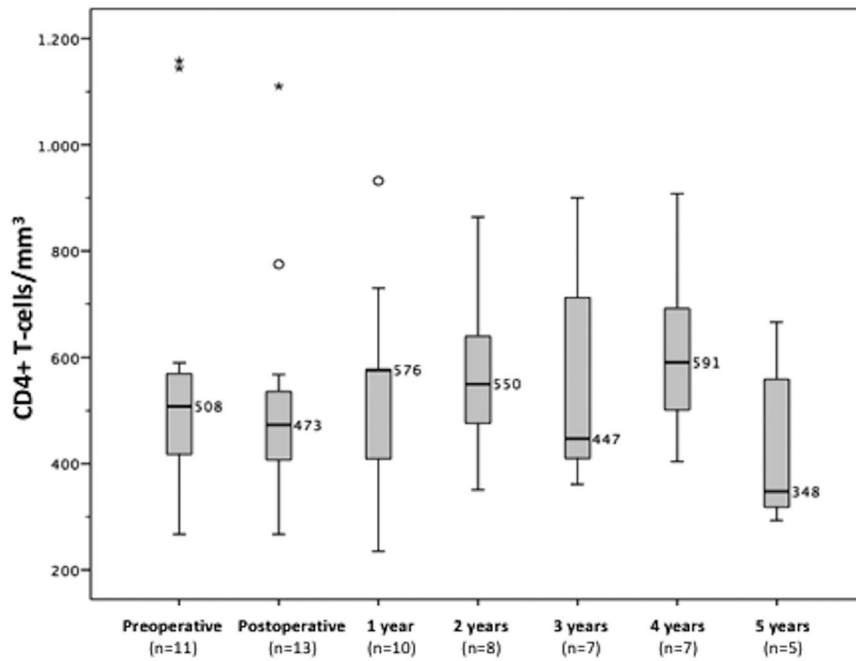


FIGURE 1 Pre- and postoperative CD4+ T cell count. Values depicted are median (interquartile range)

follow-up that occurred 3.6 years after CABG. Coronary angiography showed a patent LITA graft to the left anterior descending coronary artery (LAD) and occluded vein grafts to the circumflex and right coronary distribution, and the patient underwent PCI of the native circumflex and right coronary arteries.

3.5 | Lipid levels and lipid-lowering drug therapy

Patients presented with elevated plasma lipid levels at admission for CABG. The median total cholesterol was 199 mg/dL (interquartile range

[IQR], 157.5-222.3) with a median low-density lipoprotein cholesterol (LDL-C) of 137.0 mg/dL (IQR, 105.8-193.5), and the median triglyceride level was 189.0 mg/dL (IQR, 136.3-221.5) (Figure 3). Patients showed an improvement in their plasma lipid profile within the first postoperative year. A decrease of 25% compared with preoperative levels was observed at 1 year after CABG in LDL-C levels and a decrease of greater than 10% in total cholesterol levels, accompanied by an increase of 20% in high-density lipoprotein cholesterol levels. After the first postoperative year, the total cholesterol levels remained relatively constant, whereas the triglyceride levels increased. Thirteen patients (81.2%) were discharged on statin therapy, one patient was discharged on bezafibrate,

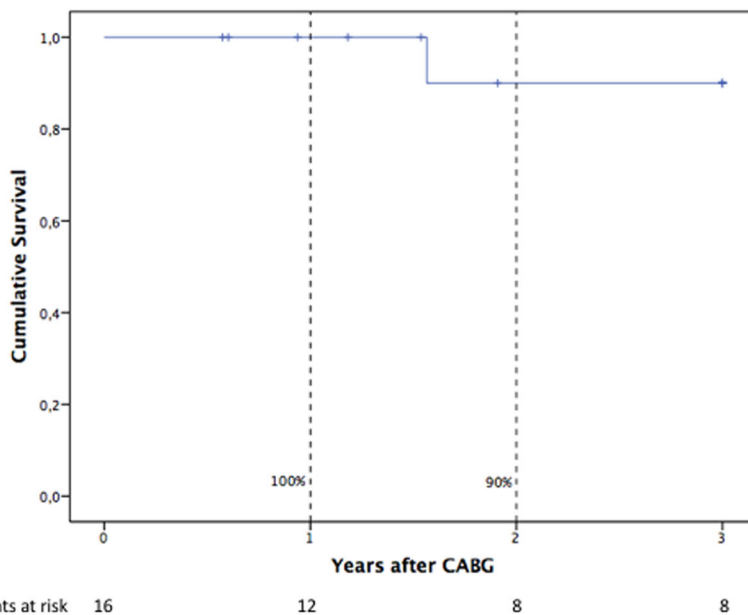


FIGURE 2 Kaplan-Meier estimate of survival for HIV+ patients undergoing isolated CABG operation. CABG, coronary artery bypass graft; HIV, human immunodeficiency virus

TABLE 4 Major adverse cardiac and cerebrovascular events

	Events, n (%)
All-cause death	2 (13.3)
In hospital	0
30 d after CABG	0
Death from cardiovascular causes	0
Stroke	0
Myocardial infarction	
Procedural	1 (6.7)
Spontaneous	1 (6.7)
Repeat revascularization	
PCI	2 (13.3)
CABG	0

Note: Data available for 15 of 16 patients with the exception of in-hospital death.

Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

and two patients were discharged without lipid-lowering therapy (Table 5). Of patients discharged on statin therapy, the majority received either atorvastatin ($n = 7$) or rosuvastatin ($n = 4$). Four of six patients (66.7%) for whom follow-up data including medications were available were taking statins at 5 years of follow-up.

4 | DISCUSSION

We have shown in our retrospective analysis carried out at the Medical University of Vienna, representing the largest HIV center in Austria that HIV+ patients with CAD requiring revascularization enjoy excellent short- and midterm survival, and freedom from MACCE after CABG surgery.

Previous studies have reported outcomes after CABG surgery in HIV+ patients, with patients undergoing CABG between 1994 and 2005, and follow-ups of up to 41 months.⁷⁻¹⁰ We report the clinical outcomes of a contemporary population of HIV+ patients undergoing CABG. The majority of our patients (approx. 80%) underwent CABG

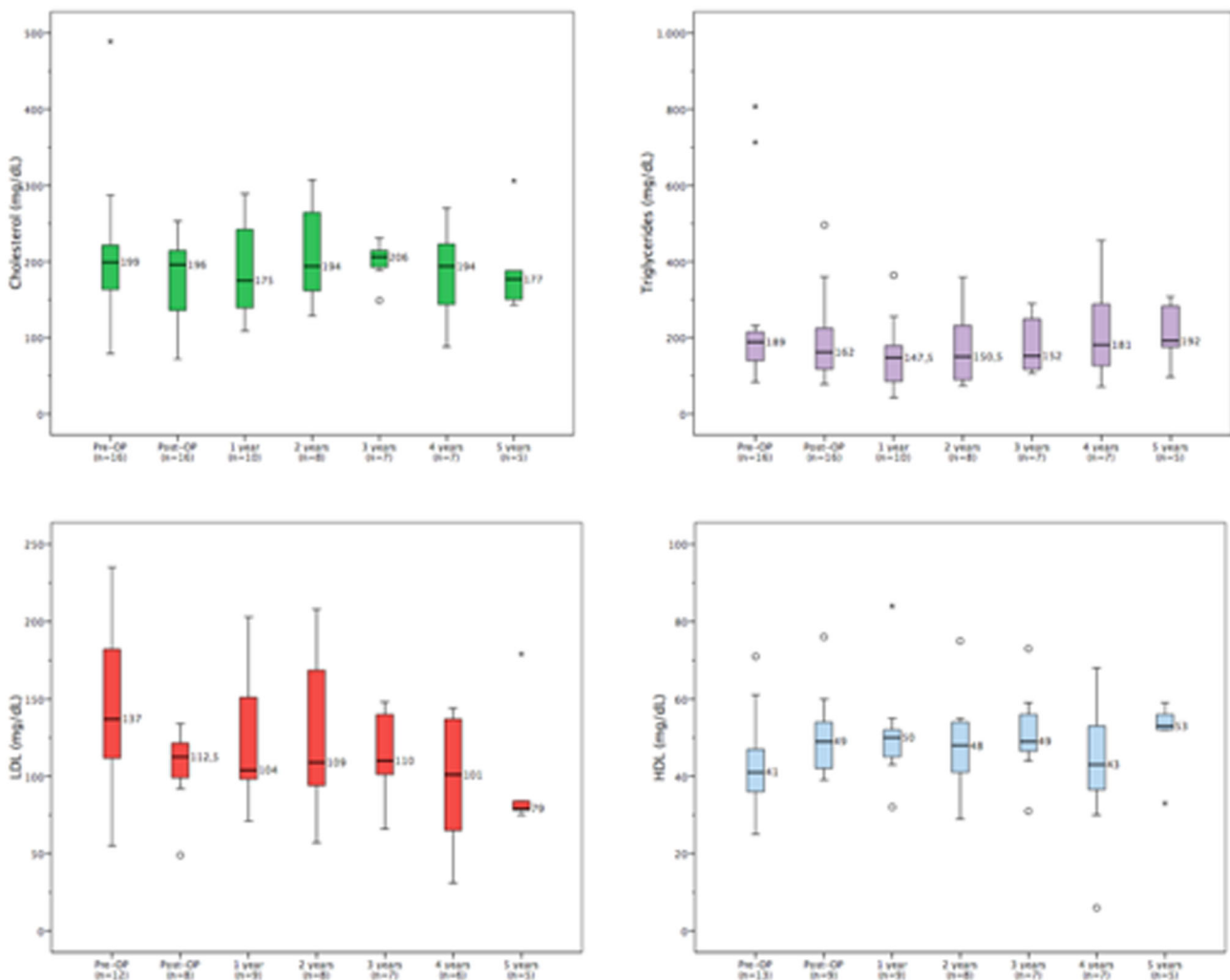


FIGURE 3 Pre- and postoperative plasma lipid levels. Values depicted are median (interquartile range)

TABLE 5 Pre- and postoperative lipid-lowering therapy

	Preoperative, n = 16	Discharge, n = 16	1 y, n = 12 ^a	2 y, n = 9 ^a	3 y, n = 8 ^a	4 y, n = 8 ^a	5 y, n = 6 ^a
Patients on statins, n (%)	10 (62.5)	13 (81.2)	10 (83.3)	7 (77.8)	6 (75.0)	6 (75.0)	4 (66.7)
Patients on other lipid-lowering medication, n (%)	1 (6.3)	1 (6.3)	2 (16.7)	2 (22.2)	2 (25.0)	2 (25.0)	2 (33.3)

^aNumber of patients for whom follow-up including current medications was available.

after 2012, and received both contemporary standard-of-care ART and cardiovascular pharmacotherapy, including antiplatelet therapy and statins. In addition, our study population has the longest follow-up published to date, with a median of 4.1 years and individual follow-up of up to 12 years after CABG.

Our study population of HIV+ CABG patients was male, with an average age of 56 years, and a high prevalence of cardiovascular risk factors, including dyslipidemia, diabetes, and smoking. This constitutes an elevated risk profile that has been described for HIV+ patients.² HIV+ patients present for revascularization approximately 10 years earlier than the average uninfected patient in Austria and Germany.^{12,13} This may reflect specific issues implicated in cardiovascular disease in HIV aside from traditional risk factors and include ART, chronic inflammation, and immune activation leading to earlier onset of complex CAD. Our study population also reflects the advancement of medical therapy available to HIV+ patients, both in terms of ART and treatment of cardiovascular disease. Our study patients were on average 10 years older at the time of surgery than those presented in the most recent studies,^{9,10} and had lived with HIV for approximately 17 years, compared with a previously described pre-CABG duration of HIV infection of 9 years.⁹

Studies on outcomes of cardiovascular surgery in HIV+ patients have shown that CABG appears safe and effective for PLHIV without advanced immunosuppression, with similar in-hospital mortality, but higher rates of longer-term MACE for HIV+ patients compared with uninfected patients.^{9,10} In our study population, in-hospital mortality was 0%; survival at 1 and 3 years was 100% and 90%, respectively. Of note, we did not observe any strokes in our patient population. We observed one procedural and one spontaneous MI in our patient population; both patients required PCI, placing the observed incidence of repeat revascularization of 13% in our cohort considerably lower than the 35% repeat revascularization rate that has been previously described in HIV+ patient populations.⁹

The increased life expectancy of PLHIV, together with outcomes after CABG comparable to uninfected patients, should lead health care providers to offer CABG as a revascularization method for complex CAD in HIV+ patients. It should also lead surgeons to offer the same strategy of revascularization to HIV+ patients as to uninfected patients. Arterial grafts have been demonstrated to show better patency rates than SVGs in CABG, and multiple observational studies have suggested that the use of multiple arterial grafts is associated with improved survival.¹⁴ Observations of a recent multicenter trial conducted primarily in Austria and Germany show that the contemporary approach to bypass grafting in patients less than 65 years of age is multiarterial grafting.¹⁵

The revascularization strategy applied in our cohort of HIV+ patients reflects this evolving approach, with 43.8% of HIV+ patients undergoing multiple arterial grafting. This may also contribute to the excellent survival and low incidence of reintervention seen in our cohort.

Among the most common adverse effects demonstrated for ART are plasma lipid alterations caused by their prolonged use.¹⁶ The impact of ART toxicity on cardiovascular disease risk among PLHIV may be attenuated by the use of antiplatelet agents and statins.¹⁷ Statin use in HIV is complicated by potential drug interactions, particularly when coprescribed with ritonavir-boosted protease inhibitors.¹⁸ Atorvastatin and rosuvastatin, the two highest-intensity statins, have modest interactions with ART and can be safely prescribed for PLHIV with lipid-lowering effects similar to those for uninfected patients.¹⁹ Addition of ezetimibe to rosuvastatin results in improved lipid indices with no adverse effects compared with dose-increase of rosuvastatin.²⁰ A recent study among 7686 HIV/hepatitis C virus-coinfected and 17 739 HIV -mono-infected persons showed that statin initiators had a lower risk of acute liver injury and death within 18 months compared with statin nonusers.²¹ Data on muscle toxicity in PLHIV is inconclusive to date, with some studies reporting increased muscle toxicity among HIV-infected adults,²² while more recent studies did not detect this association.²³ Taken together, the benefits of statin therapy in PLHIV appear to outweigh toxicities of statin therapy.¹⁸

An observational analysis from the SWEDEHEART registry²⁴ has recently shown that treatment with statins, as well as renin-angiotensin-aldosterone system inhibitors and antiplatelet medication, were individually associated with lower mortality risk after CABG. In our study cohort, 13 of 16 patients were discharged on statins, one patient was discharged on bezafibrate, and two patients were discharged without lipid-lowering therapy. Even though LDL-C levels decreased within the first postoperative year, LDL-C levels remained considerably higher than the recommended threshold of 70 mg/dL.^{25,26} Similarly, HIV-infected adults were less likely to achieve LDL targets among 543 HIV-infected men in the Multicenter AIDS Cohort Study despite statin prescription.^{18,27} Aggressive secondary prevention measures are indicated for HIV+ patients undergoing CABG and may serve to further improve longer-term postoperative outcomes.

5 | LIMITATIONS

The primary limitations of this analysis are its retrospective nature and small size of the study cohort. Results are observational only and

no direct comparison to uninfected patients undergoing CABG was conducted.

6 | CONCLUSION

For HIV+ patients with CAD requiring revascularization, CABG surgery is safe and effective with excellent survival and low rates of major adverse cardiac events.

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