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AIDS Rev. 2020;22:183-194

Course of Disease and Clinical Outcome of Infective Endocarditis in HIV-infected Individuals: A Systematic Review and Meta-analysis

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Abstract

Infective endocarditis (IE) causes substantial morbidity and mortality if untreated. The clinical course of IE might be different in HIV-positive patients as a result of immune dysfunction. This systematic review investigates the clinical course of IE in HIV-positive compared to HIV-negative patients. A systematic search was performed in PubMed, EMBASE, and Cochrane Library and registered in PROSPERO (CRD42016048649). All articles from 1996 and onward addressing the clinical outcome of HIV-positive adults suffering from IE were reviewed and included based on predefined inclusion and exclusion criteria. A meta-analysis was performed for the outcome mortality. Twenty-three articles were included of which eight included HIV-positive patients only, and 15 compared HIV-positive to HIV-negative patients. Two studies included patients on antiretroviral therapy (ART). HIV and intravenous drug use (IVDU) were closely related. Mortality was higher in HIV-positive patients with a CD4 count below 200 cells/μl than in HIV-positive patients with a higher CD4 count, while mortality was similar for HIV-positive compared to HIV-negative patients (risk ratio = 0.86 [95% confidence interval: 0.53-1.40]). No difference was found in length of hospital stay or rehospitalization. Clinical outcomes were strongly related to the right- or left-sided endocarditis. The clinical course of IE is not different for patients with and without HIV. Clinical outcomes were mainly associated with other factors, such as IVDU and side of cardiac involvement, rather than HIV status. **(AIDS Rev. 2020;22:183-194)**

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Key words

Infective Endocarditis. HIV. Clinical Outcome. HAART. Mortality.

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Received in original form: 27/09/2019
Accepted in final form: 01/09/2020
DOI: 10.24875/AIDSRev.19000117

Introduction

Infective endocarditis (IE) is a worldwide disease that results in substantial morbidity and mortality if untreated. The overall incidence of IE varies between 1.5 and 11.6 cases/100.000 individuals per year and is more common in men than in women[1,2]. Although diagnosis and treatment of IE has improved, the incidence of IE hardly changed over the years and the mortality rate remains around 20% within the first 30 days[3,4]. Eventually, almost one in four patients does not survive an IE infection[1]. The stagnating decline in incidence and mortality may be attributed to a shift in epidemiological features and risk factors for IE[3,5]. At present, risk factors are changing due to an increasing number of adults with congenital heart disease, patients with a need for prolonged vascular access (such as hemodialysis), and patients with implanted intracardiac devices and/or prosthetic material[3]. Furthermore, health care-associated bacteremia, increased age, poor immune function, and intravenous drug use (IVDU) are risk factorsfor IE[2-6].

A main contributor to poor immune function is infection with HIV[7]. Research has shown that HIV-positive patients with <200 CD4+ cells/μl have a higher mortality rate on IE infection than the population with a normal immune system[7-10]. Among HIV positives, IE occurs almost exclusively in IVDUs[7,10,11]. The occurrence of IE seems to cluster in people with IVDU as this group has a 100-fold increased risk of developing IE compared to the general population[12,13].

Since the introduction of combination antiretroviral therapy (ART) in 1996, the incidence of bacteremia in HIV positives decreased, as well as morbidity, mortality, and hospitalization associated with HIV infection[14-17]. However, a study in the early ART era did not find a decrease in IE incidence among HIV positives[18]. Furthermore, access to ART is not equally distributed among people living with HIV and access to ART is low in HIV-positive IVDUs[19,20].

Based on the immune dysfunction in HIV infection, an altered clinical course of IE in HIV-positive compared to HIV-negative patients can be expected. The aim of this systematic review is to investigate the course of disease and clinical outcome of IE in HIV-positive patients compared to HIV-negative patients in the current ART era.

Methods

Search strategy

The systematic review was registered in the PROSPERO database (CRD42016048649) and published on March 7, 2017[21]. A search was performed in PubMed (MEDLINE restriction), EMBASE, and Cochrane Library covering all evidence from 1996 onward. Synonyms and terms related to endocarditis, HIV infection, and clinical outcome were used in the search strategy (Table 1). Search terms were limited to title and abstract. Duplicates were removed manually. The search was performed in two stages. The first search was performed by CA and included literature from 1996 up to September 27, 2016. A second search was performed by JB in 2019 and included literature between September 28, 2016, and March 21, 2019.

Study selection

Selection was done in three steps and performed by three independent authors (Fig. 1). In the first step, all records were screened on relevancy based on title and abstract by CA (until 2016) and JB (2016 onward). Inclusion criteria for screening of title and abstract were original research, IE, HIV-positive patients aged 18 years and above, and ≥3 cases. Records describing animal studies, humans younger than 18 years old, and case series <3 cases were excluded from the study. Furthermore, studies published before 1996, reviews, non-English studies, studies without HIV positives, and studies not analyzing data based on HIV status were excluded from the study. Studies that only described HIV positives and studies comparing HIV positives with HIV negatives were included in the study.

In the second step, full texts of all selected abstracts were read to assess eligibility by two authors independently. Authors CA and AV assessed all articles up to publication date September 27, 2016 and authors JB and AV assessed all articles with a publication date between September 28, 2016, and March 21, 2019. The following exclusion criteria were used: studies not describing a relation between HIV status and clinical outcome, describing less than three cases, no description of clinical outcome, outcome not reported for HIV status, duplicates, reviews, language other than English, and conference abstracts. Discrepancies were discussed in a consensus meeting between authors (CA and AV or JB and AV), and agreement could be

Table 1. Search strategy

Search structure		Search terms		PubMed (Medline)	EMBASE	Cochrane
Domain #1	People with endocarditis	Endocarditis, endocarditides, valve inflammation, mitral inflammation, tricuspid inflammation, carditis, heart infection, heart inflammation, valve infection, tricuspid infection, mitral infection, cardiac inflammation, cardiac infection, endocardium infection, endocardium inflammation, intraventricular septum infection, chordae tendineae infection, aortic infection, aortic inflammation				
		Endocarditis	MeSH			
AND				19.870	29.042	3.988
Determinant #2	HIV	HIV, Human immunodeficiency virus, AIDS, acquired immunodeficiency syndrome				
		HIV	MeSH			
AND				268.930	380.887	297.444
Outcome #3	Clinical outcome	Clinical outcome, surgery, hospital stay, hospitalization, hospitalization, rehospitalization, rehospitalization, recurrence, recurrent, morbidity				
		Treatment outcome	MeSH			
AND				1.893.302	2.232.889	21.266
Final number of studies combining #1 AND #2 AND #3				176	247	40

reached in all cases. In the last step, reviewer (JB) screened the references of included articles for additional articles. Potential articles were screened through the process described above.

Validity and data extraction

On inclusion, the following data were extracted: year of publication, study design, duration of follow-up, number of patients, country, clinical setting, age, gender, HIV status, IVDU, (nadir) CD4+ cell count/μl, average CD4+ cell count/μl, viral load, ART use, type of ART, duration of HIV, duration of ART use, and endocarditis diagnosis and clinical outcome.

Selected articles were critically appraised by two authors independently using the research framework Quality in Prognostic Studies tool made by the Prognosis and Methods Group of Cochrane[22]. Authors CA and AV assessed included articles until 2016 and JB and AV from 2016 onward. Articles were appraised on the risk of selection – attrition – and measurement bias, and on the risk of bias related to the outcome measurement, risk of bias due to confounding, and risk of bias related to the statistical analysis and presentation of results. These domains were graded as having low, moderate, or high risk of bias.

Definitions

Study design

Studies were defined as “Cohort,” “Case series,” or “Case control.” Studies defined as cohort included a group of endocarditis patients while comparing patients

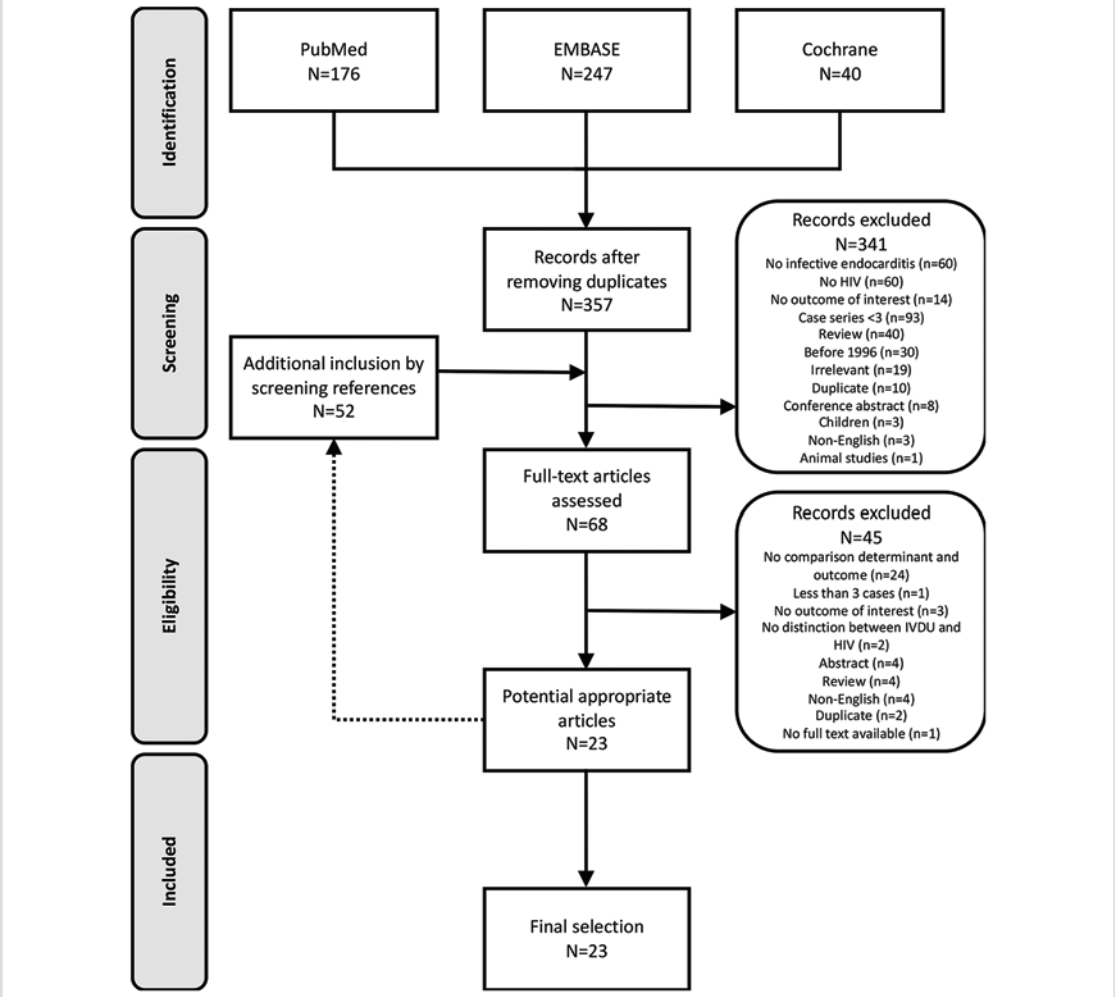

Figure 1. *Flowchart inclusion. Solid lines present a normal flow of study inclusion. Dashed line presents cross-referencing.*

with and without HIV. Studies defined as case series included only HIV-positive patients with IE. Case–control studies compared the outcome of HIV patients with or without endocarditis.

ART

Study populations were considered on ART if at least 25% of the study population received ART.

Clinical outcome

The following outcomes were assessed: mortality, number of patients receiving elective or urgent surgery, recurrent IE in patients either by the same or different bacterial species, length of hospital stay, rehospitalization, and side of endocarditis (left or right sided). Clinical outcome also comprised morbidity and this included the percentage of people with systemic emboli (pulmonary, central nervous system [CNS] or stroke, spleen, myocardial, bone, retinal, and undefined), cardiac complications, such as congestive heart failure and intracardiac abscess, and renal failure.

Analysis

For most of the outcomes, results are descriptive and grouped by HIV status and CD4+ cell count.

A quantitative meta-analysis was performed for studies describing mortality. We used Review Manager

V.5.3 (The Cochrane Collaboration, Oxford, UK) to aggregate data[23]. A random effect inverse variance analysis of proportions (P) was performed in studies with only HIV-positive patients. Heterogeneity was assessed using the I^2 statistic. A random effect generic inverse variance analysis of risk ratio (RR) was performed in studies comparing HIV-positive and -negative patients. A logit transformation of proportions was applied to correct for studies with zero or 100% mortality in both analyses. The pooled effect estimates are presented as P or RR with a 95% confidence interval (CI). For the other outcomes, data did not allow to perform a meta-analysis (either too heterogeneous or not enough data available). All two-side p = 0.05 or lower were considered statistically significant.

Results

Yield of search strategy

In total, our search strategy identified 357 articles (Fig. 1). After screening titles and abstracts, 55 articles remained for full-text screening. Of these articles, 36 did not meet our inclusion criteria and were excluded. Following screening of the references of the remaining 19 studies, 11 articles were identified, and full text assessed. Most of these articles were missed in our initial search as clinical outcome was not described in the abstract. Of these articles, four met our inclusion criteria resulting in a total of 23 articles, which are summarized in Table 2[7-9,11,24-42].

Baseline characteristics

The vast majority of studies were retrospective, only 6 out of 23 studies (26%) were prospective. All studies were performed with data from a hospital setting. Eight studies were performed in Spain, four in Italy, one in Germany, six in the USA, three in South Africa, and one internationally. The number of cases per study ranged from 3 to almost 400.000 participants. The mean age of the patients was between 25.8 and 59.7 years, and the majority of patients were male (>50% in all studies). HIV prevalence ranged between 1.8 and 76.3%, and eight studies included HIV-positive patients only. Two out of 23 studies described the use of ART. The frequency of IVDU ranged from 7.4% to 95.3%. Eight studies used IVDU as inclusion criteria (100% IVDU) and one study used IVDU as exclusion criteria (0% IVDU).

Critical appraisal

Consensus regarding critical appraisal of the articles was reached for all studies (Supplementary 1). The risk of bias is presented in figure 2. Risk of bias was in general low for at least 52% of the studies, except for the domain confounding. Most studies did not define the confounding factors or did not appropriately account for confounding in either study design or study analysis.

Outcome in IE patients

The most frequently described outcome was mortality, followed by the number of patients receiving surgery, the occurrence of emboli, development of a new episode of endocarditis, and length of hospital stay in days (Supplementary 2).

Mortality was described in 17 (74%) studies (Table 3) including eight studies with HIV-positive participants only[7,11,24,28,34,36,38,42]. Mortality in these studies ranged from 0% to 52%[7,11,24,28,34,36,38,42]. A proportional meta-analysis of mortality showed a mortality rate of 30% among HIV-positive IE patients (95% CI: 19-46%). Three studies evaluated mortality rates in HIV-positive patients based on CD4+ cell count. All studies showed a significant higher mortality in patients with a CD4+ cell count below 200 cells/μl[7-9]. One study evaluated 1 year outcomes of IE in HIV-infected patients on ART and reported that ART use was not related to mortality[34]. Other factors related to mortality in HIV-positive patients mentioned in the studies were (1) continued IVDU and high-risk behavior that lead to HIV infection, (2) poor general condition, (3) high number of comorbidities and coinfections, and (4) recurrence of infection after surgery[7,11,24,28,34,36,38,42].

The overall mortality in populations including HIV-positive and HIV-negative patients ranged from 6% to 33%[8,9,29-31,33,35,37,39]. Only one study found a significant difference in mortality between HIV-positive and HIV-negative participants, with HIV positives having a lower mortality than HIV-negative participants[31]. The overall RR of mortality in HIV-positive versus HIV-negative IE patients was 0.86 (95% CI: 0.53-1.40) with heterogeneity I^2 = 36% and p = 0.55 (Fig. 3). Other factors related to mortality in patients with IE not related to HIV were (1) left-sided valvular involvement, (2) age from 35 years, (3) fungi or *Staphylococcus aureus* etiology, (4) vegetation size >2 cm, (5) congestive heart failure during episode, (6) CNS complications caused by infection, (7) prosthetic valve or cardiac device, (8)

Table 2. Characteristics of included studies

Authors	Study design; country	Cohort	Sample characteristics						
			Comparison group or objective	Patients (n)	Age (years)	Sex (% male)	IV drug users (%)	HIV+ (%)	ART use
Abad et al. (2000)	Retrospective case series; Spain	1991-1999	Case presentation of HIV-infected patients in need of cardiac surgery	4	Median 44	100%	75%	100%	No
Alagna et al. (2014)	Prospective 1-year cohort; International	2000-2006	Risk factor and 1-year mortality of patients with repeat IE compared to single episode IE	1.874	Unknown	68%	9.2%	2.1%	No
Bor et al. (2013)	Retrospective cohort; USA	1998-2009	Evolution of IE in the US in the 21st century	382.153	Mean 59.7	57.7%	7.8%	2.8%	No
Bouza et al. (2001)	Prospective in-hospital cohort; Spain	1994-1996	Describing characteristics of IE episodes in HIV-infected patients and nosocomial acquired cases	101	Mean 50	73%	35.6%	33%	No
Chong et al. (2003)[1]	Retrospective case series; USA	1990-1999	Early and late mortality and morbidity of valve replacement among HIV-infected patients	22	Mean 37.5	68%	73%	100%	No
Cicalini et al. (2001)	Retrospective case series; Italy	1984-1999	Clinical features, sites of involvement, bacteriological findings, treatment, complications, and outcome of IE in HIV-infected patients	105	Mean 30.1	73.3%	94.3%	100%	No
Cicalini et al. (2006)	Retrospective cohort; Italy	1980-2003	Characteristics of IE in IVDU and non-IVDU and factors associated with increased risk of death	283	Mean 38.6	67.1%	59.7%	30.4%	No
De Rosa et al. (2007)	Retrospective cohort; Italy	1986-1999	IE in HIV-positive versus -negative patients	257	Mean 28	76%	100%	38%	No
Fernandez Guerrero et al. (2009)	Retrospective cohort; Spain	1985-2006	Characteristics of right-sided versus left-sided IE and HIV-positive versus -negative caused by *S. aureus*	133	Unknown	77%	47%	38.3%	No
Ferraris et al. (2013)	Retrospective cohort; Italy	2003-2010	IE in a single-center hospital in Italy	166	Median 57	63%	26%	19%	Yes (40%)
Gansera et al. (2016)	Retrospective case series; Germany	2013	Surgery in patients with IV abuse and recurrent IE	3	Mean 29.7	66.7%	100%	33.3%	No
Gebo et al. (2006)	Retrospective cohort; USA	1990-2002	HIV-infected IE patients before versus after ART era	58	Median 40	65.5%	84.5%	100%	Yes (31%)

(Continues)

Table 2. Characteristics of included studies *(Continued)*

Authors	Study design; country	Cohort	Sample characteristics						
			Comparison group or objective	Patients (n)	Age (years)	Sex (% male)	IV drug users (%)	HIV+ (%)	ART use
Losa *et al.* (2003)	Retrospective case series; Spain	1979-1999	HIV-infected IE patients not related to IVDU	8	Mean 44	100%	0%	100%	No
Martín-Dávila *et al.* (2005)	Retrospective cohort; Spain	1985-1999	Mortality and risk factors of native valve endocarditis in IVDU	220	Median 27.8	Unknown	100%	64.5%	No
Meel *et al.* (2014)	Retrospective case series; South Africa	2014	Cases of HIV-positive patients with right-sided IE due to IV nyaope use	3	Mean 26.3	100%	100%	100%	No
Meel *et al.* (2018)	Retrospective case series; South Africa	2014-2017	Characteristics of patients with IE due to IV nyaope use	68	Mean 25.8	97.1%	100%	76.1%	Yes (4.4%)
Mestres *et al.* (2003)	Retrospective case series; Spain	1985-2002	HIV-positive patients undergoing cardiac surgery	21	Mean 28.2	85.7%	95.2%	100%	No
Nel *et al.* (2014)	Prospective in-hospital cohort; South Africa	2004-2007	Describe echocardiographic features of IE patients and compare IE in HIV-positive versus -negative patients	77	Mean 31.2	54.5%	0%	22%	No
Pulvirenti *et al.* (1996)	Retrospective cohort; USA	1987-1990	HIV-positive versus -negative IVDU patients with IE	102	Unknown	75.5%	100%	44.1%	Yes (2%)
Ribera *et al.* (1998)	Prospective in-hospital cohort; Spain	1984-1995	Characteristics of HIV-positive versus -negative IVDU patients with IE	283	Mean 26.8	79%	100%	76.3%	No
Robinson *et al.* (2000)	Retrospective cohort; USA	1990-1995	HIV-positive versus -negative IVDU patients with IE	126	Mean 34.5	56%	100%	58.7%	No
Sambola *et al.* (2010)	Prospective 1-year cohort; Spain	2000-2008	Characteristics of IE in men versus women	271	Mean 57	67.5%	Unknown	7%	No
Smith *et al.* (2004)	Retrospective case control; USA	1999-2003	HIV-positive patients with versus without IE	10	Mean 37.8	80%	20%	100%	No

ART: antiretroviral therapy; IVDU: intravenous drug use. *S. aureus: Staphylococcus aureus.*

valvular or congenital heart disease, and (9) acute renal dysfunction[8,9,25-27,29-33,35,37,39-41].

The outcome "need for surgery" was reported in 13 studies (Table 4). Three studies used surgery as inclusion criterium for their study population[24,33,38]. Overall, the percentage of patients who underwent surgery ranged from 2.2% to 56.6%. Five studies compared the number of patients requiring surgery by HIV status[8,9,33,35,39]. One study showed a significant higher number of HIV-negative patients receiving surgery compared to HIV positives ($p \leq 0.001$)[8]. All HIV-positive patients that required surgery in this study

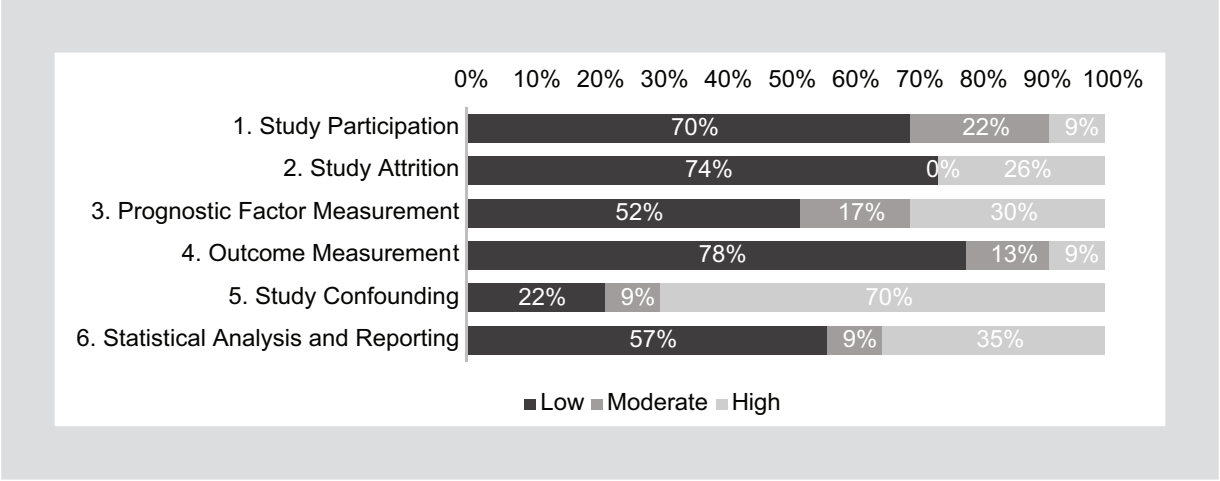

Figure 2. *Summary of risk of bias. Number of studies with low, moderate, or high is given as a percentage of the total number of studies (n = 23).*

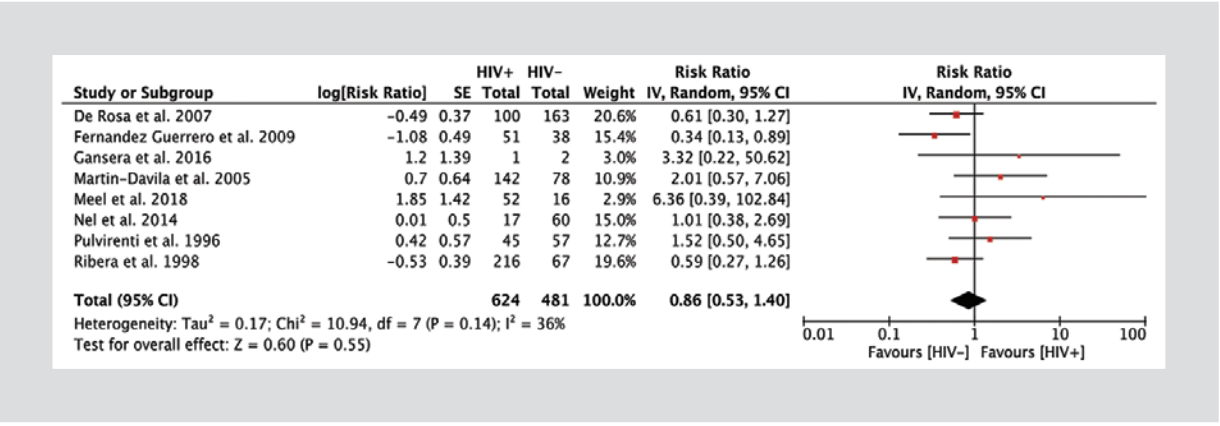

Figure 3. *Forest plot of mortality in HIV-positive (HIV+) versus HIV-negative (HIV-) patients with IE. RR lower than 1 (left side) favors mortality in HIV-negative patients and RR above 1 (right side) favors mortality in HIV-positive patients.*

had a CD4+ cell count below 200 cells/μl and right-sided surgery was solely performed in HIV-positive patients[8].

Four studies with only HIV-positive patients described the prevalence of emboli ranging from 25% to 66.7%, and emboli were predominantly pulmonary emboli (Table 4) (Supplementary 2)[7,24,34,36]. The prevalence of emboli in HIV-positive compared to HIV-negative patients was described in five other studies[8,9,27,33,39]. One study reported a significant higher occurrence of systemic emboli in HIV-negative compared to HIV-positive patients (p = 0.008)[8]. Another study also reported a high prevalence of pulmonary embolisms in HIV-positive individuals compared to HIV negatives, although not reaching statistical significance[27].

Three studies with only HIV-positive patients assessed recurrent IE and this happened in 3-20% of the cases (Table 4)[7,28,34]. In one of these studies, all cases of recurrent IE were IVDUs[28]. Two studies compared the occurrence of recurrent IE between HIV positives and negatives, and this did not reach statistical significance[8,32]. However, another study, investigating risk factors for recurrent IE, found that HIV infection was independently associated with recurrent IE (p = 0.009) (Supplementary 2)[25]. Furthermore, the incidence of right-sided IE was higher in HIV-positive compared to HIV-negative patients (Supplementary 3)[8,9,31,32].

Average length of hospital stay was reported in three studies and ranged from 28.3 to 41.1 days (Table 4).

Table 3. Mortality

Authors	Patients (n)	Overall mortality	HIV positive			HIV + negative
			All	CD4+ cell count		
				<200	>200	
Studies with HIV-positive patients only						
Abad et al. (2000)	4	25%	25%			N.A.
Cicalini et al. (2001)	105	17.8%	17.8%	72.2%*	27.8%*	N.A.
Chong et al. (2003)	22	45%	45%			N.A.
Losa et al. (2003)	8	12.5%	12.5%			N.A.
Meel et al. (2014)	3	0%	0%			N.A.
Mestres et al. (2003)	21	28.6%	28.6%			N.A.
Smith et al. (2004)	10	30%	30%	66.7%	33.3%	N.A.
Gebo et al. (2006)[1]	58	52%	52%			N.A.
Studies comparing HIV-positive to HIV-negative patients						
De Rosa et al. (2007)	257	16%	8.5%			14.5%
Fernandez Guerrero et al. (2009)	133	18%	9.8%*			28.9%*
Gansera et al. (2016)	3	33%	100%			0%
Martín-Dávila et al. (2005)[2]	220	6%	7.7%	36.4%	18.2%	3.8%
Meel et al. (2018)	68	14.7%	19.2%			0%
Nel et al. (2014)	77	23.4%	23.6%	75%	25%	23.3%
Pulvirenti et al. (1996)	102	10.8%	13.3%	83.3%*	16.7%*	8.8%
Ribera et al. (1998)	283	9.2%	7.9%	100%*	0%*	13.4%

*p<0.05; 1. Includes participants on ART, 2. 45.5% have no data on CD4+ cell count.
N.A.: not applicable; n: number; empty field: no data available.

Table 4. Other clinical outcomes (Hospital stay is given in days)

Authors	Patients (n)	Outcome							
		Surgery		Systemic emboli		Recurrent IE		Hospital stay	
		HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Studies with HIV-positive patients only									
Abad et al. (2000)	4	100%	N.A.	25%	N.A.	20%	N.A.		
Chong et al. (2003)	22								
Cicalini et al. (2001)	105	5.9%	N.A.	62.6%	N.A.	2.9%	N.A.		
Gebo et al. (2006)	58	7.8%	N.A.	31%	N.A.	16%	N.A.		
Losa et al. (2003)	8	25%	N.A.						
Meel et al. (2014)	3	33.3%	N.A.	66.7%	N.A.				
Mestres et al. (2003)	21	100%	N.A.					41.1	N.A.
Smith et al. (2004)	10	30%	N.A.						
Studies comparing HIV-positive to HIV-negative patients									
Bouza et al. (2001)	101	x	42%	70%	45%			x	31
Ferraris et al. (2013)	166	x	52%	x	44%	16.3%	7.4%		
Gansera et al. (2016)	3	100%	100%	0%	50%				
Martín-Dávila et al. (2005)	220	4.9%	5.1%						
Nel et al. (2014)	77	35.3%	56.6%	17.6%	10%				
Pulvirenti et al. (1996)	102	2.2%	10.5%	73.3%	54.4%				
Ribera et al. (1998)	283	7.4%*	23.9%*	6.9%*	17.9%*	29.2%	31.3%		
Robinson et al. (2000)	126							28.3	30.9

*Significant value; Empty field: no record available.
N.A: not applicable; x: no difference was mentioned.

None of the studies found a difference in length of hospital stay depending on HIV status[11,27,40].

Discussion

Our search strategy identified 23 articles that addressed the clinical outcome of IE according to HIV status. Participants with HIV did not seem to have a higher mortality compared to participants without HIV. However, HIV-positive participants with a CD4+ cell count below 200 cells/μl seem to have a higher mortality compared to HIV-positive patients with higher CD4+ cell counts. Furthermore, the number of patients receiving surgery was higher in HIV-negative compared to HIV-positive patients.

Our analysis showed 30% mortality (95% CI: 19-46%) in studies with only HIV-positive patients. This is in line with literature as in-hospital mortality of patients with IE, irrelevant of HIV infection, was reported to be around 20% and mortality increased to 25-30% after 6-month follow-up[3,43]. This suggests that IE-related mortality is not higher in people with an HIV infection. The effect of HIV on the course of IE is intertwined with the use of IV drugs[44]. HIV prevalence is high in the IVDU population, and IVDU is a strong risk factor for the right-sided IE[7,8,30,31,35]. The right-sided IE has, irrelevant of HIV, a lower in-hospital mortality than the left-sided IE as there are less hemodynamic consequences compared to the left-sided endocarditis[45]. As IVDU and HIV infection are closely linked, this explains why most HIV-positive patients with IE have right-sided endocarditis (Supplementary 3). Based on this, we would expect that mortality among HIV-positive IVDU patients should be lower than the mortality rate in the general population, where the left-sided IE is responsible for the majority of cases. Nonetheless, following our meta-analysis comparing HIV-positive patients, with mainly right-sided IE, to HIV-negative patients, with mainly left-sided IE, the mortality rate was similar. This might suggest a relative higher mortality for HIV-positive patients than HIV-negative patients. However, two studies described a HIV cohort with IE not related to IVDU, and hence mainly left-sided IE, and both studies reported a similar outcome in HIV-positive patients compared to HIV-negative IE patients[11,46]. Therefore, the following risk factors need to be considered to explain the observed mortality among HIV-positive patients. First of all, the side of involvement (right- or left-sided IE) is a main contributor to the clinical course. Second, mortality rates were significantly higher in immunocompromised IE patients, that is, HIV-positive patients with a CD4+ cell count below 200 cells/mm[37-9]. Third, *S. aureus* infection was also found to be associated with high mortality and *S. aureus* etiology was reported significantly higher in IVDUs compared to non-IVDUs[7,8,25,27,31,32,34,37]. Finally, continued high-risk behavior in IVDU HIV-positive patients increases the chance of a recurrent infection, and survival for patients with recurrent IE was lower than for patients with a single episode of IE[25,28].

The number of patients receiving surgery differed substantially between HIV-positive compared to HIV-negative IE patients with a higher proportion of HIV negatives receiving surgery. This was probably related to the higher frequency of the left-sided IE in HIV-negative patients compared to HIV-positive patients and likely also reflects the reluctance to operate HIV-positive patients in the early years of the epidemic[28,47].

A significant higher number of HIV-negative patients developed systemic emboli compared to HIV positives, and a high number of septic pulmonary embolisms were found in HIV-positive IVDUs, findings are strongly related to the left- and right-sided IE, respectively[7-9,27].

The low number of patients on ART can be explained by the fact that most of the studies (15 out of 23) described datasets that were partially or completely collected before 1996 (Supplementary 1). Furthermore, studies describing patient populations after 1996 hardly included patients on ART. This could be due to the following reasons. First, it could mean that IE is no longer recognized as a clinical problem in HIV-positive patients on ART and hence this topic was not studied anymore in an ART-treated population. Second, HIV-positive patients with IE were mostly IVDUs. IVDUs are known for avoiding health care institutions, hence, they might not have been aware of their HIV status. ART use is low in HIV-positive IVDUs as they probably could not yet be linked to care or retained in care[20,48,49].

Strengths and limitations

The major strength of this review is that it provides a comprehensive overview of the available literature from 1996 on the clinical course of endocarditis in patients with HIV, and it includes a range of patients with endocarditis from three different continents.

Despite the strengths, there are some limitations to be mentioned. First, although we excluded studies published before 1996 as we aimed to describe the course of IE in the current ART era, the majority of the included studies described datasets from before 1996.

As a result, this review covers mostly the course of IE in the pre-ART era, while we did not comprehensively assess the literature before 1996. Besides, as only two studies included patients on ART, we cannot make any firm statements on the course of IE for patients with a well-controlled HIV infection, although results from the pre-ART era studies show that it is rather the location of the IE, and, related to this, IVDU, than HIV that influences the course of disease. Finally, as most cases of IE in HIV-positive patients occur in IVDU, our review provides valuable information for today's clinician as ART uptake is still very low in the group of HIV-positive IVDUs.

Conclusion

HIV-positive patients with IE have a similar mortality and length of hospital stay compared to HIV-negative patients. Among HIV-positive patients, mortality was significantly higher in patients with a CD4+ cell count below 200 cells/μl. Differences in the number of patients requiring surgery and differences in frequency and location of emboli can be explained by the side of cardiac involvement rather than HIV status. ART coverage was low, and ART did not seem to alter the clinical course of IE. Moreover, IVDU prevalence was high among HIV-positive patients, and, related to this, right-sided IE was most frequently observed. Although there is a difference in clinical course of IE observed in HIV patients, this was mainly related to the side of cardiac involvement rather than HIV status. All patients with HIV should be initiated on ART on diagnosis and extra attention should be paid to patients with severe immunosuppression as mortality seems to be higher in this group than in patients with a relatively preserved immune function. Besides, our findings underline the importance of targeting IVDUs to improve screening for HIV and subsequently linkage to and retention in care.

Supplementary Data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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