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Systematic Review

Impact of human immunodeficiency virus (HIV) infection in patients undergoing cardiac surgery: a systematic review

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The clinical status and prognosis of patients with human immunodeficiency virus (HIV) infection has dramatically changed in the recent years. Cardiovascular diseases can be related to combined antiretroviral therapy and to the aging of HIV-positive population, resulting in significant mortality and morbidity in those patients. It is crucial to understand whether the HIV-status affects the indications and outcomes of cardiac surgery. A literature search was conducted through electronic databases up to 15 May 2020 following PRISMA guidelines. Variables (i.e. patients characteristics) and endpoints (i.e. postoperative complications) were considered as defined in the original publications. All paper describing post-operative outcomes after cardiac surgery were included. Methodological quality of all included studies was assessed using the Newcastle-Ottawa Scale, the Cochrane Risk of Bias tool and the US Preventive Services Task Force grade. A total of eight studies were included in this systematic review; five studies discussed the outcomes of patients with HIV infection, while three studies compared results based on HIV status. All evidences derived from retrospective observational studies with high variability and poor-to-fair quality. Most patients underwent surgical myocardial revascularization. HIV status is not associated with differences in operative mortality (P = 0.32), postoperative mediastinitis (P = 0.30) or pulmonary infective complications (P = 0.67). Cardiac surgery can be considered safe in HIV-positive patients, and HIV status alone should not be considered as a contraindication for cardiac surgery and should not be considered a risk factor for postoperative mortality or perioperative complications. Further studies are required for patients with AIDS.

Keywords

HIV; cardiac surgery; coronary artery bypass; valve replacement; heart surgery

1. Introduction

The availability and use of combined anti-retroviral therapy (CART) have dramatically improved long-term outcomes in HIV-positive patients and transformed HIV infection into a chronic disease (Erqou et al., 2020, 2019; Feinstein et al., 2016; Siegfried et al., 2010). However, the prolonged life expectancy with good quality of life is associated with increasing prevalence of cardiovascular disease, which remains responsible for a significant burden of complications, hospitalizations and adverse events (Deeks et al., 2015; Manmathan et al., 2020; Yanagawa et al., 2019). Compared with general population, patients with HIV have a 4.5-fold increased risk of sudden cardiac death after adjustment for age and gender (Tseng et al., 2012). Besides a higher incidence of traditional risk factors in patients with HIV (D'Ascenzo et al., 2012; Rethy et al., 2020; Sinha and Feinstein, 2020, 2019), infection carries an additional 1.5- to 2-fold increased independent risk of acute myocardial infarction (Freiberg et al., 2013) or coronary artery disease (Bernelli et al., 2020; Longenecker et al., 2020; Peck and Kingery, 2020). The mechanisms of HIV-related coronary artery disease have been investigated in recent years, and activation of toll-like receptor 2 and formation of neutrophil extracellular traps result in chronic inflammation and endothelial dysfunction (Pallikkuth et al., 2018; Sinha and Feinstein, 2020, 2019; Stein et al., 2014; Subramanian et al., 2012; Titanji et al., 2020). This results in a more aggressive and early-onset of the disease (Bernelli et al., 2020; Nou et al., 2016; Rethy et al., 2020; Titanji et al., 2020). HIV-accelerated coronary artery disease, non-ischemic heart disease, opportunistic infections and drug-related myocardial damage warrant special attention in this population for the near future (Bernelli et al., 2020; Erqou et al., 2020, 2019; Manga et al., 2017; Manmathan et al., 2020; Vachiat et al., 2017; Wong et al., 2020; Yanagawa et al., 2019). Treatment of coronary artery disease, valvular disease of pathologies of the ascending aorta might require cardiac surgery procedures and therefore it is crucial to understand whether the HIV-status affects the indications and outcomes of cardiac surgery. This systematic review aims to summarize the current literature about cardiac surgical management in patients with HIV.

2. Methods

We followed PRISMA guidelines for performing and reporting the present systematic review (**Supplementary Table I**). A literature search was conducted through PubMed, Embase, EBSCO, Cochrane database of systematic reviews, and Web of Science from their inception up to 15 May 2020 using the following search keywords (and their MeSH terms) in various combinations: "coronary artery bypass graft", "myocardial revascularize-

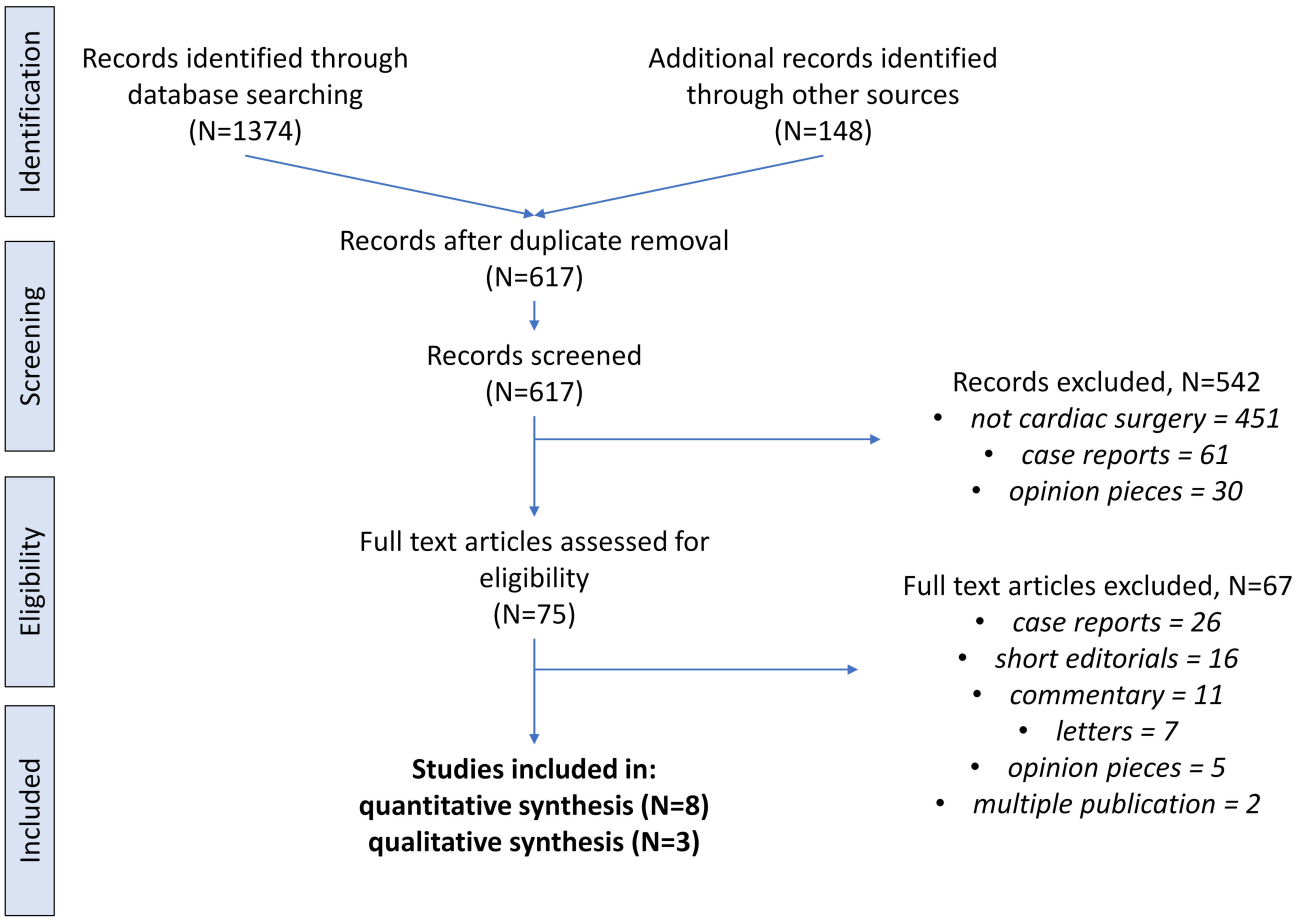


Fig. 1. PRISMA flow diagram. The flow diagram depicts the flow of information through the different phases of a systematic review. Studies included in quantitative synthesis (meta-analysis): 8. Studies included in qualitative synthesis: 3.

tion", "cardiac surgery", "extracorporeal membrane oxygenation", "transplantation", "cardiac", "heart", "valve replacement", "HIV", "AIDS". We also reviewed references of all articles from the literature. We included all papers describing post-operative outcomes after any procedure of cardiac surgery (i.e. myocardial revascularization, valve surgery,…). All investigators reviewed the studies to determine their eligibility and independently extracted all the relevant outcomes of interest. Data from all eligible studies using a standardized file, focusing on study design, study size, type of intervention and outcomes were retrieved only from the articles, and no attempt was made to get missing data from the authors. Any disagreement was solved by consensus. Inclusion and exclusion criteria were summarized according to the PICOS (population, intervention, comparator, outcomes, and study design) approach (Table 1). Year of publication, study design, sample size, number of patients in each treatment group, measured outcomes, baseline patient characteristics and outcomes were extracted. Variables (i.e. patients characteristics) and endpoints (i.e. postoperative complications) were considered as defined in the original publications. Methodological quality of all included studies was assessed using the Newcastle-Ottawa Scale, the Cochrane Risk of Bias tool and the US Preventive Services Task Force grade.

3. Results

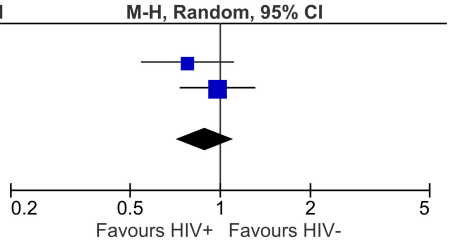
Literature search yielded a total of 1374 records, and 8 studies (Boccara et al., 2008; Brogan et al., 2020; Chong et al., 2003; Koval et al., 2019; Mestres, 2003; Polanco et al., 2014; Robich et al., 2014; Trachiotis et al., 2003) were included in the systematic review (PRISMA flow diagram, Fig. 1). Quality assessment is shown in Table 2, and study characteristics and collected outcomes are summarized in Table 3, Table 4 and Table 5.

A total of five studies discussed the outcomes of patients with HIV infection, as a single cohort of patients (Brogan et al., 2020; Chong et al., 2003; Koval et al., 2019; Mestres, 2003; Trachiotis et al., 2003), while three studies compared results from HIV-positive and HIV-negative patients (Boccara et al., 2008; Polanco et al., 2014; Robich et al., 2014). All evidences derived from retrospective observational studies with high variability and poor-to-fair quality (Table 2), as HIV-status cannot be considered a randomization factor for ethical concerns. Robich et al. (2014) reported the outcomes before and after propensity score matching, although long-term results were not investigated. In this study, propensity scores, or the conditional probability of being HIV-positive, were estimated using a multivariable logistic regression model in which the presence of HIV was the dependent variable; patient demographics, payer status, comorbidities, hospital characteristics, and procedure type were the independent variables. The aim

Mortality

Study or Subgroup	HIV+ Events	HIV+ Total	HIV- Events	HIV- Total	Weight	Odds Ratio M-H, Random, 95% CI
Boccara et al. 2008	0	27	0	54		Not estimable
Polanco et al. 2014	32	1239	26720	809701	39.8%	0.78 [0.55, 1.10]
Robich et al. 2014 (PSM)	100	1633	102	1633	60.2%	0.98 [0.74, 1.30]
Total (95% CI)		**2899**		**811388**	**100.0%**	**0.89 [0.72, 1.12]**
Total events	132		26822			

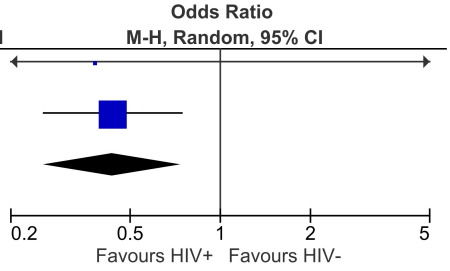
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.32); I² = 1%
Test for overall effect: Z = 1.00 (P = 0.32)



Stroke

Study or Subgroup	HIV+ Events	HIV+ Total	HIV- Events	HIV- Total	Weight	Odds Ratio M-H, Random, 95% CI
Boccara et al. 2008	0	27	2	54	2.9%	0.38 [0.02, 8.24]
Polanco et al. 2014	0	1239	0	809701		Not estimable
Robich et al. 2014 (PSM)	20	1633	45	1633	97.1%	0.44 [0.26, 0.74]
Total (95% CI)		**1660**		**1687**	**100.0%**	**0.44 [0.26, 0.74]**
Total events	20		47			

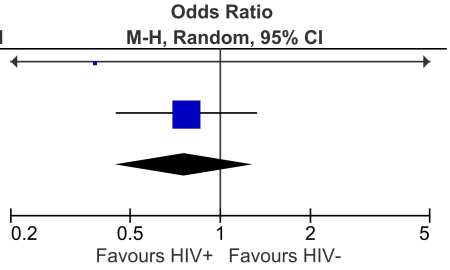
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)



Mediastinitis

Study or Subgroup	HIV+ Events	HIV+ Total	HIV- Events	HIV- Total	Weight	Odds Ratio M-H, Random, 95% CI
Boccara et al. 2008	0	27	2	54	3.0%	0.38 [0.02, 8.24]
Polanco et al. 2014	0	1239	0	809701		Not estimable
Robich et al. 2014 (PSM)	24	1633	31	1633	97.0%	0.77 [0.45, 1.32]
Total (95% CI)		**1660**		**1687**	**100.0%**	**0.75 [0.44, 1.28]**
Total events	24		33			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)



Pulmonary complications

Study or Subgroup	HIV+ Events	HIV+ Total	HIV- Events	HIV- Total	Weight	Odds Ratio M-H, Random, 95% CI
Boccara et al. 2008	11	27	27	54	18.8%	0.69 [0.27, 1.75]
Polanco et al. 2014	0	1239	0	809701		Not estimable
Robich et al. 2014 (PSM)	156	1633	129	1633	81.2%	1.23 [0.96, 1.57]
Total (95% CI)		**1660**		**1687**	**100.0%**	**1.10 [0.71, 1.72]**
Total events	167		156			

Heterogeneity: Tau² = 0.05; Chi² = 1.40, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 0.43 (P = 0.67)

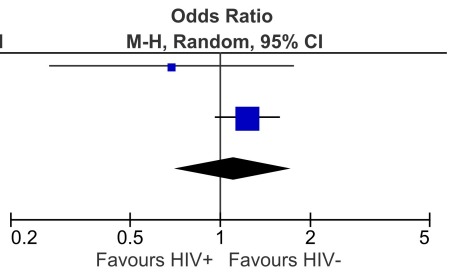


Fig. 2. Pooled results from the studies available in the literature comparing outcome of HIV-positive and HIV-negative patients. Analysis was performed comparing the number of events as described in original publications. Mortality, stroke, mediastinitis and pulmonary complications were evaluated as endpoints. A random-effect model was used with Mantel-Haenszel method. Effects were evaluated as odds ratios (OR).

of this propensity score was to balance covariates to assess outcomes without the influence from known factors. Most patients underwent revascularization with CABG, and other evaluated procedures were aortic valve replacement and mitral valve surgery (Table 3). No data about procedures on the ascending aorta are available, as well as cardiac tumours, tricuspid valve disease and combined procedures.

Table 1. PICOS criteria for inclusion and exclusion of studies.

Parameter	Inclusion criteria	Exclusion criteria
Patients	Adult patients ($\geq$ 18 years)	-
Intervention	Any procedure of cardiac surgery (myocardial revascularization, valve surgery, surgery of the thoracic aorta, …)	Percutaneous procedures
Comparator	HIV status	-
Outcomes	Primary: mortality Secondary: postoperative complications Secondary: long-term complications	-
Study design	Clinical randomised trials Controlled before-and-after studies Prospective and retrospective cohort studies Cross-sectional studies Case-control studies Meta-analyses	Repeat publications of the same dataset Conference abstracts Non-systematic review articles Review / editorials / opinion pieces Books or grey literature Case reports ($\leq$ 10 patients)

Table 2. Quality assessment of the included studies.

Study	Newcastle-Ottawa Scale			Cochrane Risk of Bias Analysis					US-PSTF grade
	Selection	Comparability	Outcome	Selection	Performance	Detection	Attrition	Reporting	
(Boccara et al., 2008)	**	**	**	High	High	High	Low	Low	Poor
(Brogan et al., 2020)	***	**	**	Low	High	High	Low	Low	Fair
(Chong et al., 2003)	**	**	**	High	High	High	Low	Low	Poor
(Koval et al., 2019)	**	**	**	High	High	High	Low	Low	Poor
(Mestres, 2003)	**	**	**	High	High	High	Low	Low	Poor
(Polanco et al., 2014)	***	***	**	Low	High	High	Low	Low	Fair
(Robich et al., 2014)	***	***	**	Low	High	High	Low	Low	Fair
(Trachiotis et al., 2003)	**	**	**	High	High	High	Low	Low	Poor

3.1 Pooled analysis

Pooled results from the 3 studies available in the literature (Boccara et al., 2008; Polanco et al., 2014; Robich et al., 2014) comparing outcome of HIV-positive and HIV-negative patients are shown in Fig. 2. Operative mortality in patients with HIV was similar to non-HIV patients (odds ratio 0.89, 95% confidence interval 0.72-1.12, $P = 0.32$). Postoperative mediastinitis and pulmonary infective complications also appeared to be independent from the HIV status ($P = 0.30$ and $P = 0.67$, respectively). Notably, stroke risk appeared to be reduced among HIV-positive patients (odds ratio 0.44, 95% confidence interval 0.26-0.74, $P = 0.002$) (Robich et al., 2014; Sullivan et al., 2015).

4. Discussion

Cardiac surgery is generally associated with a strong postoperative inflammatory reaction, related to cardiopulmonary bypass, aortic manipulation and general anaesthesia (Corral-Velez et al., 2015; Giacinto et al., 2019; Squiccimarro et al., 2019). Preliminary reports indicated an increased risk of weakening the immune system in HIV-positive patients (Yanagawa et al., 2019), although this was not subsequently documented by the clinical experience.

4.1 Cardiac surgery is safe in HIV patients

Major studies in HIV patients (Polanco et al., 2014; Robich et al., 2014) report a 2.5-fold increase in the frequency of cardiac surgery among HIV-positive patients. However, HIV status was not an independent predictor of perioperative mortality following cardiac surgery, as shown in our pooled analysis (odds ratio 0.89, 95% confidence interval 0.72-1.12). This reflects the observations of Polanco et al(Polanco et al., 2014) (odds ratio 0.88, 95% confidence interval 0.6-1.2) and Robich et al. (2014) odds ratio 0.8, 95% confidence interval 0.74-1.30). Independent predictors of mortality were age, renal failure and non-CABG procedure, similarly to HIV-negative population (Yanagawa et al., 2019). HIV status alone should not be considered as a contraindication for cardiac surgery and should not be considered a risk factor for postoperative mortality or perioperative complications. On the contrary, the observed postoperative stroke reduction in HIV-positive patients could be secondary to differences in immunomodulation, decreased inflammatory or atherosclerotic burden, younger age, reduced incidence of postoperative atrial fibrillation or reduced peripheral vascular disease (Robich et al., 2014; Sullivan et al., 2015; Yanagawa et al., 2019), but conclusive data are lacking and details about postoperative stroke are not available from Polanco et al., to support those data (Polanco et al., 2014). Similarly, it is possible to reliably speculate that HIV status does not impair long-term outcomes, but data are needed to support this conclusion.

Table 3. Details of the included studies.

Study	Patients	Design	Procedures	Age (years)
(Boccara et al., 2008)	27 HIV+ 54 HIV-	retrospective	100% on-pump CABG	47.3 ± 11.2 vs 50.4±5.4
(Brogan et al., 2020)	126 HIV+	retrospective	100% extracorporeal membrane oxygenation 34 veno-arterial 88 veno-venous	40
(Chong et al., 2003)	22 HIV+	retrospective	12 AVS 7 MVS 3 AVS+MVS	37.6
(Koval et al., 2019)	21 HIV+	retrospective	100% heart transplantation	48
(Mestres, 2003)	31 HIV+	retrospective	21 endocarditis 5 CABG 5 non-endocarditis	33.1
(Polanco et al., 2014)	1239 HIV+ 809701 HIV-	retrospective	63.7% vs 73.2% CABG 36.3% vs 26.8% valve 49.0% vs 57.9% AVS 35.7% vs 30.0% MVS	51.9 ± 9.8 vs 65.3 ± 12.4
(Robich et al., 2014), retrospective cohort	9771 HIV+ 5621817 HIV-	retrospective	16% vs 10% valve 38% vs 59% CABG	48.9 ± 0.25 vs 65.6 ± 0.05
(Robich et al., 2014), PSM cohort	1633 HIV+ 1633 HIV-	PSM	NA	NA
(Trachiotis et al., 2003)	37 HIV+	retrospective	27 CABG 10 valve surgeries	41

AVS: aortic valve surgery; CABG: coronary artery bypass graft surgery; LVEF: left ventricular ejection fraction; MVS: mitral valve surgery; NA: not available; PSM: propensity score-matched

4.2 Surgical myocardial revascularization

As for patients with coronary artery disease, the indication between percutaneous coronary intervention (PCI) or CABG is based on patient's conditions, comorbidities and coronary anatomy. For CABG and PCI, HIV-positive patients exerted similar results to those observed in the general population (Badr et al., 2015; Bundhun et al., 2017; Moran et al., 2020). HIV-status is known to be accompanied by a pro-inflammatory status with increased platelet reactivity (Hauguel-Moreau et al., 2017; Rethy et al., 2020), but this does not seem to directly translate into clinically observable adverse events. A recent metanalysis of 821 HIV-positive and 1147 HIV-negative patients undergoing PCI demonstrated that HIV-positive patients have similar mortality (odds ratio 1.16, 95% confidence interval 0.50-2.68, P = 0.74), no significant increase in recurrent myocardial infarction (odds ratio 1.32, 95% confidence interval 0.88-2.12, P = 0.17), target vessel revascularization (odds ratio 1.22, 95% confidence interval 0.72-2.06, P = 0.46) or major adverse events (odds ratio 1.47, 95% confidence interval 0.44-4.89,P = 0.53) (Bundhun et al., 2017). Those results seem to corroborate the outcomes observed in the CABG scenario. Therefore, CABG can be performed safely with good outcomes in HIV-positive patients.

4.3 Surgical valve replacement

As for patients with valvular heart disease, data are still lacking to draw definitive conclusions, but supporting evidences support that HIV-positive patients should be equal candidates for cardiac surgery in Heart Team discussion. The choice of valve prosthesis can be performed similarly to the overall population, weighting the life expectancy, patient's preference and risk of anticoagulation (Baumgartner et al., 2017; Nishimura et al., 2017). Patients ineligible for surgical aortic valve replacement could be evaluated for transcatheter approaches, regardless of their HIV status.

4.4 Surgery for heart failure

As for patients with advanced heart failure requiring cardiac surgery, besides small case series of short-term success with left ventricular assist devices or heart transplantation (Brozzi et al., 2020; Yanagawa et al., 2019), recent data from the ELSO Registry confirmed that survival in HIV-positive patients is similar to the general population in case of cardiac failure requiring veno-arterial extracorporeal membrane oxygenation (Brogan et al., 2020). Similarly, HIV-positive patients have similar survival rates to HIV-negative patients after heart transplantation (Koval et al., 2019). Therefore, recent studies confirm that HIV status does not modify outcomes of veno-arterial extracorporeal membrane oxygenation or heart transplantation compared with HIV-negative patients (Brogan et al., 2020; Koval et al., 2019). A recent analysis from the Veterans Health Affairs confirmed that HIV-positive patients have increased presence of cardiovascular risk factors and their heart failure results in a higher risk of mortality and hospitalization (Erqou et al., 2020). Worse outcomes were reported in case of lower ejection fraction, lower $CD4^+$ count ($<$ 200 cells/mL) or higher HIV viral load ($>$75 copies/muL) (Erqou et al., 2020), and therefore those patients should be adequately evaluated for adequate treatment in case of mechanical circulatory support.

Table 4. Early outcomes.

Study	In-hospital mortality	Myocardial infarction	Stroke	Pulmonary infection	Reoperation for bleeding	Mediastinitis
(Boccara et al., 2008)	0 vs 0	1 vs 0	0 vs 2	11 vs 27	4 vs 1	0 vs 2
(Brogan et al., 2020)	81	4	8	NA	NA	NA
(Chong et al., 2003)	0	NA	1	NA	0	0
(Koval et al., 2019)	0	NA	NA	NA	NA	NA
(Mestres, 2003)	7	NA	1	2	2	0
(Polanco et al., 2014)	32 vs 26720 (CABG: 1.5% vs 2.4%)	NA	NA	NA	NA	NA
(Robich et al., 2014), retrospective cohort	704 vs 242404	NA	113 vs 128967	1091 vs 296141	NA	125 vs 68094
(Robich et al., 2014), PSM cohort	100 vs 102	NA	20 vs 45	156 vs 129	NA	24 vs 31
(Trachiotis et al., 2003)	1	0	0	2	2	1

Results are presented as "events in HIV-positive patients" vs "events in HIV-negative patients". NA: not available.

Table 5. Long term outcomes.

Study	Follow up	Mortality	Cardiac mortality	MACE definition	MACE events
(Boccara et al., 2008)	median 41 months (range 34-60)	2 vs 1	0 vs 0	death for cardiac cause, non-fatal MI and repeated revascularization (including PCI and re-CABG)	11 vs 10
(Brogan et al., 2020)	NA	NA	NA	NA	NA
(Chong et al., 2003)	mean 5 years	10	NA	NA	NA
(Koval et al., 2019)	median 35 months (range 4-106)	5	NA	described as single outcomes	infections at 1 year: 8 rejection at 1 year: 14
(Mestres, 2003)	mean 3.4 years	9	NA	NA	NA
(Polanco et al., 2014)	NA	NA	NA	NA	NA
(Robich et al., 2014), retrospective cohort	NA	NA	NA	NA	NA
(Robich et al., 2014), PSM cohort	NA	NA	NA	NA	NA
(Trachiotis et al., 2003)	3 years	0	0	angina, death, myocardial infarction, repeat revascularization, and congestive heart failure	freedom from MACE: 81%

Results are presented as "events in HIV-positive patients" vs "events in HIV-negative patients". CABG: coronary artery bypass graft surgery. MACE: major adverse cardiac events. NA: not applicable. PCI: percutaneous coronary intervention.

4.5 Patients with AIDS

Patients with AIDS (HIV-positive, low $CD4^+$ count, opportunistic infections, secondary cancers) have limited long-term survival and literature lacks reliable data on cardiac surgery procedures. Patients with AIDS are generally considered candidate for surgery for life-saving procedures only (i.e. surgery for aortic dissection) and are generally excluded from clinical trials (Clement et al., 2018). Also, there is no consensus about the $CD4^+$ count that is considered safe.

4.6 Limitations

Many studies did not report long-term outcomes which could not be analytically evaluated; moreover, pooled analysis could not be comprehensive due to the single-arm nature of some studies. Myocarditis either due to viral or toxoplasma pathogenesis seem not to be adequately investigated in previous studies and might represent a promising field of research for the future.

5. Conclusions

Prognosis of HIV-positive patients has dramatically improved in recent years, and patients can manifest heart disease requiring cardiac surgery. HIV status should be neither considered a contraindication for cardiac surgery nor a risk factor for postoperative complications. Therefore, HIV-positive patients should be considered normal candidates for cardiac surgery. Certainly, long-term outcomes and specific data for AIDS patients represent an important area of uncertainty, warranting further future investigations.

Authors' contributions

Conception of the study (all authors), acquisition of data (all authors), interpretation of data (all authors), drafting the article (CD), revision of the article (MC), final approval of the manuscript (all authors).

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Conflict of interest

All authors declare no conflicts of interests.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm.2020.03.104.

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