JACC: HEART FAILURE VOL. 7, NO. 2, 2019

PUBLISHED BY ELSEVIER

CLINICAL RESEARCH

Cardiac Dysfunction Among People Living With HIV

A Systematic Review and Meta-Analysis

Sebhat Erqou, MD, PhD,[a,b,*] Bereket Tessema Lodebo, MD, MPH,[c,*] Ahmad Masri, MD,[d] Ahmed M. Altibi, MD,[d] Justin B. Echouffo-Tcheugui, MD, PhD,[e] Anastase Dzudie, MD,[f] Feven Ataklte, MD, MPhil,[g] Gaurav Choudhary, MD,[a,b] Gerald S. Bloomfield, MD, MPH,[h] Wen-Chih Wu, MD, MPH,[a,b] Andre Pascal Kengne[i]

ABSTRACT

OBJECTIVE To synthesize existing epidemiological data on cardiac dysfunction in HIV.

BACKGROUND Data on the burden and risk of human immunodeficiency virus (HIV) infection–associated cardiac dysfunction have not been adequately synthesized. We performed meta-analyses of extant literature on the frequency of several subtypes of cardiac dysfunction among people living with HIV.

METHODS We searched electronic databases and reference lists of review articles and combined the study-specific estimates using random-effects model meta-analyses. Heterogeneity was explored using subgroup analyses and meta-regressions.

RESULTS We included 63 reports from 54 studies comprising up to 125,382 adults with HIV infection and 12,655 cases of various cardiac dysfunctions. The pooled prevalence (95% confidence interval) was 12.3% (6.4% to 19.7%; 26 studies) for left ventricular systolic dysfunction (LVSD); 12.0% (7.6% to 17.2%; 17 studies) for dilated cardiomyopathy; 29.3% (22.6% to 36.5%; 20 studies) for grades I to III diastolic dysfunction; and 11.7% (8.5% to 15.3%; 11 studies) for grades II to III diastolic dysfunction. The pooled incidence and prevalence of clinical heart failure were 0.9 per 100 person-years (0.4 to 2.1 per 100 person-years; 4 studies) and 6.5% (4.4% to 9.6%; 8 studies), respectively. The combined prevalence of pulmonary hypertension and right ventricular dysfunction were 11.5% (5.5% to 19.2%; 14 studies) and 8.0% (5.2% to 11.2%; 10 studies), respectively. Significant heterogeneity was observed across studies for all the outcomes analyzed ($I^2 > 70\%$, $p < 0.01$), only partly explained by available study level characteristics. There was a trend for lower prevalence of LVSD in studies reporting higher antiretroviral therapy use or lower proportion of acquired immune deficiency syndrome. The prevalence of LVSD was higher in the African region. After taking into account the effect of regional variation, there was evidence of lower prevalence of LVSD in studies published more recently.

CONCLUSIONS Cardiac dysfunction is frequent in people living with HIV. Additional prospective studies are needed to better understand the burden and risk of various forms of cardiac dysfunction related to HIV and the associated mechanisms. (Cardiac dysfunction in people living with HIV–a systematic review and meta-analysis; CRD42018095374) (J Am Coll Cardiol HF 2019;7:98–108) © 2019 by the American College of Cardiology Foundation.

From the [a]Department of Medicine, Providence VA Medical Center, Providence, Rhode Island; [b]Department of Medicine, Alpert Medical School of Brown University, Providence, Rhode Island; [c]Department of Medicine, Harbor-UCLA Medical Center, Los Angeles, California; [d]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; [e]Department of Medicine, Johns Hopkins University, Baltimore, Maryland; [f]Faculty of Medicine and Biomedical Sciences, University of Yaounde, Yaounde, Cameroon; [g]Department of Medicine, Boston University, Boston, Massachusetts; [h]Duke Clinical Research Institute, Duke Global Health Institute and Department of Medicine, Duke University, Durham, North Carolina; and the [i]South African Medical Research Council and University of Cape Town, South Africa. *Drs. Erqou and Lodebo contributed equally to this work and are joint first authors. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 11, 2018; revised manuscript received September 26, 2018, accepted October 4, 2018.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2018.10.006

About 36.7 million people are infected with human immunodeficiency virus (HIV) globally. In the United States, it was estimated that 1.1 million people were living with HIV in 2016 (1). The advent of highly active antiretroviral treatment (HAART) signified a defining moment for people living with HIV (PLHIV), with patients achieving longer life expectancy (2). This shift to longer-term survival has led to increased prevalence of chronic diseases in PLHIV, including cardiovascular disease (CVD) (3–5). A significant proportion of the CVD morbidity and mortality in PLHIV is due to HIV-associated cardiac dysfunction (3,5). Although the frequency of HIV-associated cardiomyopathy is thought to have decreased in the past decade, HIV patients still have a nearly 1.5- to 2-fold higher risk of clinical cardiac dysfunction (5–7). The proposed mechanisms include chronic inflammation, toxicity from certain HAART regimens, opportunistic infections, direct viral infection of the myocardium, nutritional disorders, and cardiac autoimmunity, among others (6,8).

SEE PAGE 109

Accruing epidemiological studies have reported on the frequency of cardiac dysfunction among PLHIV and the risk of cardiac dysfunction in relation to HIV infection; however, in these studies, the extent of cardiac dysfunction burden or risk is highly variable. In addition, differences in burden or risk by type of ventricular dysfunction (i.e., left ventricular systolic dysfunction [LVSD], left ventricular diastolic dysfunction [DD], right ventricular dysfunction [RVSD]) have not been well established. There is a need for a quantitative synthesis of the evidence to allow easier interpretation and application of the extant data.

We sought to perform a systematic review and meta-analysis of published literature on the frequency and relative risk of clinical heart failure (HF), LVSD, dilated cardiomyopathy (DCM), DD, pulmonary hypertension (PH), or RVSD among PLHIV.

METHODS

This study is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (9) guideline and is registered with International Prospective Register of Systematic Reviews (PROSPERO). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is provided in Online Table 1.

Three investigators (S.E., B.T.L., A.M.A.) independently performed the search, study selection, and data extraction. Complete details of the methods used in this meta-analysis are provided in the Online Methods. Briefly, we searched the electronic databases (Online Table 2) and the reference lists of relevant articles (2,6,10–14). We included studies of HIV-infected adults, reporting on the prevalence, incidence, or relative risk of HF, LVSD, DCM, DD, PH, or RVSD. Exclusion criteria were study size <50, studies including children <15 years of age, studies of HIV patients in which participants were selected based on suspected or known cardiac disease, and reports based on autopsy examination to diagnose heart disease. For the purpose of the meta-analysis, we pooled studies with a sufficiently similar definition of cardiac dysfunction. For LVSD, our main definition was ejection fraction <50% or fractional shortening <26%, but we also included other studies that were deemed to have used sufficiently close definition of LVSD. DCM was defined as presence of both LVSD and LV dilatation. For DD, we pooled studies that reported grades I to III DD separately from those that reported advanced (grades II to III) DD. For PH, we pooled studies that defined the outcome as echocardiogram-estimated pulmonary artery systolic pressure >35 mm Hg or >40 mm Hg. RVSD was defined as RV systolic dysfunction (reduced RV function, RVEF <50% or RVEF <44%), RV dilatation, or both. We pooled the study-specific measures (i.e., prevalence, incidence, relative risk) with random-effects model meta-analysis using the DerSimonian and Laird's method (15). The Freeman-Tukey single arcsine transformation helped limit the effects of extreme values on the pooled estimates (16). We assessed the methodological quality of the individual studies using the Newcastle-Ottawa Scale (NOS) (17). We assessed between-study heterogeneity using Q and I^2 statistics. We explored sources of heterogeneity using subgroup analyses and/or meta-regression by the following a priori-defined study-level characteristics: publication year, study region, study quality, study size, average age, proportion males, proportion with acquired immune deficiency syndrome (AIDS), average CD4 T-cell count, and proportion on antiretroviral therapy (ART). For subgroup analyses, publication year was divided "pre-1996," "1996–2004," and "post-2004" to represent the different eras of ART availability to HIV patients. We further tested the hypotheses that the prevalence of LVSD is declining in the post-ART era after taking the effect of regional variation in ART uptake into account by fitting study region (categorical) and publication year (continuous) in a meta-regression

ABBREVIATIONS AND ACRONYMS

AIDS = acquired immune deficiency syndrome
ART = antiretroviral therapy
CI = confidence interval
CVD = cardiovascular disease
DCM = dilated cardiomyopathy
DD = diastolic dysfunction
HAART = highly active antiretroviral treatment
HF = heart failure
HIV = human immunodeficiency virus
LVSD = left ventricular systolic dysfunction
NOS = Newcastle-Ottawa Scale
PH = pulmonary hypertension
PLHIV = people living with HIV
RVSD = right ventricular dysfunction

model. We assessed publication or small-study bias using Egger regression test for funnel-plot asymmetry (18). We further assessed heterogeneity and publication bias by subgrouping the studies into larger and smaller size based on the number of participants and comparing the pooled estimates between the 2 subgroups. Statistical tests were 2-sided and used a significance level of $p < 0.05$. Analyses were conducted with Stata 13 (Stata Corp LP, College Station, Texas).

RESULTS

STUDY SUMMARY. The study flow diagram is shown in Online Figure 1. Of the 3,778 citations (2,013 in PubMed-Medline; 1,715 in Embase) screened, we included 63 reports (Online Refs. 8-70) representing data from 54 studies comprising 125,382 adults with HIV infection and 12,665 cases of various cardiac dysfunction outcomes. The design and characteristics of the included studies are shown in **Table 1** and Online Table 3. Eighteen studies were from North America, 15 from Europe, 11 from Africa, and 10 from Asia. Most studies were cross-sectional, case-control, or retrospective in design. The average age across the studies was 47 years (range 28 to 53 years; 50 studies). The average proportion of males across the studies was 82% (range 26% to 100%; 48 studies) and the average proportion of blacks was 45% (range 12% to 100%; 19 studies). The proportion with AIDS across the studies was 47% (range 0% to 100%; 20 studies) and the proportion on ART was 77% (range 0% to 100%; 31 studies). The average CD4 count of participants across the studies was 380 cells/mm^3 (range 42 to 670 cells/mm^3; 31 studies). The reported cardiac dysfunction outcomes and corresponding definitions are provided in Online Table 4. Most studies reported on >1 cardiac outcome. The quality score of the studies assessed using NOS is shown in **Table 1** (Online Table 5 for detail of scoring). The majority of the studies were graded as having low risk of bias, and >95% were graded as having low or moderate risk of bias.

META-ANALYSIS. The pooled prevalence of LVSD across 26 studies was 12.3% (95% confidence interval [CI]: 6.4% to 19.7%) (**Figure 1**, Online Figure 2); the corresponding prevalence for DCM across 17 studies was 12.0% (95% CI: 7.8% to 17.2%) (**Figure 1**, Online Figure 3). One study (19) reported an incidence rate of LVSD of 18 per 100 person-years (95% CI: 9.2 to 32.8 per 100 person-years); another study (20) reported an incidence rate of DCM of 1.6 per 100 person years (95% CI: 1.3 to 2.0 per 100 person-years).

The pooled prevalence of grades I to III DD across 20 studies was 29.3% (95% CI: 22.6% to 36.5%) (**Figure 1**, Online Figure 4); the corresponding prevalence for grades II to III DD across 11 studies was 11.7% (95% CI: 8.5% to 15.3%) (**Figure 1**, Online Figure 5). The relative risk of all grades of DD among HIV patients compared with healthy control patients was 3.0 (95% CI: 1.8 to 5.1; 3 studies) (Online Figure 6). The pooled incidence and prevalence of HF were 0.9 per 100 person-years (95% CI: 0.4 to 2.1 per 100 person-years; 4 studies) and 6.5% (95% CI: 4.4% to 9.6%; 8 studies), respectively (**Figure 2**). The relative risk of HF among patients with HIV, compared with healthy controls, was 1.7 (95% CI: 1.4 to 2.0; 3 studies) (Online Figure 6). The combined prevalence of PH defined as PASP >35 mm Hg across 14 studies (except 1 study using a >40 mm Hg cutoff) was 11.5% (95% CI: 5.5% to 19.2%) (**Figure 1**, Online Figure 7). The pooled prevalence of RV dysfunction across 10 studies was 8.0% (95% CI: 5.2% to 11.2%) (**Figure 1**, Online Figure 8).

ASSESSING HETEROGENEITY. There was evidence of substantial heterogeneity across the studies for all outcomes analyzed (I^2 >70%; $p < 0.01$) that was only partly explained by available study level characteristics, including study region, publication year, average age of participants, percentage male, percentage with AIDS, percentage on ART mean CD4 count, and number of cases (**Figures 3 and 4**, Online Figures 9 to 13). The prevalence of LVSD was higher among studies reporting higher proportion of participants with AIDS ($n = 10$; $p = 0.03$; $R^2 = 0.91$), and was lower among studies reporting higher proportion of participants on ART ($n = 12$; $p = 0.05$, $R^2 = 0.40$) (**Figure 3**). We did not find a significant difference in prevalence of LVSD between subgroups of studies published pre- and post-ART era; however, after taking into account the effect of regional variation, we found evidence of lower prevalence of LVSD in more recent studies ($p = 0.03$). The prevalence of LVSD was also higher in studies with a higher proportion of younger participants and those with moderate to high risk of bias (**Figure 4**). The prevalence of DCM was higher in studies from the African region (Online Figure 9). The prevalence of DD decreased with publication year of studies (i.e., studies published later reported lower prevalence [$n = 20$; $p < 0.001$, $R^2 = 0.53$]) (**Figure 3**). There was a trend for the prevalence of advanced DD to be lower in studies with higher mean CD4 count of participants ($n = 6$; $p = 0.05$; $R^2 = 0.44$) (**Figure 3**).

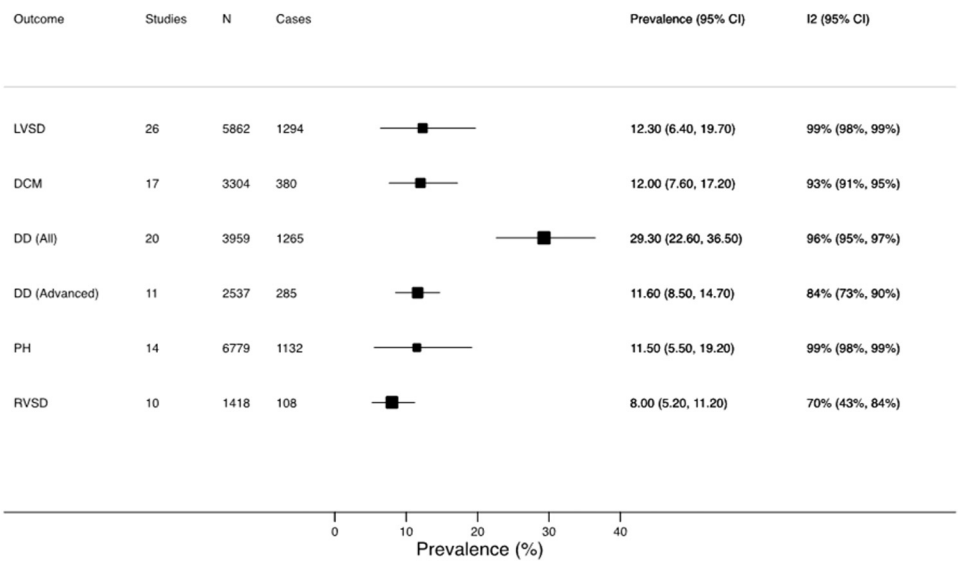
SECONDARY ANALYSES. For PH, in a secondary analysis grouping studies that reported PASP cutoffs of 30, 35, and 40 mm Hg to define PH yielded pooled prevalence estimates of 20.3% (95% CI: 4.6% to 43.0%), 12.2% (95% CI: 6.7% to 19.0%), and 11.3% (95% CI: 2.2% to 26.0%), respectively (**Figure 5**). For

TABLE 1 Characteristics of 54 Studies Included in Meta-Analysis

First Author, Year	Place	Year	Design	Outcome Reported	N	Male, %	Age, yrs	ART, %	AIDS, %	CD4 Count	NOS
Agrawal, 2016	India	2012–2013	CS	LVSD, DCM, DD	100	54	36.8	NA	34	248	8
Akhras, 1994	UK	1991–1992	CS	LVSD, DCM, RVSD	124	100	37	NA	81	NA	6
Al-Kindi, 2016	USA	2014–2015	Db	HF	36,400	69	NA	NA	NA	NA	7
Badie, 2017	Iran	2013–2014	CS	LVSD, DD, PH	231	75	41	100	NA	408	3
Bahrami, 2014	USA	2007–2008	RC	HF	21,729	NA	52.6	NA	NA	NA	7
Barbaro, 1996	Italy	1993–1996	PC	LVSD	1,236	72	28	NA	NA	670	7
Bijl, 2001	the Netherlands	1999	CS	LVSD, RVSD	105	76	41.5	100	NA	340	8
Blanchard, 1991	USA	1987–1989	CS	LVSD, RVSD	70	NA	38.1	NA	NA	NA	6
Cardoso, 1998	Portugal	1991–1995	CS	HF, LVSD, DCM, DD, RVSD	181	76	33	46	48	NA	8
Chaudhary, 2017	India	NA	CS	DD, PH	75	73.3	35.8	43	73	NA	8
Chillo, 2012	Tanzania	2009	CS	DCM, PH	102	30	42	70	13	297	8
Corallo, 1988	Italy	1987	CS	HF, LVSD	102	79	29	NA	100	NA	5
Currie, 1994	UK	1990–1994	CS	HF, DCM, RVSD	296	NA	32.7	NA	NA	153	5
DeCastro, 1993	Italy	1988–1991	PC	HF, DCM	72	79	34.6	82	100	NA	7
El Hattaoui, 2008	Morocco	2004	CC	LVSD, DD	158	56	35	NA	56	NA	6
Esser, 2012	Germany	2004–2006	CS	HF, LVSD, DD, PH	803	83.4	43	85	NA	509	8
Fontes-Carvalho, 2015	Portugal	2012–2013	CS	DD	206	70	41.7	57	NA	499	9
Freiberg, 2017	USA	2003	RC	HF, PH	31,523	97.1	47.9	73.9	NA	382	9
Gillis, 2014	Canada	1995–2011	PC	HF	4,584	85	36	100	NA	250	9
Hadadi, 2010	Iran	2007–2008	CS	LVSD	134	73.1	36.5	NA	38	296	6
Hakim, 1996	Zimbabwe	1994	CS	HF, LVSD, DCM	157	51	34.4	NA	NA	NA	5
Hamadou, 2017	Cameroon	2016	CC	LVSD, DD	59	32.2	47	79.7	19	NA	7
Herskowitz, 1993	USA	1988–1991	PC	LVSD, HF	59	82.6	34.8	NA	NA	139	7
Himelman, 1989	USA	NA	CC	DCM	70	96	36	13	72	261	5
Hsue, 2010	USA	NA	CS	LVSD, DD, PH	196	85	47	82	NA	420	8
Isasti, 2013	Spain	2011	CS	LVSD, DD, PH, RVSD	196	85	46.4	94	28	544	8
Isiguzo, 2013	Nigeria	2010	CS	PH	200	29	39	NA	NA	312	6
Jain, 2014	India	2010	CS	LVSD, DD, PH	91	78	37.3	51	52	304	6
Kendall, 2014	Canada	2009	RC	HF	14,005	89.5	45	NA	NA	NA	7
Kjaer, 2006	Denmark	NA	CS	RVSD	90	86	43	86	NA	NA	5
Lebech, 2004	Denmark	2000–2001	CC	LVSD, RVSD	95	87	43	84	NA	540	8
Levy, 1988	USA	NA	CS	LVSD, DCM	60	98	36	NA	NA	NA	5
Longo-Mbenza, 1995	Congo Kinshasa	1991–1992	CS	DCM	83	NA	NA	NA	NA	NA	4
Longo-Mbenza, 1998	Congo Kinshasa	1987–1994	CS	DCM, DD	157	56.7	38	NA	NA	NA	8
Luo, 2010	China	2007–2008	CC	DD	84	40	39.6	50	50	419	7
Luo, 2014	China	2008–2010	CC	LVSD, DD, PH	325	73	38.2	NA	NA	NA	8
Marwadi, 2014	India	2012–2013	CS	DD	100	75	32.2	NA	NA	NA	7
Mondy, 2011	USA	2004–2006	CS	LVSD, DD, PH	652	76	41	73	19	462	9
Morris, 2012	USA	2007–2010	CS	LVSD, DD, PH	116	69.8	47.7	89	NA	578	6
Nayak, 2009	USA	2004–2005	CS	DD	91	96	38	100	0	NA	8
Nzuobontane, 2002	Cameroon	1996	CS	DCM	54	NA	NA	NA	55	195	4
Olusegun-Joseph, 2012	Nigeria	NA	CC	LVSD, DD	100	43	33.2	NA	NA	232	6
Owusu, 2014	Ghana	2010–2011	CS	LVSD, DCM, DD, PH	200	25.5	40.6	0	NA	NA	8
Pugliese, 2000	Italy	1989–1998	Db	DCM, PH	1,042	77	36	100	NA	NA	6
Quezada, 2012	Spain	2009–2011	CS	PH	392	83	46.9	84	NA	577	8
Rasoulinejad, 2014	Iran	2011–2013	CS	PH	170	63.5	41	100	NA	401	7
Roy, 1999	USA	1994–1995	CS	DCM	84	77	38.9	62	NA	42	3
Schwarze-Zander, 2015	Germany	2009–2012	CS	PH	374	80	46	87	31	476	8
Simon, 2014	USA	2009–2011	CS	LVSD, PH, RVSD	104	71	47	89	NA	591	6
Steverson, 2017	USA	2000–2016	CS	HF	5,041	83	47	84	NA	390	9
Tseng, 2012	USA	2001–2010	Db	HF, LVSD	230	87	39	NA	NA	353	8
Twagirumukiza, 2007	Rwanda	2005	CS	DCM	416	62	34.6	0	16	200	7
Vadivel, 2014	India	2008	CS	DCM	150	41	30.9	0	NA	473	8
Werneck, 1999	Portugal	NA	CS	LVSD	84	NA	NA	NA	NA	NA	NA

AIDS = acquired immune deficiency syndrome; ART = antiretroviral therapy; CC = case-control; CS = cross-sectional; Db = database; DCM = dilated cardiomyopathy; DD = diastolic dysfunction; HF = heart failure; LVSD = left ventricular systolic dysfunction; NA = not available; NOS = New Castle Ottawa Scale; PC = prospective cohort; PH = pulmonary hypertension; RC = retrospective cohort; RVSD = right ventricular systolic dysfunction.

FIGURE 1 Meta-Analysis of 6 HIV-Associated Cardiac Dysfunction Outcomes



CI = confidence interval; DCM = dilated cardiomyopathy; DD = diastolic dysfunction; LVSD = left ventricular systolic dysfunction; PH = pulmonary hypertension; RVSD = right ventricular dysfunction.

incident HF, including 1 study (21) that was reported in a conference proceeding only yielded comparable pooled estimate (incidence: 1.7 per 100 person-years; 95% CI: 0.25 to 11.8 per 100 person-years).

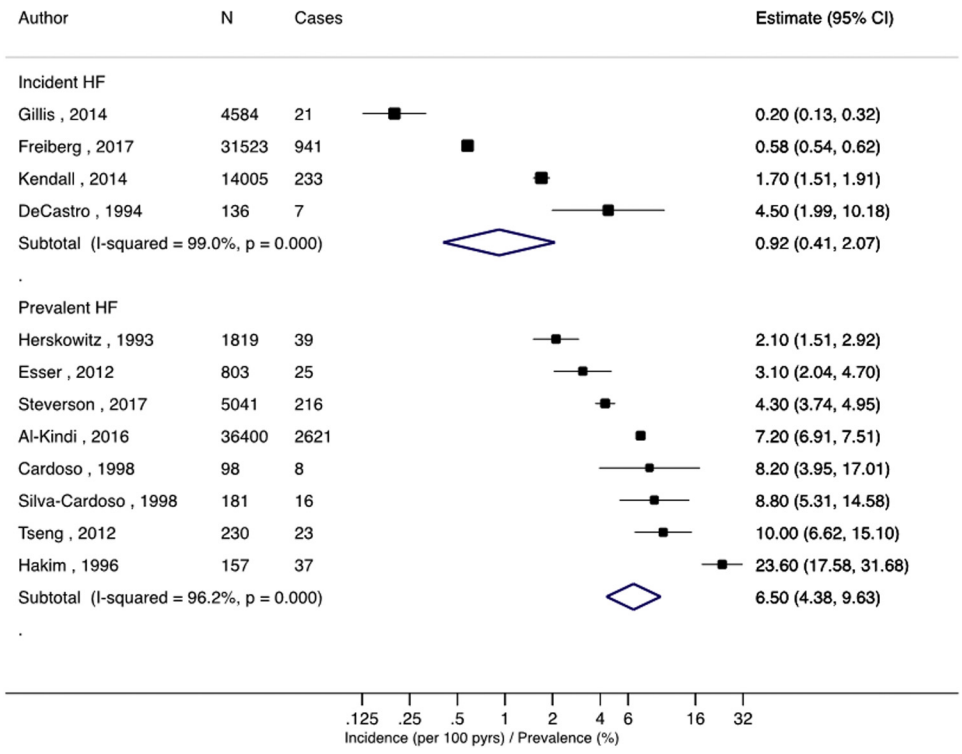
ASSESSING PUBLICATION BIAS. Funnel plots of the studies included in the meta-analyses for the various outcomes are shown in Online Figures 14 and 15. There was evidence of publication bias (in which small studies appeared to report more extreme values) for DCM and RVSD outcomes (p for Egger test of publication bias <0.05). The p values of the Egger test remained statistically significant after excluding studies reporting the most extreme 1 or 2 prevalence estimates; however, comparison of larger and smaller sized studies yielded comparable pooled estimates (Online Figures 9 and 13). The imputation of frequency estimates to achieve funnel plot symmetry using the trim and fill method attenuated the results; however, these imputed estimates were highly implausible (negative prevalence estimates), suggesting that the findings of funnel plot asymmetry were artifactual.

DISCUSSION

SUMMARY OF FINDINGS. In this meta-analysis comprising 125,382 PLHIV and 12,665 cases of cardiac dysfunction, we found a significant burden cardiovascular dysfunction among PLHIV across the spectrum of immune dysfunction, HIV disease, or treatment. The pooled prevalence estimates for LVSD, DCM, grades I to III DD, grades II to III DD, PH, and RVSD were 12.3%, 12.0%, 29.3%, 11.7%, 11.5%, and 8.0%, respectively. The pooled incidence and prevalence estimates of clinical HF were 0.9 per 100-person years and 6.5%, respectively. The pooled relative risk of HF and DD across a few studies comparing PLHIV with non-HIV-infected control patients was 1.7 and 3.0, respectively. We found that studies with a higher proportion of participants with AIDS or a lower proportion using ART reported a higher prevalence of LVSD. Studies from the African region reported a higher prevalence of DCM.

COMPARISON WITH PREVIOUS STUDIES AND EXPLANATION OF RESULTS. The present meta-analysis provides a comprehensive quantitative synthesis of available data on the epidemiology of cardiac dysfunction in the context of HIV. Compared with previous reviews (2,6,10-14), our study included a larger number of participants, and provided significant complementary information through the comprehensive inclusion of several outcomes including both left- and right-sided cardiac dysfunction (LVSD, DCM, DD, and RVSD), and PH. We also investigated the potential effects of several characteristics, including ART, immunodeficiency (as assessed by CD4 count, or symptomatic HIV infection or AIDS), and age, by performing meta-regression and

FIGURE 2 Meta-Analysis of HF Incidence and Prevalence in HIV



CI = confidence interval; HF = heart failure.

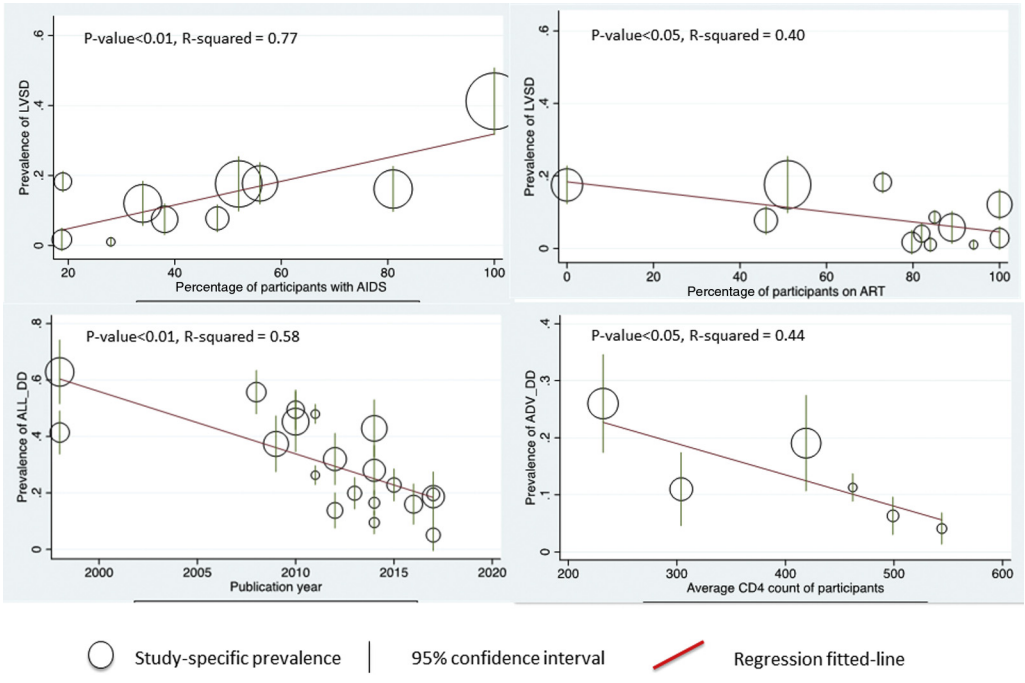
subgroup analyses. Previously, Cerrato et al. (11) performed quantitative meta-analyses of studies reporting the prevalence of HIV-associated systolic and diastolic dysfunction with focus on pauci symptomatic HIV patients in the HAART era (11). The review included 11 studies published after the year 2000, with >75% of participants known to be on HAART, yielding pooled analyses in up to 2,242 patients with HIV.

The frequency of cardiomyopathy in PLHIV reported in this review is materially higher than that reported by studies of general populations, which is in the range of 4% to 6% (22,23). Similarly, the prevalence of DD is 1.5- to 2-fold higher when compared with those reported for individuals in general populations (23,24). Such differences are likely to be underestimates because the participants represented in the general populations were significantly older than the studies on PLHIV included in this meta-analysis. PLHIV have also been shown to have materially higher risk of ischemic heart disease compared with non-HIV-infected patients (3), which taken together with nonischemic heart disease represents a substantial burden of CVD in this population.

The higher frequency of cardiac dysfunction related to the proportion of participants with AIDS might reflect the role that immunodeficiency, and opportunistic infections, play in the pathogenesis of cardiac dysfunction (6,7). Given the proposed role of immunodeficiency and opportunistic infections (among other factors) in pathogenesis of HIV-associated cardiac dysfunction, we anticipated that studies published in the pre-ART era and those from regions with lower coverage of ART would report higher prevalence. We did find that studies from the African region reported higher prevalence of DCM. Similarly, although we did not find significant difference in subgroup analyses of LVSD between studies published pre- and post-ART era, we found lower prevalence of LVSD in more recently published studies after taking into account the effect of regional variation. These findings suggest that regional variations in ART uptake may influence the previously reported decline in LVSD in post-HAART era.

Studies published in more recent years and those with higher average CD4 count reported a significantly lower prevalence of DD. The finding of reduced prevalence of DD in more recent studies is likely a

FIGURE 3 Meta-Regression of LVSD and DD by Various Study Level Characteristics

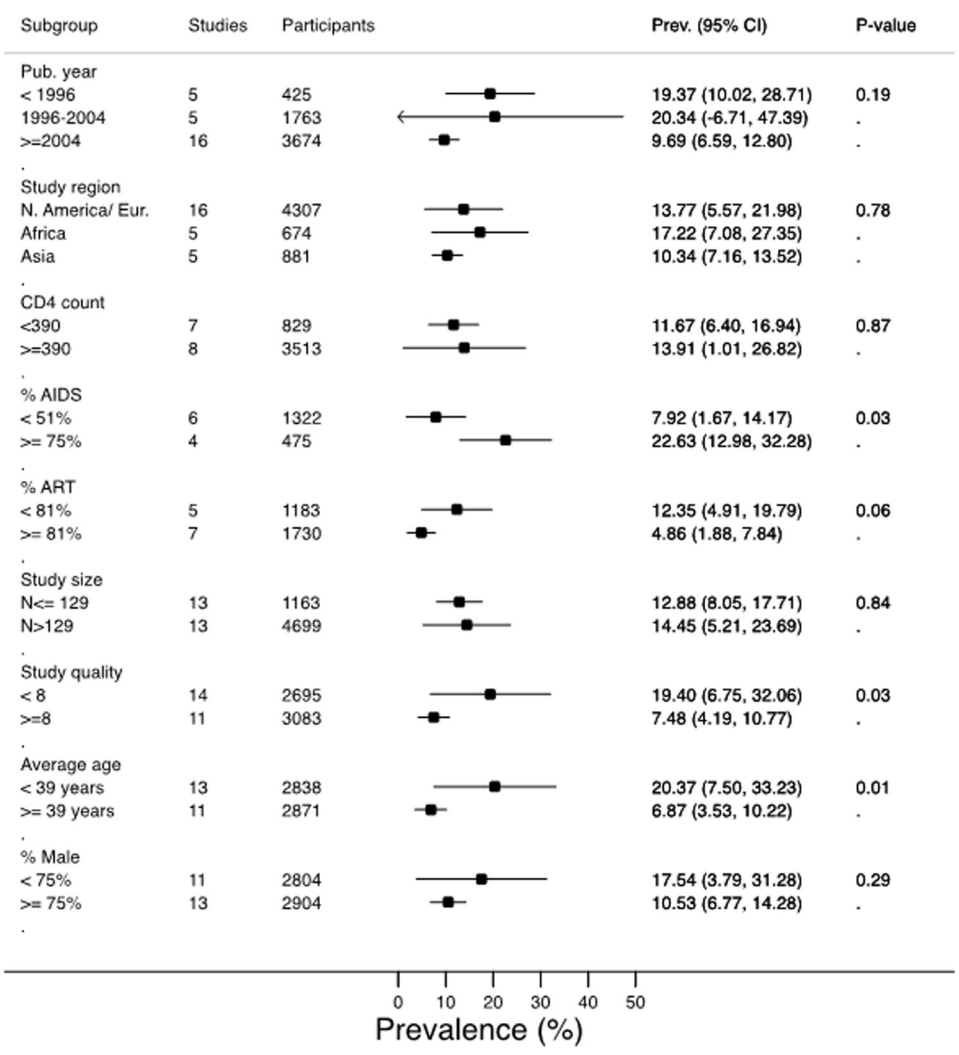


Black circles = the study-specific prevalence estimates; **vertical bars** = 95% CI; **red straight line** = regression fitted line. The **size of the circles** is proportional to study size. ALL_DD = All diastolic dysfunction; ART = antiretroviral therapy; ADV_DD = advanced diastolic dysfunction; CD4 = CD4 T-cell count; CI = confidence interval; DD = diastolic dysfunction; LVSD - left ventricular systolic dysfunction.

reflection of the change in the standardized echocardiographic diagnostic criteria over the years (25-27). On the other hand, the finding of inverse association between average study CD4 T-cell count and prevalence of advanced DD is consistent with the report by Hsue et al. (28) that showed LV mass in PLHIV is inversely proportional to CD4 T-cell count nadir. It is important to take caution in interpreting these findings because these are study-level associations and may not hold true for individuals because of ecological fallacy.

IMPLICATIONS OF OUR FINDINGS. Our findings are important in several ways. First, the substantial risk of various types of cardiac dysfunction in PLHIV helps create awareness within the medical community caring for these patients to watch for complications and implement early intervention when indicated (6). In addition to subclinical cardiac dysfunction identified using imaging modalities, PLHIV have materially increased risk of clinical HF, indicating that asymptomatic cardiac dysfunction identified on imaging can be progressive in a subset of participants. Epidemiological studies indicate that HIV-associated ventricular dysfunction and PH are associated with increased risk of mortality (2). Together, these data suggest that early detection of cardiac dysfunction in PLHIV could provide a window of opportunity in which it may be possible to institute intervention to reverse the course, as has been proposed for individuals in the general population with asymptomatic cardiac dysfunction (22,29). Our study specifically highlights the clinical importance of RVSD and PH in HIV infection because these conditions are associated with worse survival, especially in the context of HF with preserved ejection fraction (30,31), keeping in mind that the echocardiogram is not sensitive for PH diagnosis (32) or RV dysfunction (33). Second, our review highlights the need to understand the course of asymptomatic cardiac dysfunction in PLHIV through imaging and longitudinal follow-up, as has been done for general populations (22). There is a significant paucity of data detailing the natural course of cardiac dysfunction identified in PLHIV. There is also a need to further characterize and understand the pathogenesis of HIV cardiac dysfunction to foster the development of evidence-based and effective preventive interventions. In the past, smaller scale studies using cardiac magnetic resonance imaging

FIGURE 4 Subgroup Analyses of HIV-Associated LVSD

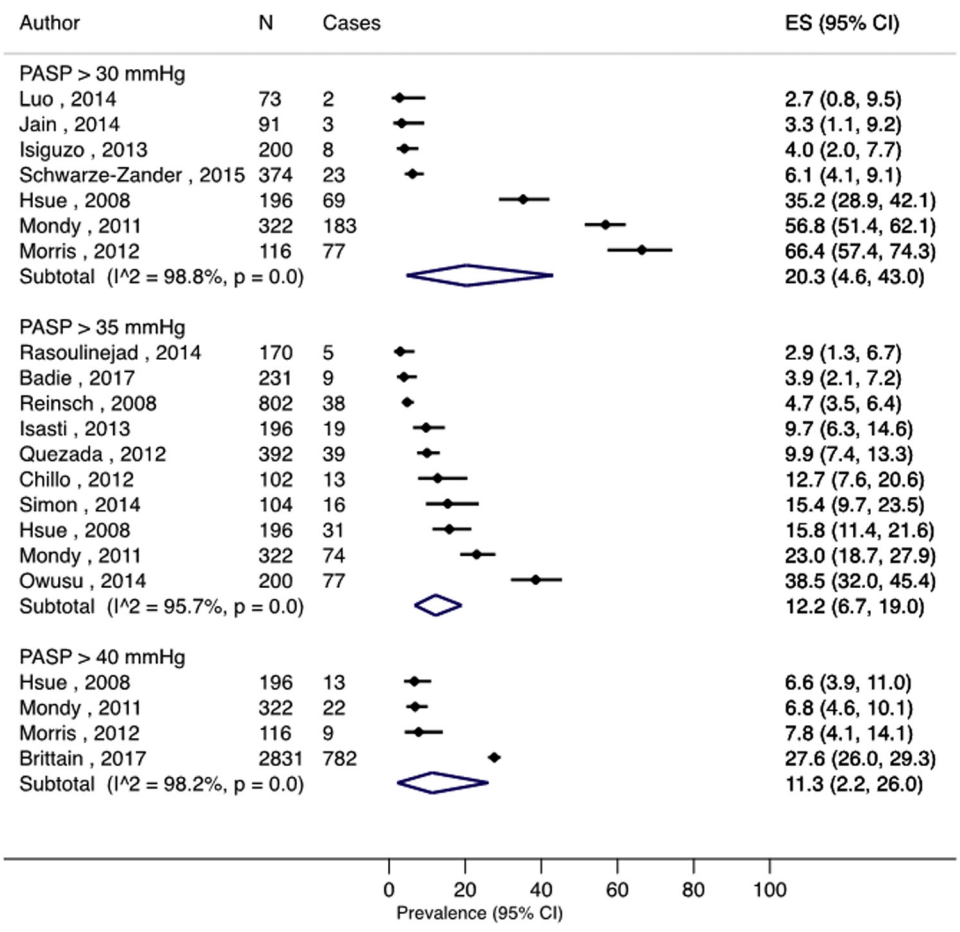


AIDS = acquired immune deficiency syndrome; ART = antiretroviral therapy; CI = confidence interval; Eur = Europe; LVSD = left ventricular systolic dysfunction; N. America = North America; Pub = publication.

have demonstrated a higher prevalence of cardiac steatosis, edema, and fibrosis in PLHIV, which may underlie the mechanism of cardiac dysfunction (34-36). Finally, this review, by pooling data from available studies on the subject, provides more precise estimates of the various HIV-associated cardiac dysfunction outcomes than was possible before. These data highlight the urgency for finding strategies to reduce the potential HIV-related burden of HF and associated cardiac disorders.

STUDY LIMITATIONS. First, the study is based on generally small-scale, medium quality, cross-sectional and retrospective studies that somewhat limited the quality of the data used to calculate the pooled estimates. Some of these studies are older and the definition of DD has changed across the years. Indeed, former DD grading systems not using tissue Doppler imaging, strain, and strain rates could lead to significant misclassifications; however, we found similar estimates between smaller and larger studies and between studies published at different times, suggesting that the effect of such bias is likely limited. Second, there was significant heterogeneity across the studies for all outcomes evaluated that

FIGURE 5 Meta-Analysis of Pulmonary Hypertension in HIV by PASP Cutoff



CI = confidence interval; ES = estimate; I^2 = I-squared; PASP = pulmonary artery systolic pressure.

was only partially explained by available study level characteristics, which limits the generalizability of the findings. We used random-effects model meta-analysis to mitigate the effect of heterogeneity, which assumes that the underlying population parameter is different across studies and attempts to determine the mean of those parameters. Another consequence of heterogeneity is that the meta-analysis yielded wider confidence intervals than would be expected for the size of the data. Third, there was evidence of significant publication bias for DCM, PH, and RVSD outcomes, which indicate that the smaller studies were more likely to be published if they reported more extreme estimates compared with the larger studies. Comparison of pooled estimates between the smaller and larger studies, or meta-regression of the estimates by the study size (i.e., number of participants or number of cases), however, yielded similar results between larger and smaller studies, indicating that the magnitude of any such bias is likely to be small.

ADDRESS FOR CORRESPONDENCE: Dr. Sebhat Erqou, Providence VA Medical Center, 830 Chalkstone Street, Providence, Rhode Island 02908. E-mail: sebhaterqou@gmail.com. Twitter: @GChoudharyMD, @MasriAhmadMD.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In meta-analysis of available observational studies in PLHIV, we found that the incidence of cardiac dysfunction was substantial. These findings should help raise awareness of clinicians taking care of PLHIV to consider early investigation and referral of those with cardiac dysfunction and allow institution of guideline-based treatment, while ongoing research seek to identify further preventive and therapeutic strategies.

TRANSLATIONAL OUTLOOK: There is a need for prospective epidemiological studies to better understand the burden and progression of cardiovascular complications in PLHIV, including a comprehensive evaluation of left and right ventricles that views them as a continuum rather than separate entities, and leveraging new imaging modalities such as cardiac magnetic resonance imaging to increase precision of diagnoses. Extensive phenotyping of patients with HIV-associated cardiac dysfunction, including genetic, proteomic, and metabolic studies, can form the basis for translational research.

REFERENCES

1. Centers for Disease Control and Prevention. HIV Surveillance Report, 2016. 2017;28.

2. Remick J, Georgiopoulou V, Marti C, et al. Heart failure in patients with human immunodeficiency virus infection: epidemiology, pathophysiology, treatment, and future research. Circulation 2014;129:1781–9.

3. Vachiat A, McCutcheon K, Tsabedze N, Zachariah D, Manga P. HIV and ischemic heart disease. J Am Coll Cardiol 2017;69:73–82.

4. Manga P, McCutcheon K, Tsabedze N, Vachiat A, Zachariah D. HIV and nonischemic heart disease. J Am Coll Cardiol 2017;69:83–91.

5. Butt AA, Chang CC, Kuller L, et al. Risk of heart failure with human immunodeficiency virus in the absence of prior diagnosis of coronary heart disease. Arch Intern Med 2011;171:737–43.

6. Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human immunodeficiency virus and heart failure in low- and middle-income countries. J Am Coll Cardiol HF 2015;3:579–90.

7. Zanni MV, Schouten J, Grinspoon SK, Reiss P. Risk of coronary heart disease in patients with HIV infection. Nat Rev Cardiol 2014;11:728–41.

8. Lumsden RH, Bloomfield GS. The causes of HIV-associated cardiomyopathy: a tale of two worlds. Biomed Res Int 2016;2016:8196560.

9. Moher D, Liberati A, Tetzlaff J, et al., PRISMA-P Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

10. Magula NP, Mayosi BM. Cardiac involvement in HIV-infected people living in Africa: a review. Cardiovasc J S Afr 2003;14:231–7.

11. Cerrato E, D'Ascenzo F, Biondi-Zoccai G, et al. Cardiac dysfunction in pauci symptomatic human immunodeficiency virus patients: a meta-analysis in the highly active antiretroviral therapy era. Eur Heart J 2013;34:1432–6.

12. Cannillo M, D'Ascenzo F, Grosso Marra W, et al. Heart failure in patients with human immunodeficiency virus: a review of the literature. J Cardiovasc Med (Hagerstown) 2015;16:383–9.

13. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestations of acquired immunodeficiency syndrome. Arch Intern Med 2000;160:602–8.

14. Afshar RK, Joneidi NJ, Imani R, Fazel M. Human immunodeficiency virus (HIV) and cardiomyopathy: a systematic review. Int J Travel Med Global Health 2013;1:75–88.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

16. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. J Epidemiol Community Health 2013;67:974–8.

17. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. Available at: https://www.ncbi.nlm.nih.gov/books/NBK99082/bin/appb-fm4.pdf. Accessed October 29, 2018.

18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

19. Herskowitz A, Vlahov D, Willoughby S, et al. Prevalence and incidence of left ventricular dysfunction in patients with human immunodeficiency virus infection. Am J Cardiol 1993;71:955–8.

20. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS. N Engl J Med 1998;339:1093–9.

21. Bahrami H, Fonarow G, Heidenreich P. Heart failure admission in HIV-infected patients. American College of Cardiology. 2014. Available at: http://www.onlinejacc.org/content/63/12_Supplement/A1351. Accessed October 29, 2018.

22. Echouffo-Tcheugui JB, Erqou S, Butler J, Yancy CW, Fonarow GC. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis. J Am Coll Cardiol HF 2016;4:237–48.

23. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

24. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol 2014;63:407–16.

25. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009;22:107–33.

26. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

27. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.

28. Hsue PY, Hunt PW, Ho JE, et al. Impact of HIV infection on diastolic function and left ventricular mass. Circ Heart Fail 2010;3:132–9.

29. Roger VL. Asymptomatic left ventricular dysfunction: to screen or not to screen? J Am Coll Cardiol HF 2016;4:249–51.

30. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart

failure with preserved ejection fraction. Eur Heart J 2014;35:3452–62.

31. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. JAMA Cardiol 2018;3:298–306.

32. Selby VN, Scherzer R, Barnett CF, et al. Doppler echocardiography does not accurately estimate pulmonary artery systolic pressure in HIV-infected patients. AIDS 2012;26:1967–9.

33. Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. Circulation 2009;120:992–1007.

34. Holloway CJ, Ntusi N, Suttie J, et al. Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. Circulation 2013;128:814–22.

35. Ntusi N, O'Dwyer E, Dorrell L, et al. HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. Circ Cardiovasc Imaging 2016;9:e004430.

36. Breuckmann F, Nassenstein K, Kondratieva J, et al., Network German Heart Failure Network and Competence Network HIV/AIDS. MR characterization of cardiac abnormalities in HIV+ individuals with increased BNP levels. Eur J Med Res 2007;12:185–90.

KEY WORDS cardiac dysfunction, cardiomyopathy, HIV, human immunodeficiency virus, meta-analysis

APPENDIX For supplemental material including tables and figures, please see the online version of this paper.