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Review Article

Prevalence, risk factors, and outcomes of infective endocarditis in people living with HIV: A systematic review and meta-analysis of intravenous drug use and microbiological profiles

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Abstract

Background: Infective endocarditis (IE) poses a significant challenge in people living with human immunodeficiency virus (PLWH), with risk factors and outcomes potentially differing from HIV-negative counterparts. This systematic review and meta-analysis aimed to explore the prevalence, risk factors, mortality, and clinical characteristics of IE in PLWH versus HIV-negative patients.

Methods: Six databases (PubMed, Web of Science, Scopus, ScienceDirect, Embase, and ProQuest) were searched up to January 2025 using terms including "Infective Endocarditis" and "Human Immunodeficiency Virus." Random-effects meta-analyses with Freeman–Tukey transformation were used to estimate pooled prevalence, mortality, and odds ratios (ORs) for IE by HIV status. Between-study heterogeneity (I^2) and meta-regression were assessed to explore sources of variation.

Results: Seventeen independent studies collectively reported 3,082 IE cases (2,095 among PLWH and 987 among HIV-negative individuals), analyzed as separate study-level data rather than a single combined cohort. The pooled prevalence of IE among PLWH was 33.2% (95% CI: 14.97–54.45%), with substantial heterogeneity ($I^2 > 90\%$), highlighting the exploratory nature of these estimates. Among PLWH with IE, 85.5% (95% CI: 65.8–98.1%) reported intravenous drug use (IVDU), and 60–80% had right-sided IE (predominantly tricuspid valve), contrasting with left-sided predominance in HIV-negative patients. Mortality among PLWH with IE was 14.7%, compared with 22.3% in HIV-negative individuals. Staphylococcus aureus was the leading pathogen (24–73%).

Conclusions: Given the high and persistent heterogeneity, findings should be interpreted as exploratory. PLWH with IE frequently exhibit IVDU and right-sided involvement, while mortality appears comparable to HIV-negative patients after accounting for IVDU, emphasizing behavioral rather than virologic determinants of risk.

Keywords: Infective endocarditis, Human immunodeficiency Virus (HIV); intravenous drug use (IVDU), Prevalence, Mortality.

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Infective endocarditis (IE) remains a severe infectious disease characterized by inflammation of the endocardial surface, affecting heart valves and surrounding cardiac structures, with substantial morbidity and mortality, particularly among vulnerable populations such as people living with HIV (PLWH) and intravenous drug users (IDUs) (1). Historically linked to congenital or acquired structural heart disease and poor dental hygiene, the epidemiology of IE has shifted over recent decades, driven by rising rates of IVDU and healthcare-associated infections (2). IDUs now account for a significant proportion of new IE cases, a trend compounded by HIV co-infection, which amplifies risk through immunosuppression, lowered CD4 counts, and increased susceptibility to aggressive pathogens like *Staphylococcus aureus* (3).

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Among PLWH individuals, IVDU emerges as a critical risk factor for IE, introducing pathogens directly into the bloodstream while exacerbating immune system vulnerabilities (4). Studies highlight a high prevalence of IE in this group, often complicated by multidrug-resistant organisms, fungal co-infections, and frequent relapses, with *S. aureus* as the predominant causative agent (5, 6). The advent of combination antiretroviral therapy (cART) has transformed HIV care, potentially altering IE incidence and outcomes in PLWH, yet the persistent global rise in IVDU sustains a significant disease burden (7).

HIV-related immunosuppression, co-infections (e.g., hepatitis viruses), and socio-economic barriers such as limited healthcare access and inconsistent ART adherence further complicate IE presentation and treatment, driving poorer health outcomes compared to HIV-negative counterparts (8). Advances in diagnostic tools, such as the Duke and modified Duke criteria (figure 1), have improved IE identification, but gaps persist in understanding its evolving risk factors and optimal management in these high-risk populations (9). This systematic review and meta-analysis address a gap in understanding infective endocarditis among people living with human immunodeficiency virus compared with HIV-negative patients. Unlike prior reviews, our study integrates prevalence, mortality, microbial profiles, and clinical outcomes while accounting for intravenous drug use. By highlighting persistent uncertainties, such as recurrent infections and the role of immunosuppression, we provide new insights to guide clinical management and future research in this evolving field.

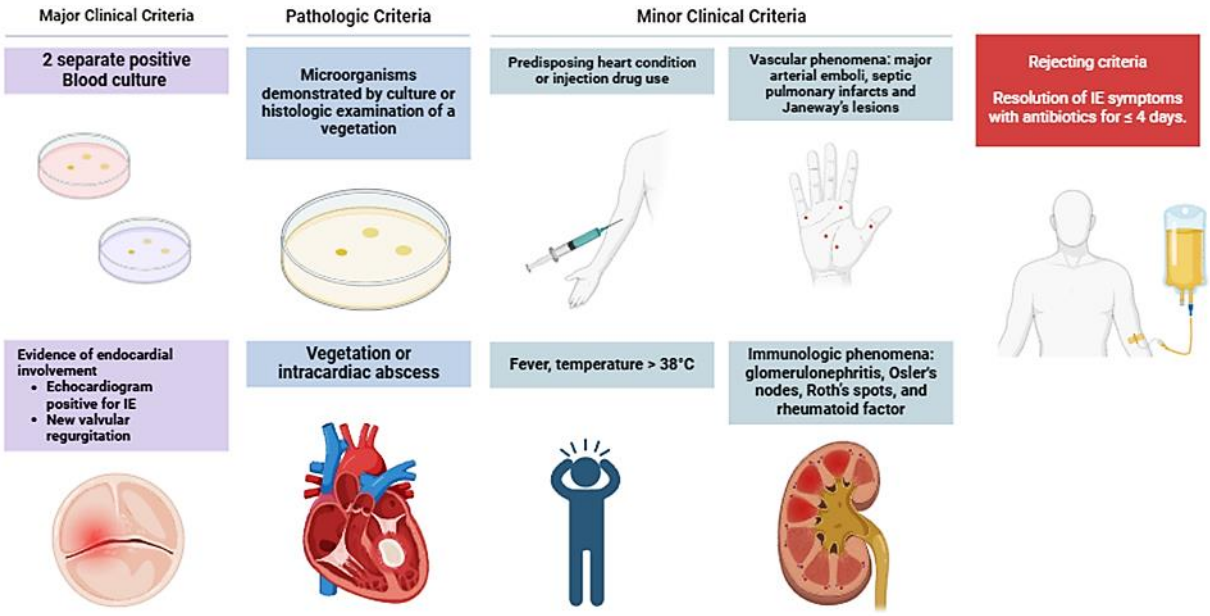

Figure 1. Modified duke criteria

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Methods

Literature search: A systematic literature search was conducted to identify studies examining IE in patients with HIV infection. The search was performed across 6 electronic databases, including PubMed, Scopus, Embase, ProQuest, ScienceDirect and Web of Science, with no restriction on publication date up to January 18, 2025. The following keywords were used in combination: ("Endocarditides" OR "Infective Endocarditis" OR "Infective Endocarditides") AND ("HTLV-III" OR "Human Immunodeficiency Virus" OR Human T Cell Lymphotropic Virus Type III"). Full search syntax is available in supplementary table 1. Study protocol is registered in OPEN SCIENTIFIC FRAMEWORK (https://osf.io/z4fc2/).

Inclusion criteria

1. Observational studies (cohort, cross-sectional, case-control) reporting IE in PLWH and/or HIV-negative adults, focusing on IVDU.
2. Adults (≥18 years) with definite/possible
3. Studies reporting HIV status (via serology) and IVDU, with data on PLWH and/or HIV-negative groups.
4. At least one primary outcome: IE prevalence in PLWH, IVDU prevalence, mortality, or ORs for IE risk. Secondary

outcomes (valve involvement, microbiology, manifestations) included if reported.

Exclusion criteria

1. Case reports, case series (<10 participants), reviews, editorials, or interventional studies.
2. Pediatric (<18 years) or animal studies, non-IE infections, or non-infectious endocarditis.
3. Studies lacking HIV status, IVDU data, or standardized IE diagnostic criteria.
4. No primary outcome (IE prevalence, IVDU, mortality, ORs) or insufficient quantitative data.
5. Studies prior to 2000; limitation explicitly missing ART regimen/adherence data.

Data extraction: Data were extracted from included studies by two reviewers (P.E.2 and A.D.I.) and verified for accuracy by a third reviewer (P.E.1). For each study, the following information was collected where available: (1) number of PLWH with IE and total PLWH population for prevalence estimates; (2) number of IVDU cases and total IE cases in PLWH and HIV-negative patients; (3) number of in-hospital deaths and total IE cases in PLWH and HIV-negative patients; and (4) ORs with 95% confidence intervals (CIs) for IE risk associated with HIV status. Additional variables, such as valve involvement, microbiological profiles, and clinical manifestations, were noted but not meta-analyzed due to inconsistent reporting across studies. Study characteristics (e.g., author, year, sample size) were recorded to facilitate analysis and reporting.

Statistical analysis: Meta-analyses were conducted to estimate the pooled prevalence of IE in PLWH, the prevalence of IVDU among PLWH and HIV-negative patients with IE, the in-hospital mortality rates in PLWH and HIV-negative patients with IE, and the OR for IE associated with HIV status. For prevalence estimates, the number of events and total sample sizes were used to calculate study-specific proportions, expressed as percentages. For ORs, reported effect sizes and their 95% CIs were directly extracted. Studies lacking sufficient quantitative data were excluded from specific analyses. A random-effects model was used for all meta-analyses. To stabilize variances in prevalence estimates, we applied the Freeman–Tukey double arcsine transformation, which performs better than the logit method for extreme proportions near 0% or 100%. Between-study variance (τ^2) was estimated with the DerSimonian–Laird method, and Hartung–Knapp adjustments were applied to confidence intervals. Exact (Clopper–Pearson) CIs were calculated for individual studies. Heterogeneity was assessed using I^2 and τ^2. Pooled estimates were back-transformed to percentages, and forest plots were generated to show study estimates and pooled effects. All analyses were performed using statistical R software Version 4.5 with the meta package, and results were reported separately for PLWH and HIV-negative groups where applicable.

Quality assessment: The PRISMA checklist guided reporting (10). The GRADE framework assessed the certainty of evidence for each meta-analyzed outcome (prevalence, IVDU, mortality, OR) (11), starting at 'Low' for observational studies and downgrading for risk of bias, inconsistency, indirectness, imprecision, and publication bias, with potential upgrades for large effects, dose-response, or confounding. The quality of each study included in the meta-analysis was evaluated using the Newcastle–Ottawa Scale (NOS) for cohort studies (12). This assessment covered three main categories: (i) selection (4 criteria), (ii) comparability (2 criteria), and (iii) outcome assessment (3 criteria). The NOS score ranges from 0 to a maximum of 9 points, with study quality classified as follows: good (green), medium (yellow), fair (orange), and poor (red).

Result

Study selection: A total of 758 records were identified through database searching, including PubMed (n = 76), Web of Science (n = 274), Scopus (n = 240), ScienceDirect (n = 299), Embase (n = 52), and ProQuest (n = 87). After removal of 360 duplicates, 398 records remained for screening. Following title and abstract screening, 342 records were excluded. The full texts of 56 reports were assessed for eligibility, of which 34 were excluded due to insufficient quantitative data (n = 25) or non-comparable outcomes (n = 14). Finally, 17 studies met the inclusion criteria and were included in the qualitative synthesis. (Figure 2)

Baseline characteristics: Studies were conducted in diverse settings: Italy (4 studies), the United States (4 studies), Spain (3 studies), South Africa (2 studies), and Iran (1 study). This geographic diversity highlights variations in healthcare systems, diagnostic practices, and access to treatment, with sample sizes ranging from 68 to 5667 participants. The total number of IE cases reported across these studies is 3082, with 2095 cases in PLWH and 987 in HIV-negative individuals. Additionally, 821 PLWH without IE and 365 HIV-negative individuals without IE were reported, where data were available. The mean or median age of participants ranged from 25.8 to 46 years, with most studies reporting a predominance of male participants (50% to 97.1%).

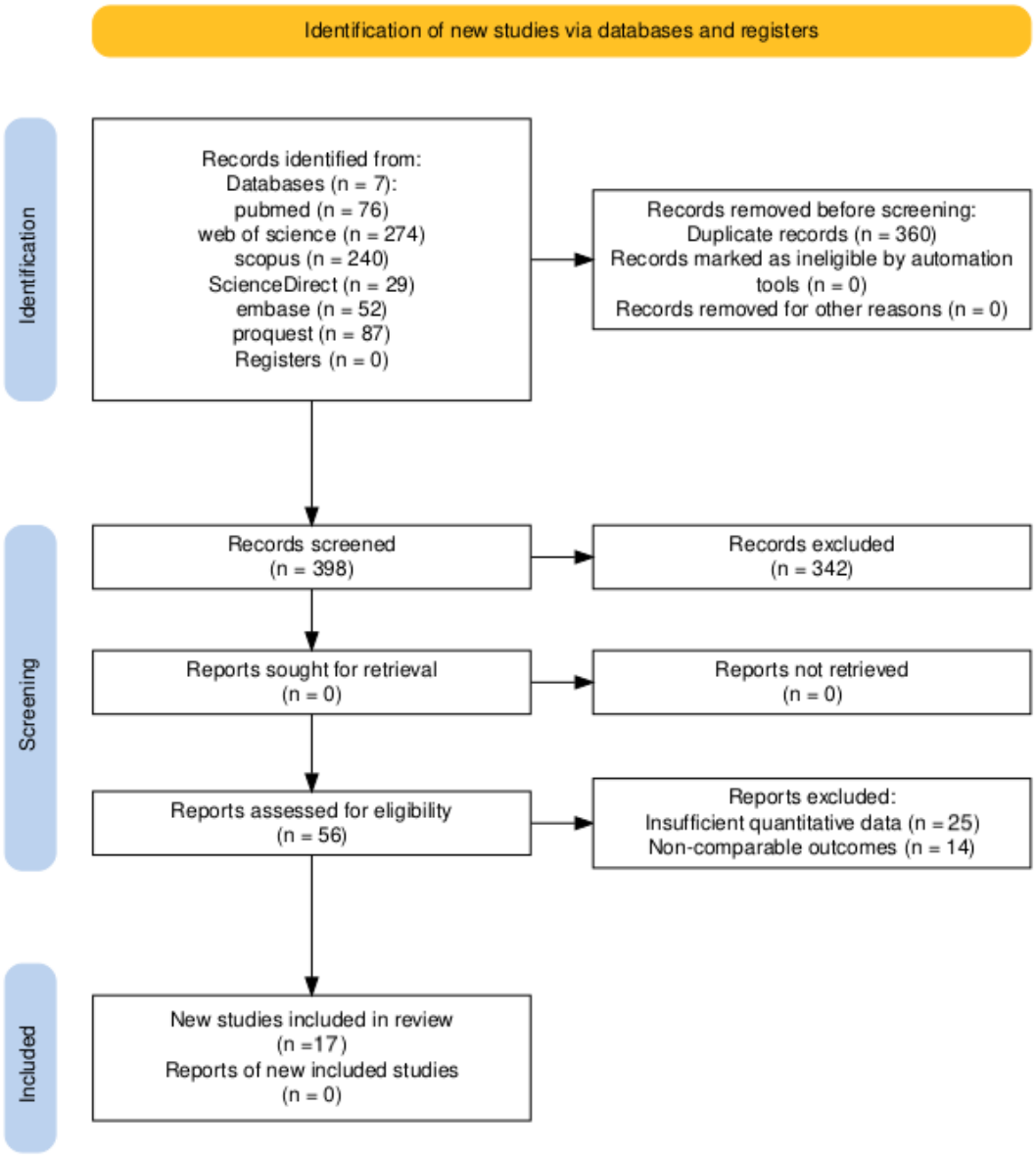

Figure 2. PRISMA flow chart of literature review

The mean or median age of participants ranged from 25.8 to 46 years, with most studies reporting a predominance of male participants (50% to 97.1%). Specific data on PLWH included 2095 with IE and 821 without IE, while HIV-negative individuals included 987 with IE and 365 without IE, based on studies providing these breakdowns. Diagnostic approaches were consistent across studies, primarily relying on the modified Duke criteria, echocardiography (transthoracic [TTE] and transesophageal [TEE]), and microbiological tests (including blood or valve cultures and serology).

TTE was used in nearly all cases (up to 97.3% in some studies), with TEE employed selectively, particularly in HIV-negative patients. Additional imaging, such as chest radiographs (which are abnormal in 75% of cases in one U.S. study) and CT/MRI, was used in specific contexts. Autopsy and surgical findings supplemented diagnoses in select cases. Treatment primarily involved antibiotics, with regimens tailored based on microbiological findings or empirical treatment for resistant pathogens, such as (Community-Associated Methicillin-Resistant Staphylococcus Aureus) CA-MRSA. Surgical intervention rates varied, ranging from 5.9% to 40%. Surgery was less common among PLWH with IE (7.5% vs. 27% in HIV-negative patients in one Italian study). Indications for surgery included heart failure (47.9%–70%), persistent infection (20%), large vegetations (28.8%), and emboli (2%) (table 1).

Table 1 Identified studies for systematic review according to PRISMA guidelines

Author(s)	Study Design	Country/ Location	Sample Size	Past medical history	Inclusion criteria	Exclusion criteria	Clinical Manifestations	Diagnostic Methods	Treatment Administered	Follow-Up Duration
J.Abraham et al. (2003) (13)	Cohort	USA	177	Diabetes, renal failure in HIV− patients	Patients with suspected infective endocarditis (IE) who were referred for echocardiography and had ≥2 positive blood cultures for the same microorganis.	not meeting inclusion criteria	Fever, embolic events	Transthoracic & Transesophageal Echocardiography (TEE)	na	na
Fernandez Guerrero et al. (2009) (14)	cross-sectional	spain	89	na	Patients with Staphylococcus aureus endocarditis	not meeting inclusion criteria	Right-sided IE: More pleuritic chest pain Left-sided IE: More cardiac failure, neurological events, and peripheral stigmata Hepatosplenomegaly and abnormal liver function tests were common in PLWH due to HCV co-infection (84.3%)	Transthoracic & Transesophageal Echocardiography (TEE)	na	na
Furuno et al. (2011) (15)	cohort	USA	131	Diabetes Mellitus, Hepatitis C , Hypertension	HIV-infected patients with MRSA bacteremia	Duplicate cultures from the same admission, patients treated for endocarditis in the last 90 days	Fever, septic pulmonary emboli (11 CA-MRSA, 6 non-CA-MRSA), deep abscesses (lung, psoas, spinal, renal, brain, pericardial)	Transthoracic (TTE) and Transesophageal Echocardiography (TEE), modified Duke criteria	Empiric antibiotics (31% were initially ineffective for CA-MRSA)	na
Alavi et al. (2010) (16)	cross-sectional	Iran	323	HBV, HCV, HIV, TB	IVDU patients between 2001–2006 meeting Duke Criteria for IE	not meeting inclusion criteria	- Fever (89.7%) - Sweating (83.3%) - Fatigability (86%) - Shortness of breath (66.7%) - Cough (57.8%)	Echocardiography, microbiological tests	na	na

Author(s)	Study Design	Country/ Location	Sample Size	Past medical history	Inclusion criteria	Exclusion criteria	Clinical Manifestations	Diagnostic Methods	Treatment Administered	Follow-Up Duration
E.Cecchi et al. (2006) (17)	cohort	Italy	201	Predisposingheart disease	Adult intravenous drug users (IVDU) with suspected IE from 1993 onwards, classified as definite, possible, or rejected IE per Duke criteria	not meeting inclusion criteria	Fever, new heart murmur, vascular/immunologic phenomena (similar in both groups)	Duke criteria, echocardiography (TTE in all, TEE selectively, used more in HIV− patients)	Antibiotics; surgery performed in 27% of HIV− IE cases vs. 7.5% in HIV+ IE cases (p=0.03)	3 months
S. Cicalini et al. (2001) (18)	cross-sectional	Italy	105	11 patients (10.5%) had prior IE, 3 had pre-existing valvular disease, 2 had prosthetic valves	Diagnosis of IE based on Duke criteria, HIV seropositivity confirmed via ELISA and Western blot.	not meeting inclusion criteria	Congestive heart failure (16.9%), septic pulmonary emboli (51.8%), stroke (4.8%), systemic emboli (6%), acute renal failure (2.4%)	Clinical, echocardiographic, surgical, post-mortem examination	Medical treatment: 95 cases (94.1%), Combined medical and surgical treatment: 6 cases (5.9%)	na
S. Cicalini et al. (2006) (19)	cross-sectional	Italy	283	23.7% of non-IVDUs had no predisposing conditions for IE	Patients with a discharge diagnosis of IE (January 1, 1980 – December 31, 2003) who met Duke criteria	Cases not meeting Duke criteria; patients admitted before 1985 without HIV status data	na	Duke criteria, echocardiography, microbiological data (blood/valve cultures, serology)	na	na
Nel et al. (2014) (20)	observational	South Africa	77	na	Patients with definite IE based on modified Duke criteria	Patients classified as possible or rejected IE	Clubbing: 11 PLWH Heart failure: 5 PLWH Hepatomegaly: 5 PLWH (29.4%), 28 HIV-negative patients (46.7%)	Modified Duke criteria Transthoracic echocardiography (TTE) Transesophageal echocardiography (TEE) Blood cultures CD4 count for HIV patients	Medical therapy: 6 weeks of antibiotics Surgery: 40 patients underwent valve replacement (34 HIV-negative, 6 PLWH)	at least one year for surgically treated patients
F. G. De Rosa et al. (2007) (21)	Cohort	Italy	993	16.7% had additional predisposing conditions (e.g., prior IE, valvular disease, congenital heart disease, prosthetic valves, catheter use)	Definite cases of IE according to Duke criteria	not meeting inclusion criteria	Not explicitly detailed for HIV+ vs HIV- patients, but complications included embolization (36.1% lung, 8.3% CNS, 3.4% spleen, 0.7% retina), renal failure (1.9%)	Transthoracic echocardiography (TTE) in 97.3%, transesophageal echocardiography (TEE) in some, autopsy in select cases	16.7% underwent surgery (heart failure 70%, persistent infection 20%, abscess 8%, emboli 2%); 77.1% received medical therapy alone	na

Author(s)	Study Design	Country/ Location	Sample Size	Past medical history	Inclusion criteria	Exclusion criteria	Clinical Manifestations	Diagnostic Methods	Treatment Administered	Follow-Up Duration
Gebo et al. (2006) (22)	case-control	United States	290	- 75% co-infected with hepatitis C - High prevalence of IVDU history	Patients receiving longitudinal primary HIV care before Jan 1, 2003	Cases with inadequate information to confirm IE diagnosis	- Fever (62.1%) - Chills (31.0%) - Shortness of breath (25.9%) - Myalgia (15.5%) - Chest pain (13.8%)	- 82.8% had echocardiograms (96% transthoracic, 4% transesophageal) - 27.6% classified as "possible IE" (Duke Criteria)	- Antibiotics, including prophylaxis for PCP and MAC - 7.8% required surgery (valve replacement, amputations, abscess debridement)	1 year
M. Martinez-Selles et al. (2024) (7)	observational	Spain	5667	PLWH had fewer comorbidities except for liver disease and IVDU	Patients with possible or definite IE (defined by modified Duke criteria)	not meeting inclusion criteria	More common vascular and cutaneous foci, vegetations, vascular phenomena, splenomegaly, and embolization in PLWH	Based on modified Duke criteria (echocardiography and clinical evaluation)	Surgery was less common in PLWH	na
M. Muñoz-Moreno et al. (2019) (23)	cohort	Spain	1800	Increased rates of comorbidities over time: substance abuse (drugs, alcohol, tobacco), diabetes, hypertension, coronary artery disease, liver disease, COPD, CKD. High prevalence of hepatitis co-infections (HCV 40.1%, HBV increasing from 4% to 10.3%).	HIV-infected patients (ICD-9-CM codes: 042 or V08) diagnosed with IE (ICD-9-CM codes: 421.0, 421.1, 421.9) between 1997 and 2014	not meeting inclusion criteria	na	Standard hospital-based diagnostic procedures (not explicitly described)	na	from 1997 to 2014
Ortiz et al. (2014) (24)	cross-sectional	Spain	866	Higher prevalence of HIV, anemia, previous IE in IDUs; cardiac disease & local infections in device carriers; renal failure, COPD, diabetes, and cancer in "3 noes" group	Patients diagnosed with IE from 1996 to 2012; right-sided IE cases included	14 episodes excluded due to concomitant left valve infection	Pulmonary embolism (53% in IDUs), renal failure (30% in "3 noes" group), septic shock (15%), uncontrolled infection (55%) in "3 noes" group	Duke and modified Duke criteria, transthoracic & transesophageal echocardiography, blood cultures, imaging techniques (CT, MRI, echography)	Empirical antibiotics followed by targeted therapy, device removal in 91% of device carriers, cardiac surgery in 40% of "3 noes" group, rarely performed in IDUs	During hospital admission

Author(s)	Study Design	Country/ Location	Sample Size	Past medical history	Inclusion criteria	Exclusion criteria	Clinical Manifestations	Diagnostic Methods	Treatment Administered	Follow-Up Duration
Meel et al. (2017) (25)	cohort	South Africa	68	HIV (76.1%), hepatitis C (58.1%), hepatitis B (8.2%), systemic hypertension (2 patients)	Patients aged ≥18 years with definite or possible IE (modified Duke criteria) and a history of IV nyaope use	IE cases not related to IV nyaope use	Septic pulmonary emboli (61.8%), systemic emboli (11.8%), pulmonary TB (36.3%), renal failure requiring dialysis (2.9%)	Modified Duke criteria, echocardiography, microbiological cultures	Antimicrobial therapy, 4 patients underwent surgery (1 tricuspid valvulectomy, 1 mitral valve replacement, 1 tricuspid valve replacement, 1 aortic valve replacement)	Until hospital discharge
N.Naidoo et al. (2022) (26)	cohort	South Africa	97	100% of HIV+ cases had underlying Rheumatic Heart Disease (RHD)	Patients with definite IE based on modified Duke criteria (clinical or pathological)	Patients with possible IE (n=54) and rejected cases (n=10)	Pallor (80.4%) High-grade dyspnea (67%) Clubbing (75% in HIV+, 35.3% in HIV−, p=0.009) Haematuria (58.3% in HIV+, 29.4% in HIV−, p=0.046) Splenomegaly (33.3% in HIV+, 9.4% in HIV−, p=0.018) Heart failure (66.7% in HIV+, 61.2% in HIV−, p=0.714) Acute kidney injury (33.3% in HIV+, 28.2% in HIV−, p=0.280) Embolic events (33.3% in HIV+, 45.5% in HIV−, p=0.503)	Blood cultures (positive in 64.9%) Transthoracic echocardiography (vegetations present in 87.6%)	All patients received antibiotics 73 patients underwent surgery (HIV+ n=8, HIV− n=65) Indications for surgery: heart failure (47.9%), large vegetations (28.8%), ongoing sepsis (15.1%)	na
D.Smith et al. (2004) (27)	case-control	United States	87	High incidence of bacteremia History of IV drug use present in some patients Presence of diabetes, renal failure, and predisposing heart disease were recorded but not specified for IE patients	Adult PLWH (≥18 years old) At least two blood cultures positive for the same microorganism Underwent transesophageal echocardiography (TEE) or had clear valvular vegetations seen on transthoracic echocardiography (TTE)	Patients without two positive blood cultures for the same microorganism Patients without echocardiographic evidence of IE	Blood cultures Echocardiography (TEE or TTE) Duke Criteria for diagnosis	Three patients required cardiothoracic surgery Specific antibiotic regimens not specified	na	na

Author(s)	Study Design	Country/ Location	Sample Size	Past medical history	Inclusion criteria	Exclusion criteria	Clinical Manifestations	Diagnostic Methods	Treatment Administered	Follow-Up Duration
L. Wilson et al. (2002) (28)	cohort	United States	2566	History of prior IE before study enrollment was associated with an increased risk.	Age >17 years. History of injecting drugs at least once after 1977. Absence of an AIDS diagnosis at study entry.	Participants who did not return for at least one follow-up appointment Potential IE cases with inadequate information or those occurring after December 1998.	Fever >38°C in 96% of cases. Heart murmur at admission in 68%. Positive blood cultures in 97%. Embolic phenomena in 30% (pulmonary emboli, Janeway lesions, renal emboli, brain emboli, petechiae, splinter hemorrhages, Osler nodes, meningitis, mycotic aneurysm).	Blood cultures. Echocardiograms (performed in 76% of cases; transesophageal echocardiograms in 5%). Chest radiographs (abnormal in 75% of cases; common findings: infiltrates, atelectasis, densities, pleural effusions, cardiomegaly, cavities).	na	na

IE: infective endocarditis, TEE: Transthoracic & Transesophageal Echocardiography (TEE), CA-MRSA: Community-Associated Methicillin-Resistant Staphylococcus Aureus, IVDU: intravenous drug users, PLWH: people living with human immunodeficiency virus, HIV: human immunodeficiency virus

Prevalence of infective endocarditis in PLWH: Eight studies (13, 15-18, 22, 27, 28) comprising 1,692 participants and 477 IE events were included in the prevalence meta-analysis. The pooled prevalence of IE among PLWH was 33.2% (95% CI: 14.97–54.45%) using a random-effects model, reflecting exploratory pooled evidence characterized by substantial between-study variability (I^2 = 97.7%, p < 0.0001). Subgroup analyses suggested regional variation, with the prevalence of IE among PLWH highest in Europe (54.95%), followed by the Middle East (31.67%) and North America (23.59%), though these differences were not statistically significant (P= 0.3850). Study design influenced estimates, with cross-sectional studies reporting the highest prevalence (96.19%), while prospective cohort, retrospective cohort, and case–control studies ranged from 22.63% to 28.43%. Meta-regression indicated that study design accounted for 64.08% of heterogeneity, whereas publication year and geographic region had minimal effects (supplementary table 2, supplementary figure 1).

Risk of infective endocarditis in PLWH vs. HIV-negative patients: Three studies (13, 16, 17) Three studies (13, 16, 17) (n = 701; 214 PLWH and 487 HIV-negative individuals) reported odds ratios for infective endocarditis by HIV status, with a total of 187 IE events. The pooled analysis under a common-effect model suggested no significant association (OR = 0.79, 95% CI: 0.55–1.15, P = 0.22). However, heterogeneity was considerable (I^2 = 95.8%, 95% CI: 91.0–98.1), and thus, these findings should be interpreted as exploratory due to persistent between-study variability. Mixed-effects modeling suggested that study-level covariates explained much of this heterogeneity (R^2 = 97.3%). Meta-regression using year of publication as a moderator did not account for between-study differences; however, given the small number of studies, this analysis was low power and primarily exploratory (supplementary table 3, figure 4).

Valve involvement patterns: Fourteen studies (7, 14, 16-18, 20, 21, 25-31) reported that PLWH had higher right-sided IE. Right-sided IE was consistently more frequent among PLWH, with reported rates ranging from 60–80% in most series, compared to substantially lower rates in HIV-negative controls. In contrast, left-sided IE was more common among HIV-negative patients, with studies from Spain and Italy showing markedly higher involvement of left-sided valves in HIV-negative individuals. Tricuspid valve disease was a predominant feature among PLWH, reported in 33–60% of cases across multiple studies, while rarely described in HIV-negative populations. Mitral and aortic valve involvement was also observed in PLWH but generally at lower frequencies than right-sided disease, with several studies showing higher prevalence in HIV-negative patients.

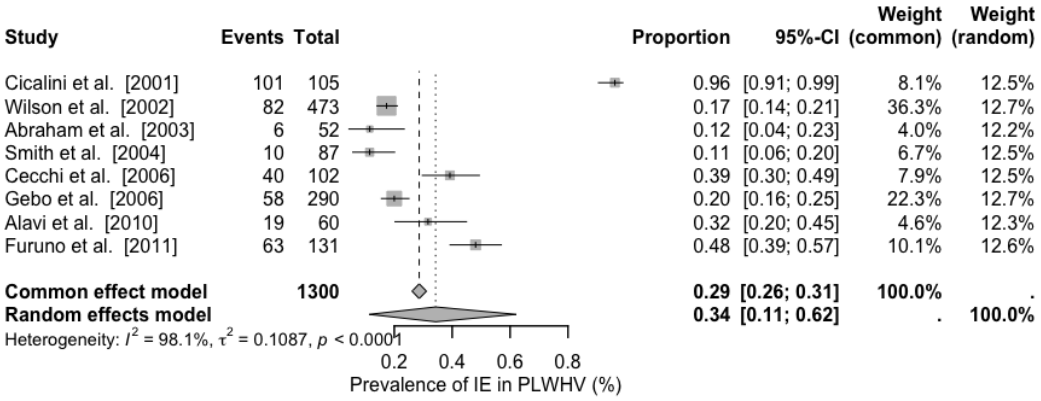

Figure 3. Forest plot for prevalence of infective endocarditis in PLWH

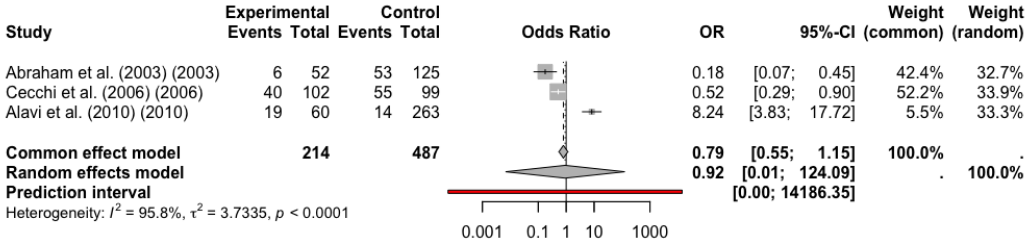

Figure 4. Odds Ratio (PLWH vs HIV- for IE)

Multiple valve involvement was less common but documented in both groups, with variable frequencies across studies. Given the heterogeneity of study designs and populations, these pooled patterns should be considered exploratory (supplementary table 3).

Intravenous drug use (IVDU): Fourteen studies (7, 13-15, 17-19, 22, 24-28, 32) reporting the prevalence of intravenous drug use (IVDU) among PLWH with IE were included in the meta-analysis. The pooled prevalence of IVDU among PLWH with IE was high but heterogeneous, estimated at 89.0% (95% CI: 86.4–91.4%) under the common-effect model and 85.5% (95% CI: 65.8–98.1%) under the random-effects model (I^2 = 94.6%, τ^2 = 0.1216). In comparison, eight studies assessing the prevalence of IVDU among HIV-negative patients with IE demonstrated considerably lower and more variable estimates. The common-effect model yielded a pooled prevalence of 2.9% (95% CI: 2.4–3.3%), whereas the random-effects model indicated 49.6% (95% CI: 5.8–93.9%), with very high heterogeneity (I^2 = 99.6%, τ^2 = 0.3898) (figures 5, 6). Meta-regression analyses showed that study design accounted for the largest proportion of heterogeneity (R^2 = 53.3%), while publication year explained 8.4% and geographic region none (R^2 = 0%). Leave-one-out sensitivity analyses indicated that no single study disproportionately influenced heterogeneity. Given the magnitude of variability, these results are exploratory and should not be generalized without caution (supplementary table 4).

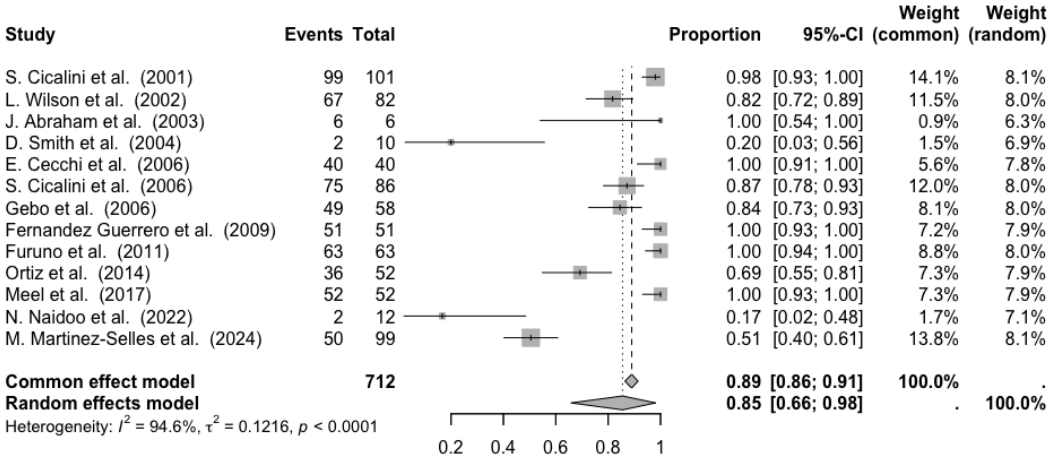

Figure 5. Prevalence of IVDU in PLWH with IE.

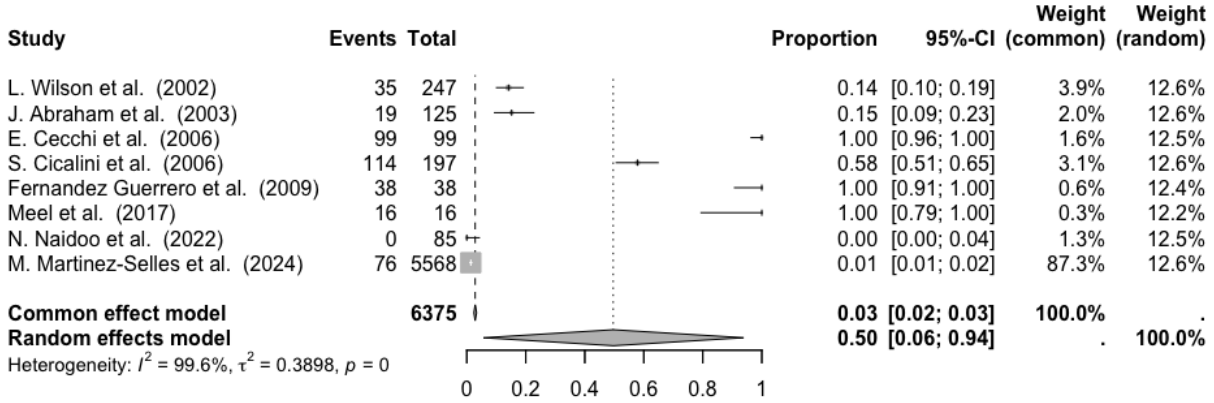

Figure 6. Prevalence of IVDU in HIV-negative IE patients.

Microbiological profile: *Staphylococcus aureus* was the predominant pathogen across studies (24–73%), including both methicillin-sensitive and resistant strains. Coagulase-negative staphylococci were also common (1–40%), while streptococci, particularly *Viridans* group, accounted for 5–25% of cases. *Enterococcus* species contributed 3–7%, and gram-negative bacilli such as *Pseudomonas* appeared less frequently (2–10%). Fungal infections, mainly *Candida albicans*, were sporadic, and polymicrobial infections were rare. Blood culture negativity was reported in up to 13% of cases. In PLWH, atypical organisms (*Bacillus cereus*, *Klebsiella pneumoniae*, *Micrococcus*, *Staphylococcus epidermidis*) were more frequent compared to HIV-negative patients. Staphylococcal infections predominated in intravenous drug users, while streptococci were more common in non-IVDU cases. Some cohorts noted an increase in culture-negative endocarditis over time. These microbiological trends, derived from heterogeneous data, should be viewed as exploratory patterns rather than definitive associations.

Clinical manifestations: Patients with infective endocarditis commonly presented with fever, which was reported in 62% to 96% of cases (13, 15-17, 22, 28). Heart murmurs were frequently detected at admission or during evaluation (17, 28). Congestive heart failure occurred in 16.9% to 66.7% of patients (18, 20, 26). Embolic complications were observed in multiple organs, including lungs, brain, spleen, and kidneys, with septic pulmonary emboli reported in 51.8% to 61.8% of patients (18, 24, 25). Additional vascular and cutaneous manifestations included clubbing, splenomegaly, pallor, and peripheral vascular phenomena (7, 14, 26). Renal impairment ranged from acute kidney injury to renal failure requiring dialysis in a minority of cases (18, 21, 25).

Right-sided infections were associated with pleuritic chest pain, while left-sided infections were more likely to cause neurological events and heart failure (14). Blood cultures were positive in most patients, supporting the diagnosis (27). Overall, HIV-positive patients showed a higher frequency of vascular and cutaneous phenomena, embolization, and splenomegaly compared with HIV-negative patients (7, 26).

Impact of immunological status on outcomes: Immunological status, as measured by CD4 counts, influenced the risk and severity of infective endocarditis in PLWH. Low CD4 counts were common, with 38% of tested patients having CD4 <200 cells/mm³ and a median of 90 in one cohort (18). Patients with CD4 200–400 cells/mm³ had an increased risk of IE, while those with CD4 <200 cells/mm³ showed significantly higher risk compared with the reference group (CD4 >500 cells/mm³) (28).

Median CD4 counts ranged from 68–142 cells/mm³ in IVDU (19, 22), and 90–300 cells/mm³ in other cohorts21. Some studies reported higher median CD4 counts, such as 437 cells/μL and 386.5±262.3 cells/μL, with a minority of patients remaining below 200 cells/mm³ (25, 26). Overall, lower CD4 counts were associated with more severe disease and complications, highlighting the influence of immunodeficiency on outcomes in HIV-positive patients with IE7,15,17,20 .

Mortality: Using a random-effects model, the overall mortality proportion among PLWH with IE was 14.7% (95% CI: 9.8–20.3%), with moderate heterogeneity (I^2 = 60.6%, τ^2 = 0.0065) and a slightly lower estimate under the common-effect model (13.9%; 95% CI: 11.3–16.9%) (figure 7). In HIV-negative patients, eight studies were included, yielding a higher and more variable pooled mortality of 22.3% (95% CI: 1.0–57.5%) in the random-effects model, with very high heterogeneity (I^2 = 96.7%, τ^2 = 0.1783); the common-effect model gave a lower estimate of 15.7% (95% CI: 12.9–18.7%) (figure 8). These mortality estimates should be considered exploratory due to the

persistent heterogeneity across studies and limited adjustment for confounding variables. Meta-regression analyses indicated that study year, design, and country did not significantly explain heterogeneity, and leave-one-out analyses showed that no single study substantially influenced overall estimates.

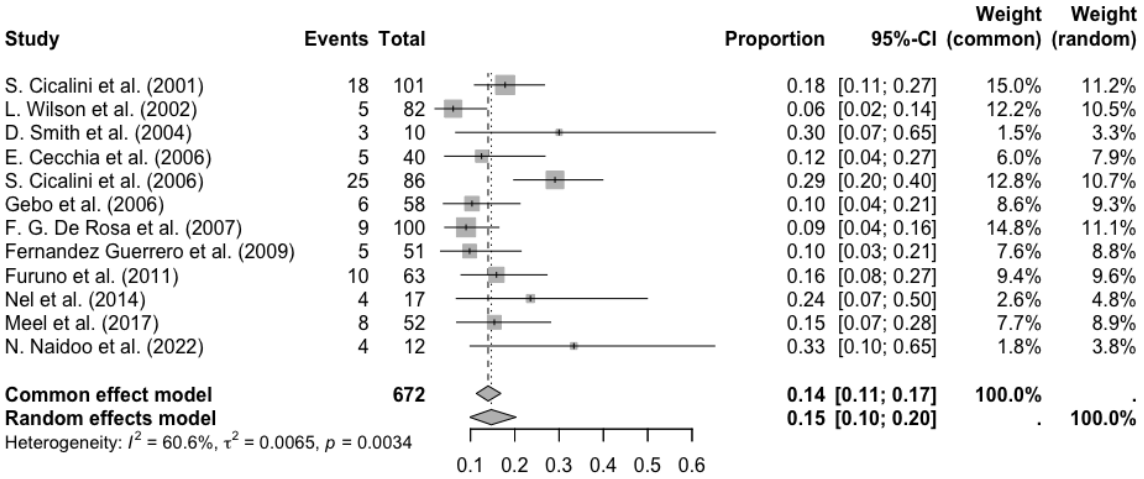

Figure 7. Mortality in HIV-positive IE patients.

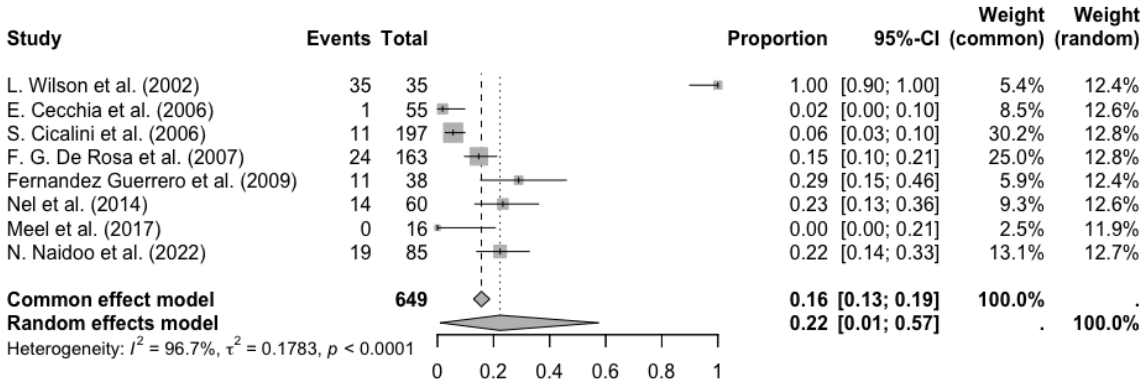

Figure 8. Mortality in HIV-negative IE patients.

Quality assessment: The quality of the 17 included studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates cohort studies across three domains: selection, comparability, and outcome, with a maximum score of 9. Across all studies, the NOS scores ranged from 5 to 9 (median 7), reflecting overall moderate methodological quality. Selection: Representativeness of the exposed cohort (PLWH with IE) and selection of the non-exposed cohort (HIV-negative patients with IE) were generally strong, with 15 studies earning stars for both. Ascertainment of exposure (HIV status) was consistently reliable, as all studies received a star. However, only three studies clearly demonstrated that the outcome of interest (IE) was not present at baseline, indicating potential selection bias. Comparability: Adjustment for confounding variables varied. Ten studies received one star, while two studies (Cicalini 2006; Naidoo 2022) achieved two stars by controlling for key factors such as IVDU or ART status. Nonetheless, inconsistent adjustment across studies remained a notable limitation. Outcome: Outcome assessment was robust, with nearly all studies relying on medical records or standardized diagnostic criteria. Adequacy of follow-up was strong, with 14 studies receiving stars, although four studies lacked sufficient follow-up duration to fully capture outcomes such as mortality. Overall, while most studies demonstrated reliable exposure and outcome assessment, variability in confounder adjustment and limited baseline outcome exclusion reduced comparability and increased risk of bias. (Supplementary tables 6, 7)

Discussion

This review elucidates the epidemiology, clinical characteristics, microbiology, and outcomes of IE in PLWH and HIV-negative patients. Staphylococcus aureus emerged

as the leading pathogen across both groups, with MRSA more prevalent in PLWH cases. Mortality was slightly higher in PLWH exacerbated by low CD4 counts (<200 cells/mm³) and left-sided IE, though high heterogeneity suggests study-specific influences (14, 22, 29). Microbiologically, Staphylococcus aureus dominated, with prevalence from 24.2% to 75% in PLWH and up to 86% in HIV-negative patients (16, 30). MRSA was more common in PLWH cases (up to 27.5%), often community-acquired (OR 2.73, 95% CI: 1.30–5.71), while HIV-negative patients showed lower MRSA rates (12.5%) (15, 31). Streptococci (e.g., S. viridans, 5%–14.1%) were more frequent in HIV-negative patients, aligning with left-sided IE, while PLWH exhibited higher rates of atypical pathogens (e.g., 58.3%, Bacillus cereus) and culture-negative IE, possibly due to immunosuppression (19, 26). Enterococci rose over time in IVDUs (1.3% to 4.4%), with mortality risks (OR 4.6, P = 0.07), and fungal infections (Candida albicans, 1.8%) remained rare (18, 25). Comparatively, studies on streptococcal IE in the general population (non-PLWH) offer context. Kim et al. reported the Mitis group (33%) and Pyogenic group (17%) as frequent causes among 296 IE cases, though they excluded non-IE BSIs, limiting prevalence estimates (33). Nilson et al. analyzed 201 IE cases versus 850 streptococcal BSIs, linking Mitis and Mutans groups to IE but identifying only 26% at species level, omitting Pyogenic streptococci (34). Another study, using a population-based design, achieved >95% species-level identification across all streptococcal blood stream infections, including Pyogenic and *S. pneumoniae*, addressing prior coding gaps. It identified *S. mitis/oralis* as a common high-prevalence IE cause, with *S. agalactiae* and *S. dysgalactiae* notable despite moderate prevalence, and *S. gallolyticus*, *S. sanguinis*, and *S. gordonii* showing high IE risk (35).

These patterns in non-PLWH parallel our microbiological profile, where *S. aureus* predominated (24.2–75%) in PLWH, yet streptococci (5–14.1%) remained relevant, suggesting overlapping bacterial etiologies across IE contexts. Research in non-HIV patients shows *S. aureus* as the leading pathogen in IVDU-IE, a trend linked to higher *S. aureus* skin colonization in IVDU individuals due to damaged nasal mucosa and needle-induced skin breaches (36-38). studies also note increased isolation of rare pathogens like *Pseudomonas*, polymicrobial infections, and fungi, differing from non-IVDU-IE, with saliva use in injections associated with atypical organisms (*H. parainfluenzae*, *E. corrodens*, *S. milleri*) (39, 40). Studies on IE in non-HIV chronic liver disease patients report heightened complications, underscoring IVDU-IE's complexity 41. Non-HIV IVDU-IE patients experience longer hospital stays due to addiction treatment, yet show lower mortality than non-IVDU-IE peers, possibly due to younger age and fewer comorbidities (stroke, heart failure) (42). This lower mortality parallels our pooled rates (16.9% in PLWH vs. 14.6% in HIV-negative), though CD4 counts in PLWH suggest additional risk factors (table 2).

Table 2. Microbiological profile of IE in PLWH vs. HIV-negative patients

Pathogen / Feature	PLWH (HIV-Positive)	HIV-Negative Patients	Notes / Context
Staphylococcus aureus	24.2–75% of cases; MRSA up to 27.5%, often community-acquired (OR 2.73, 95% CI: 1.30–5.71)	Up to 86% of cases; MRSA ~12.5%	Leading cause in both groups; more MRSA in PLWH
Streptococci	5–14.1%; less frequent than in HIV-negative patients	More frequent; linked to left-sided IE	Non-PLWH studies show Mitis (33%), Pyogenic (17%), S. mitis/oralis, S. agalactiae, S. dysgalactiae, S. gallolyticus common
Enterococci	Rare, but increased in IVDUs over time (1.3% → 4.4%); associated with higher mortality (OR 4.6, p=0.07)	Reported, but less highlighted	Rising trend in IVDUs
Gram-negative bacteria	Atypical organisms frequent (e.g., Bacillus cereus 58.3%, Klebsiella, Micrococcus)	Rare pathogens (e.g., Pseudomonas, H. parainfluenzae, E. corrodens) more in IVDU-IE	Saliva use in IVDU linked to unusual pathogens
Fungi	Candida albicans (1.8%) – rare	Rare (also Candida, sporadic cases)	Low prevalence in both

Pathogen / Feature	PLWH (HIV-Positive)	HIV-Negative Patients	Notes / Context
Polymicrobial infections	Occasional, with culture-negative IE more common (due to immunosuppression)	Seen in IVDU-IE (higher risk of polymicrobial/fungal)	Culture-negative cases rising in some cohorts
IVDU-related trends	Staphylococci predominate; atypical/culture-negative more common in PLWH IVDUs	S. aureus leading cause in IVDUs; longer hospital stays, lower mortality than non-IVDU-IE	IVDU-IE differs from non-IVDU-IE in pathogen profile and outcomes

IE: infective endocarditis, TEE: Transthoracic & Transesophageal Echocardiography (TEE), CA-MRSA: Community-Associated Methicillin-Resistant Staphylococcus Aureus, IVDU: intravenous drug users, PLWH: people living with human immunodeficiency virus, HIV: human immunodeficiency virus

Valve involvement patterns reinforced these differences. Right-sided IE, particularly tricuspid (up to 60.4%), prevailed in PLWH, often linked to IVDU and lower CD4 counts, while HIV-negative patients favored mitral (55.8%) and aortic (52.0%) involvement (7, 19). Some studies showed balanced distributions in PLWH (e.g., aortic 37.4%, tricuspid 36.4%), contrasting with minimal tricuspid involvement (4.7%) in HIV-negative patients (7, 29). Vegetation size differed, with HIV-negative patients having larger vegetations (23.7±7.1 mm vs. 13.6±6.8 mm, P= 0.001), associated with increased mortality when >15 mm, while PLWH had higher multivalvular involvement (up to 37.5%) (17, 22, 31).

Clinical presentations diverged significantly. PLWH frequently exhibited pulmonary symptoms, with septic emboli rates of 51.8%–61.8% versus 13.2% in HIV-negative patients ($p < 0.001$), alongside pleuritic chest pain tied to right-sided IE (18, 25). HIV-negative patients showed more left-sided complications, such as heart failure (38.6% vs. 19.3%, $p < 0.001$) and systemic emboli (23.5% vs. 12.7%, $p < 0.001$) (14, 29). Fever was near-universal, though shorter in PLWH (9.7 vs. 15.7 days, P= 0.007), with additional symptoms like clubbing (75% vs. 35.3%, P= 0.009), hematuria (58.3% vs. 29.4%, P = 0.046), and splenomegaly (33.3% vs. 9.4%, P = 0.018) more prevalent in PLWH cases (26, 29). Renal failure varied, with rates up to 30% in non-IVDU cohorts versus 2.9% in PLWH requiring dialysis (24, 25).

Mortality outcomes showed nuanced trends. Pooled in-hospital mortality was 16.9% (95% CI: 11.5–23.0%) in PLWH versus 14.6% (95% CI: 7.5–23.7%) in HIV-negative patients, with an unadjusted risk ratio of 1.71 (95% CI: 1.32–2.21) reduced to 1.34 after IVDU adjustment (7, 21). Some studies reported higher HIV-negative mortality (28.9% vs. 9.8%), while others favored PLWH (12.5% vs. 1.8%), with left-sided IE (OR 5.2–5.9) and negative blood cultures (AOR 7.85, P = 0.001) as key predictors (14, 17). A prior systematic review in the general population identified key predictors of IE mortality, ranked by odds ratio for clinical relevance. Left ventricular dysfunction, marked by hemodynamic instability and preoperative congestive heart failure (CHF), consistently emerged as a dominant factor, strongly predicting mortality across multiple analyses, aligning with our higher heart failure prevalence (38.6% vs. 19.3%) in HIV-negative patients tied to left-sided IE. Sepsis and septic shock also stood out as critical, particularly with perivalvular abscesses, a finding resonant with our PLWH cohort's frequent septic emboli (51.8–61.8%). Renal failure, indicated by elevated plasma creatinine, emerged as a significant predictor in some analyses, reflecting systemic complications, though less evident in our data (43).

Balancing IVDU and immunosuppression: Low CD4 counts reflect underlying immunosuppression, which may predispose patients to more severe infections and poorer outcomes, while IVDU introduces a distinct set of risks related to pathogen exposure and recurrent bacteremia. Immunological status, measured by CD4 cell counts, showed a consistent relationship with IE severity and mortality. Across studies, approximately 38% of tested patients had CD4 <200 cells/mm³, with median counts often below 150 cells/mm³ among IVDU populations. Patients with CD4 counts between 200 and 400 cells/mm³ exhibited increased IE risk, while those with CD4 <200 cells/mm³ had the highest susceptibility compared with the reference group (CD4 >500 cells/mm³). CD4 counts <200 cells/mm³ doubled mortality risk in PLWH (OR 2.38, 95% CI: 1.62–3.49, $p < 0.001$), with no deaths above 500 cells/mm³, contrasting with stable outcomes in some cohorts possibly due to ART (7, 18, 19).

Limitations: This meta-analysis has several limitations. High heterogeneity across outcomes reflects diverse study populations, settings, and definitions, incomplete reporting of ART regimens and usage precludes stratification by ART era, thereby limiting the relevance to current practice. The implausibly high IVDU prevalence suggests inconsistent reporting, with sensitivity analyses reducing estimates but not heterogeneity. Sparse reporting of CD4 counts and HIV-

negative IVDU status hinders subgroup analyses. The limited number of studies for some outcomes reduces statistical power and the reliability of bias assessment. Reliance on observational studies introduces confounding, particularly from IVDU and ART, despite adjustments for these factors.

Clinical implications: Clinicians should prioritize routine screening for intravenous drug use in PLWH presenting with fever or septic symptoms, given the high IVDU prevalence and its association with right-sided IE. Additionally, monitoring CD4 counts below 200 cells/mm³ is critical, as this threshold significantly elevates mortality risk, warranting aggressive antiretroviral therapy optimization to improve immunological status and outcomes. Targeted antimicrobial strategies against MRSA are advisable in PLWH due to elevated prevalence, while emphasizing harm reduction programs for IVDU could reduce overall IE incidence in high-risk cohorts.

This meta-analysis suggests broadly comparable risks of infective endocarditis (IE) and mortality between people living with HIV (PLWH) and HIV-negative individuals, while indicating a possible higher prevalence of IVDU-related right-sided IE and MRSA infection among PLWH. However, the substantial heterogeneity across studies warrants cautious interpretation and limits the generalizability of these findings. The results highlight potential areas for clinical attention, such as considering IVDU screening in PLWH presenting with fever and supporting ART adherence to reduce adverse outcomes. Further studies incorporating detailed ART data and temporal analyses are needed to clarify these associations and improve risk estimation in diverse populations.

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