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Risk factors associated with pulmonary arterial hypertension among HIV-infected adults: A meta-analysis and systematic review

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Abstract

Pulmonary arterial hypertension (PAH) occurs more frequently in patients with HIV infection than in the general population. The predictive value of HIV-related factors and traditional cardiovascular factors with PAH is inconsistent across studies. The objective is to determine the roles of HIV-related risk factors and traditional cardiovascular risk factors in the development of PAH in adults with HIV. We searched Pubmed/Medline, Embase, Web of Science, and Google Scholar to identify studies published between January 1, 2000 and February 23, 2021 on risk factors associated with PAH among people living with HIV (PLWH). Ten studies were included for final analysis. PLWH with PAH had higher mean age (weighted mean difference [WMD] = 2.27, 95% confidence interval [CI] 0.31 ~ 4.24), and lower mean CD4 cell count (WMD = –95.8, 95% CI –153.41 ~ –38.2). Meanwhile, they were more likely to have detectable viral load (odds ratio [OR] = 1.36, 95% CI 1.16 ~ 1.60), to accompany arterial hypertension (OR = 2.02, 95% CI 1.51 ~ 2.71) and less likely to receive antiretroviral therapy (ART) (OR = 0.84, 95% CI 0.72 ~ 0.99). Besides, more intravenous drug users were observed in HIV-infected adults with PAH (OR = 2.25, 95% CI 1.51 ~ 3.33). HIV infection itself and ART impact PAH in two opposite ways. Traditional cardiovascular factors such as arterial hypertension, and older age are also important to the development of PAH. Screening HIV-related factors and traditional cardiovascular factors may help to target and manage patients at risk.(AIDS Rev. 2021;23:59-68)

Keywords

HIV. Pulmonary arterial hypertension. Risk factor.

Introduction

With the introduction of antiretroviral therapy (ART), survival of HIV-infected patients has markedly improved and death from immunodeficiency and opportunistic infections has decreased. In high-income countries, the life expectancy of people living with HIV (PLWH) increased by 9-10 years between 1996 and 2010[1,2]. However, cardiovascular complications, such as pulmonary arterial hypertension (PAH), cause great burden in PLWH[3,4]. Regardless of ART introduction, the prevalence of HIV-related PAH is 0.5%, whatever before and after ART era, which is 25-fold higher than that in the general population[5]. The prevalence of HIV-related PAH, as reported by studies using echocardiography, is as high as 2.6-27.8%[6,7]. Among PLWH, the

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development of PAH is an independent predictor of death and has often been associated with poor survival[8]. The proposed mechanisms include immune activation[9], action of HIV proteins[10,11], intravenous drug use[12], and coinfection of other viruses[13].

Many studies have identified some of the factors associated with PAH in PLWH, although these studies are limited by a small sample size, and no systematic review and meta-analysis have been performed to date. Moreover, the specific contribution of infectious and noninfectious causes to PAH remains poorly characterized. Thus, the present meta-analysis and systematic review aimed to critically evaluate the risk factors for PAH in PLWH.

Methods

Design

The study background, rationale, and methods were specified in advance and are documented in a study protocol registered in the PROSPERO database (CRD42021243334).

Eligibility criteria

We systematically identified and evaluated the reports of observational studies conducted in different settings.

The inclusion criteria were as follows:

a. Observational cross-sectional or cohort studies of individuals exposed to HIV.
b. Studies describing the criteria used to define PAH.
c. Studies involving PAH diagnosis diagnosis of PAH based on echocardiography.
d. Studies must be released between 1 January 2000 and 23 February 2021 and reported in English.

The exclusion criteria were as follows:

a. Studies conducted among children or pregnant women infected with HIV.
b. Studies lacking of sufficient original statistics of factors associated with PAH to analyze.
c. Reviews, commentaries, editorials, case reports, and case series.

Information sources

We performed a comprehensive and exhaustive search of PubMed/Medline, Embase, Web of Science, and Google Scholar to identify all relevant articles published on PAH in PLWH. In addition, we searched the reference lists of relevant articles and previous systematic reviews for additional eligible publications.

Search strategy and selection of studies

We searched the studies fulfilling the inclusion criteria and published between 1 January 2000 and 23 February 2021 in the aforementioned sources with the following search keywords: “human immunodeficiency virus and PAH,” “HIV and PAH,” “acquired immunodeficiency syndrome and PAH,” and “AIDS and PAH.”

Data extraction

We extracted the following data from each study on certain forms: authors, year of publication, study design, location of the study group, size of the study population, criteria used to define PAH, study population, age of participants (mean or median), percentage of males, percentage of people receiving ART, duration of HIV infection, CD4 cell counts, HIV-RNA copies, and prevelance for PAH.

Risk of bias and quality assessment of included studies

The cross-sectional studies’ methodological quality was assessed using an 11-item checklist, which was recommended by the Agency for Healthcare Research and Quality[14]. In the checklist, an item is scored “0” if the answer is “No” or “Unclear;” if the answer is “Yes”, the item is scored “1.” Study quality and risk of bias were assessed as the following standards: low quality (high risk of bias) = 0–3, moderate quality (moderate risk of bias) = 4–7, and high quality (low risk of bias) = 8–11. The Newcastle–Ottawa Scale was used to assess the methodological quality of retrospective cohort studies. The quality of each study’s quality was assessed based on three broad areas: selection of study groups, comparability of the groups, and ascertainment of either the exposure or the outcome of interest. A study was awarded a maximum of 9 stars, with ≤ 3, 4–6 and 7–9 stars denoting weak, moderate, and strong, respectively[15].

Data synthesis and analysis

The main characteristics of the studies are summarized in a table and a flow diagram. Continuous variables are reported as mean (± SD) or median (range).

Categorical variables are expressed as n (%). Forest plots were drawn to visualize the risk factors and the extent of statistical heterogeneity between the studies. The χ^2 test on Cochrane's Q statistic was used to assess the statistical heterogeneity[16], which was quantified by calculating the I^2 value[17]. If I^2 was < 50% and the p value for the heterogeneity test was ≥ 0.1, the studies were considered homogenous, and a fixed-effects meta-analysis was used to estimate the potentially related factors for PAH; otherwise, a random-effects meta-analysis was undertaken[18]. In general, I^2 values > 60–70% indicate the presence of substantial heterogeneity. If the included studies were too heterogeneous to be pooled together, we summarized their findings in a narrative form. Subgroup analyses were conducted to assess variations in the prevalence of PAH across different age groups and individual with different immune status. We could not perform meta-regression analyses to assess the potential effect of study-level covariates on the pooled estimate because of the insufficient number of studies (< 10 studies for each variable). A $p < 0.05$ was considered indicative of statistically significant publication bias. Data were analyzed using Stata15.1 for Windows (Stata Corp, Texas, USA).

Results

Study selection

Applying the search strategy, 413 papers were found. Of these, 38 full-text articles were assessed for eligibility, and finally, 10 articles were included for the qualitative synthesis. Overall, 28 studies were excluded after screening for the full-text (15 studies did not provide stratified statistics of factors associated with PAH; 6 studies were performed in children with HIV infection; 4 studies were excluded because of unclear diagnostic criteria for PAH and 3 studies merely compared the PLWH and healthy controls). Finally, 10 studies were included, of which 7 were cross-sectional studies, 2 were prospective cohort trials, and 1 was a retrospective study. The full screening process is represented according to the PRISMA protocol in the flowchart of figure 1.

Methodological quality of included studies

Among the studies included in the meta-analysis, 6 (60%) and 4 (40%) studies were categorized as having a low and moderate risk of bias, respectively; None of the studies were found to have a high risk of bias (Supplementary Table 1).

Study characteristics

Overall, 10 studies comprising 5968 PLWH (including 1046 patients with PAH) were included. In total, 6, 2, and 2 studies were from Europe[6,19-23], Africa[24,25] and America, respectively[7,26]. Most studies were cross-sectional. General descriptive study data, along with HIV-cohort specific data, are presented in supplementary table 1. The mean age at entry of the participants was 50 years (range, 40-57 years). The proportion of males included in the studies was 76% (range, 27-98%). The mean duration from diagnosis of HIV infection was 117.2 months (range, 93-228 months), The percentage of people exposed to ART was 73% (range, 54-100%). The mean CD4 count was 506 cells/μL (range, 400-587 cells/μL). In all studies, PAH was diagnosed through transthoracic echocardiography (TTE), except in the study conducted by Sibton et al., which defined PAH as pulmonary arterial systolic pressure (PASP) > 30 mmHg and confirmed diagnosis through RHC. Overall, 5, 3, and 1 studies defined PAH as PASP estimated by TTE ≥ 35 mmHg[19,21,22,24,25], > 40 mmHg[6,7,26], and > 30 mmHg, respectively, as estimated through TTE[20,23]. The prevalence of PAH estimated by TTE across the studies ranged from 2.6% to 27.6%[6,7,19,21-24,26], whereas the incidence of PAH in the study by Sibton et al. was 0.46%[20]. Overall, 5 studies excluded patients with secondary PAH (chronic obstructive pulmonary disease, interstitial lung disease, chronic thrombo embolic disease, left ventricular dysfunction, and anemia)[6,7,20,21,25,26]. Sangal et al. exclusively included patients coinfected with hepatitis C virus (HCV)[26]. Sibton et al. included only patients with symptoms of dyspnea[20]. Inclusion and exclusion criteria of the study population and PAH definition varied across studies, leading to high clinical heterogeneity.

Meta-analysis of the factors associated with PAH

As shown in forest plots, individuals with PAH had high mean age (weighted mean difference [WMD] = 2.27, 95% confidence interval [CI] 0.31 ~ 4.24, p = 0.023, Fig. 2A) and low mean $CD4^+$ T cell counts (WMD = –95.80, 95% CI –153.41 ~ –38.20, p = 0.001, Fig. 2B). Mean-

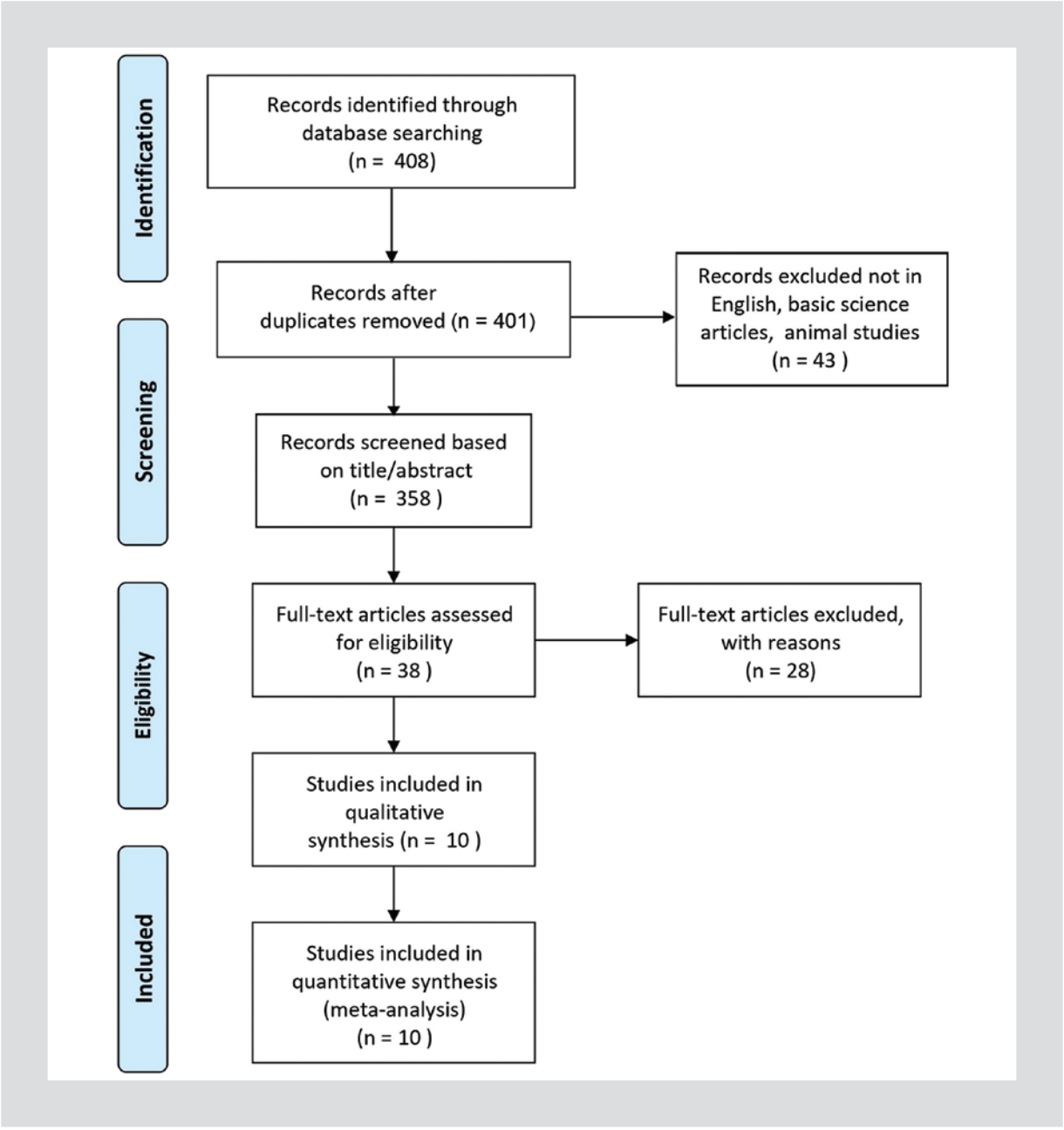

Figure 1. *The PRISMA flow diagram of full screening and selection process.*

while, these individuals were more likely to have a detectable viral load (odds ratio [OR] = 1.36, 95% CI 1.16 ~ 1.60, p < 0.001, Fig. 3A), to accompany arterial hypertension (OR = 2.02, 95% CI 1.51 ~ 2.71, p < 0.001, Fig. 3B) and less likely to receive ART (OR = 0.84, 95% CI 0.72 ~ 0.99, p = 0.038, Fig. 3C). In addition, more intravenous drug users (IVDUs) were found in PLWH with PAH (OR = 2.25, 95% CI 1.51 ~ 3.33, p < 0.001, Fig. 3D).

The duration of HIV infection was not associated with PAH (WMD = −6.77, 95% CI −22.88 ~ 9.35, p = 0.411, Fig. 2C). The proportion of men (OR = 1.50, 95%CI 0.84 ~ 2.69, p = 0.169, Fig. 3E) and smoking history did not significantly differ between the patients with and without PAH (OR = 0.95, 95% CI 0.51 ~ 1.76, p = 0.870, Fig. 3F). However, significant heterogeneity was observed between the included studies (I^2 = 76.7%) when we conducted a meta-analysis of males, suggesting that our result was not robust. Therefore, the results should be interpreted with caution.

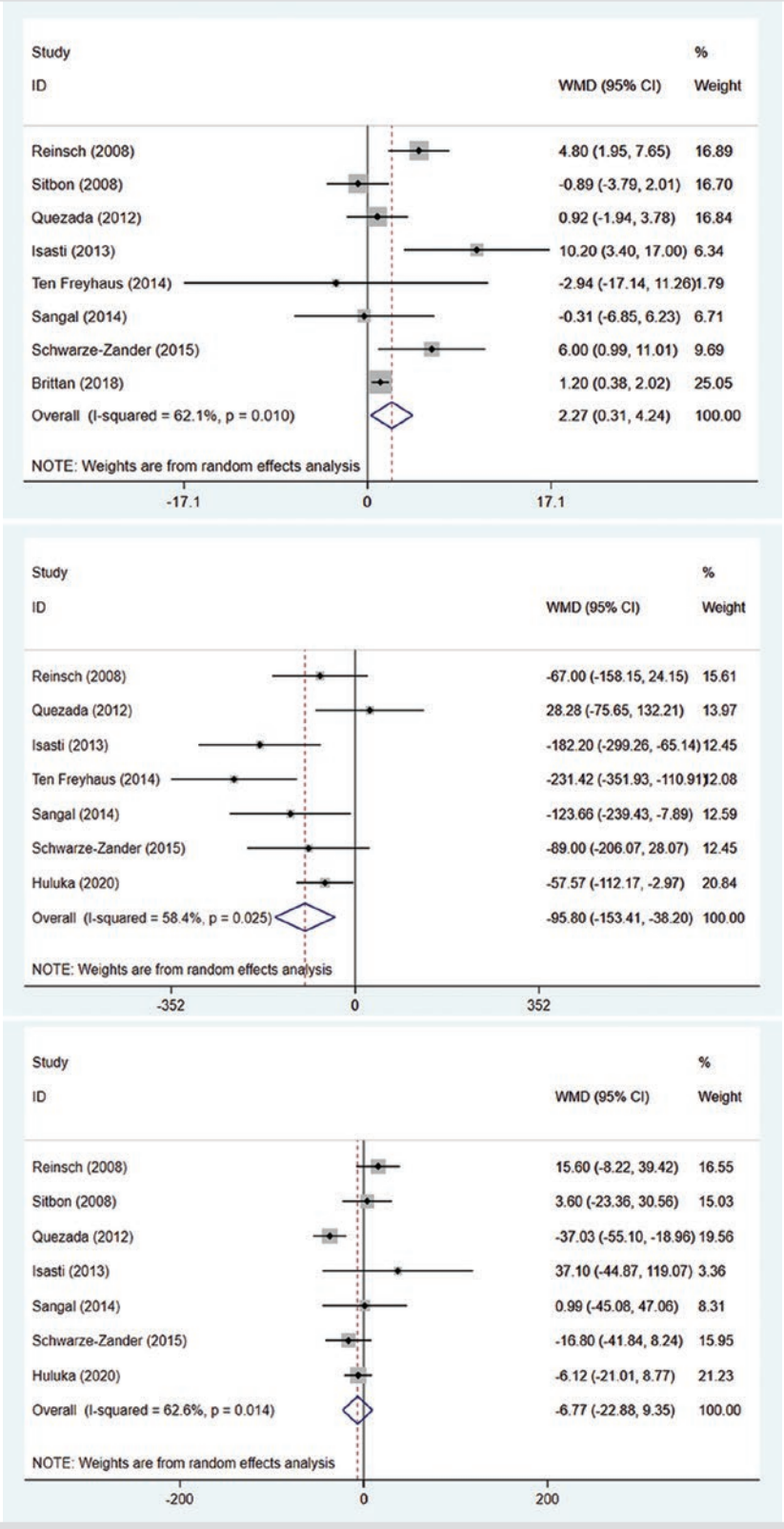

Figure 2. *Forest plot of meta-analysis for* **A:** *the age,* **B:** *CD4 cell counts, and* **C:** *duration of HIV infection in PLWH. PLWH: people living with HIV; 95% CI: 95% confidence interval.*

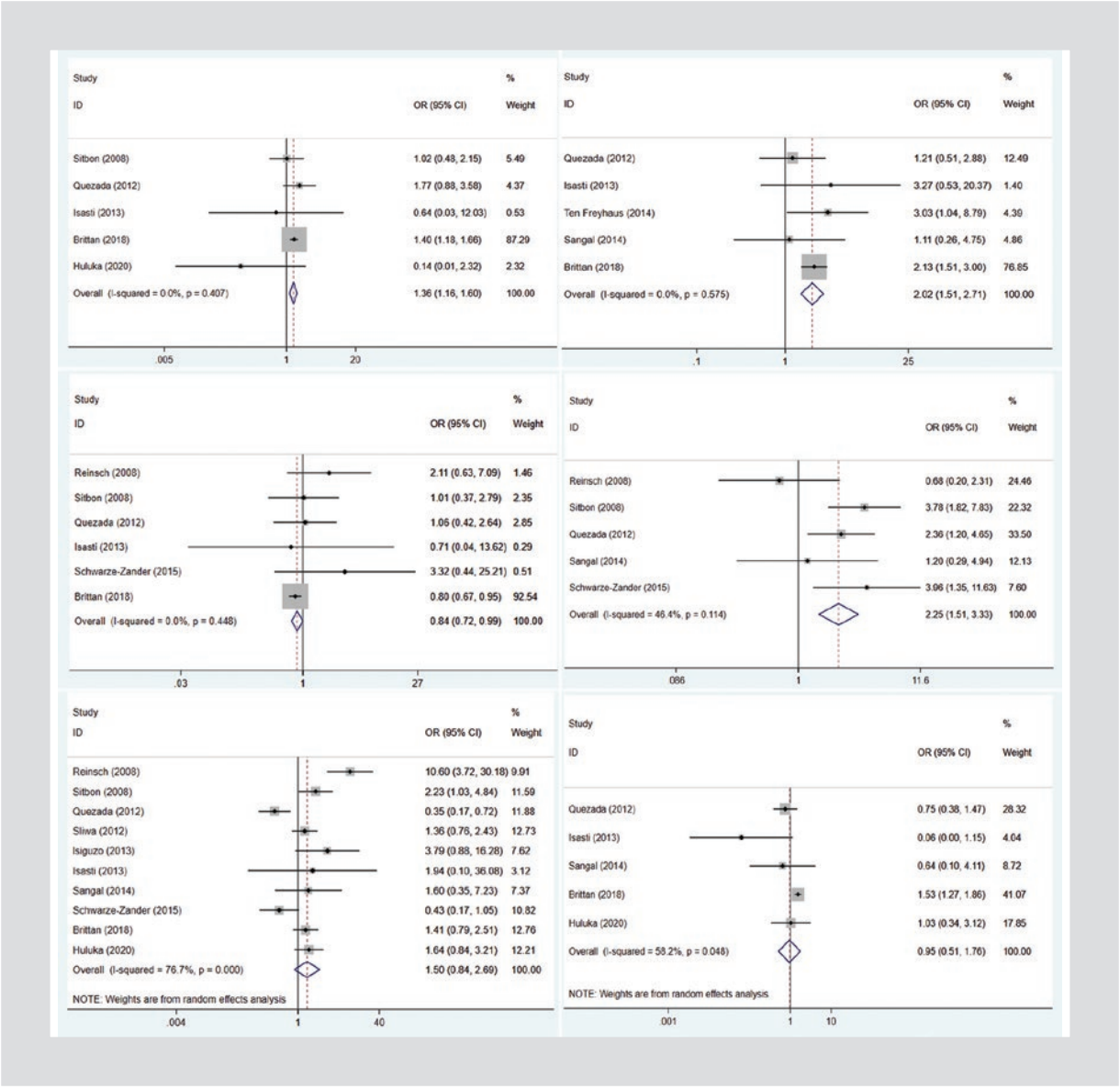

Figure 3. *Forest plot of meta-analysis for the prevalence of* **A:** *detectable viral load,* **B:** *arterial hypertension,* **C:** *ART using,* **D:** *IVDUs,* **E:** *male gender, and* **F:** *smoking history in PLWH. ART: antiretroviral therapy; IVDUs: intravenous drug users; 95%CI: 95% confidence interval.*

In addition, we conducted the subgroup analysis for mean age and mean CD4 cell counts. We grouped the studies by different mean age (group a: ≤ 45-years-old group and group b: > 45-years-old-group). Patients with PAH were significantly older in the > 45-year-old group than patients without PAH (WMD = 2.63, 95% CI 0.09 ~ 5.17, p = 0.042) but we did not observe the same outcome in the ≤ 45-year-old group (WMD = 1.47, 95% CI −3.5 ~ 6.44, p = 0.042, Fig. 4). Then we grouped the studies by different mean CD4 cell counts (group a: ≥ 500 cells/μL group and group b: < 500 cells/μL group). Patients with PAH had lower CD4 cell counts in the < 500 cells/μL group than patients without PAH (WMD = −126.31, 95% CI −193.57 ~ −59.05, p < 0.001) but we did not observe the same outcome in the ≥ 500 cells/μL group (WMD = −22.77, 95% CI −115.90 ~ 70.37, p = 0.632, Fig. 5).

In addition to the aforementioned factors, the prevalence of some factors associated with PAH and HIV-related data reported in each study by PAH status are presented in Supplementary table 2. Most of the included studies reported no significant difference in ART duration, MSM, dyslipidemia, African descent and HCV infection between patients with and without PAH[6,7,19-21,23,25,26]. Only the study by Sliwa et al., conducted in South Africa, reported higher proportion of African de-

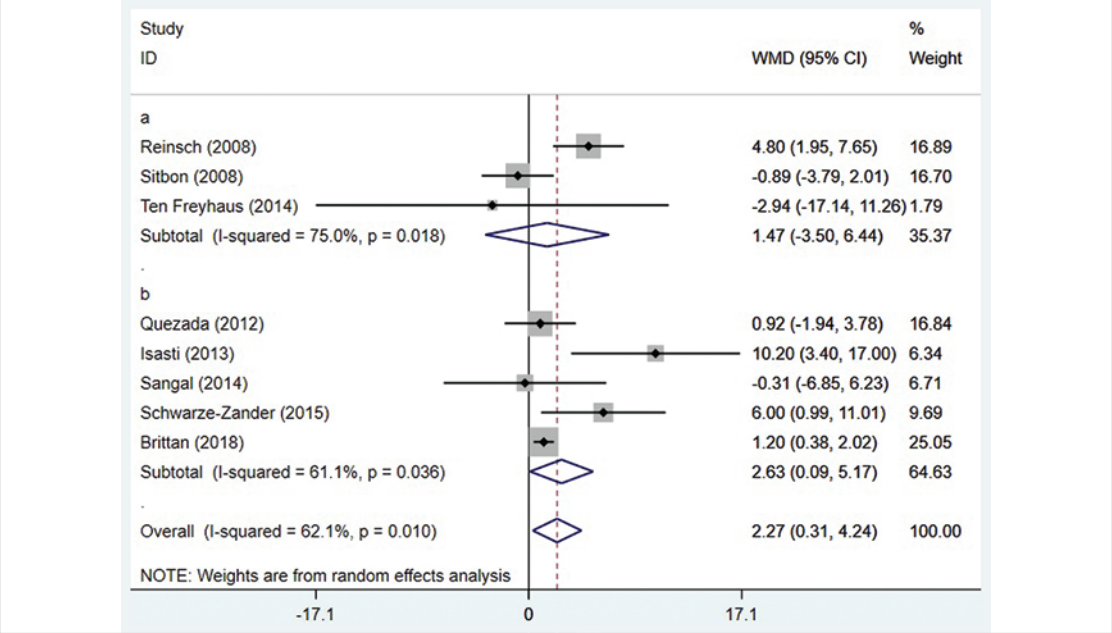

Figure 4. *Forest plot of subgroup analysis for different mean age (group a: ≤ 45 years old, group b: > 45 years old).*

scent among patients with PAH (97% vs. 86%, p < 0.001)[24]. Schwarze - Zander et al. reported that the percentages of MSM in the PAH group was low[23].

Discussion

At present, patients with HIV infection live longer because of the availability of effective ART. However, the cardiovascular risk of morbidity and death increases with a longer survival. In cases of HIV-related PAH, a relatively rare cardiovascular disease, survival is usually determined by pulmonary vascular disease and concomitant right heart failure[27]. TTE is an non-invasive technique, which is easy to perform, and it provides useful information about the possible presence of PAH and the right ventricular function. However, TTE is not routinely used to screen asymptomatic individuals with HIV infection. At present, no established guidelines are available for TTE screening in patients wih HIV infection. Most of the patients with HIV and PAH are diagnosed in the final stages of the disease when the right ventricle exhibits irreversible damage[28].

Moreover, the prognosis of HIV-positive patients is worse than that of HIV-negative patients, probably because of additional factors that can alter the clinical course and survival[27,29,30]. The early diagnosis of PAH is thus highly warranted. Therefore, we conducted the present meta-analysis and systematic review to summarize 10 studies examining potential predictive factors for PAH in the context of HIV infection to obtain evidence for the influence of HIV infection itself, ART and traditional factors on PAH.

When analyzing the immunovirological status and ART as the contributors of PAH, we found that the cumulative duration of HIV infection was not a significant factor. The patients having PAH were less likely to receive ART to achieve viral suppression or complete immune reconstruction. Other studies have reported that the occurrence of PAH was not related to the duration of HIV infection, reflecting the fact that HIV-related PAH can occur in any stages of HIV infection[19-21,23,25,26].

Some studies have indicated pulmonary hemodynamic improvements in patients receiving ART. By contrast, several other studies have demonstrated no reduction in the prevalence of HIV-related PAH in patients with effective ART and no observed difference between patients with or without PAH in the duration of ART. These observations suggest that ART does not exert a dramatic impact on the prevention of HIV-related PAH. Moreover, it has been reported that ART can

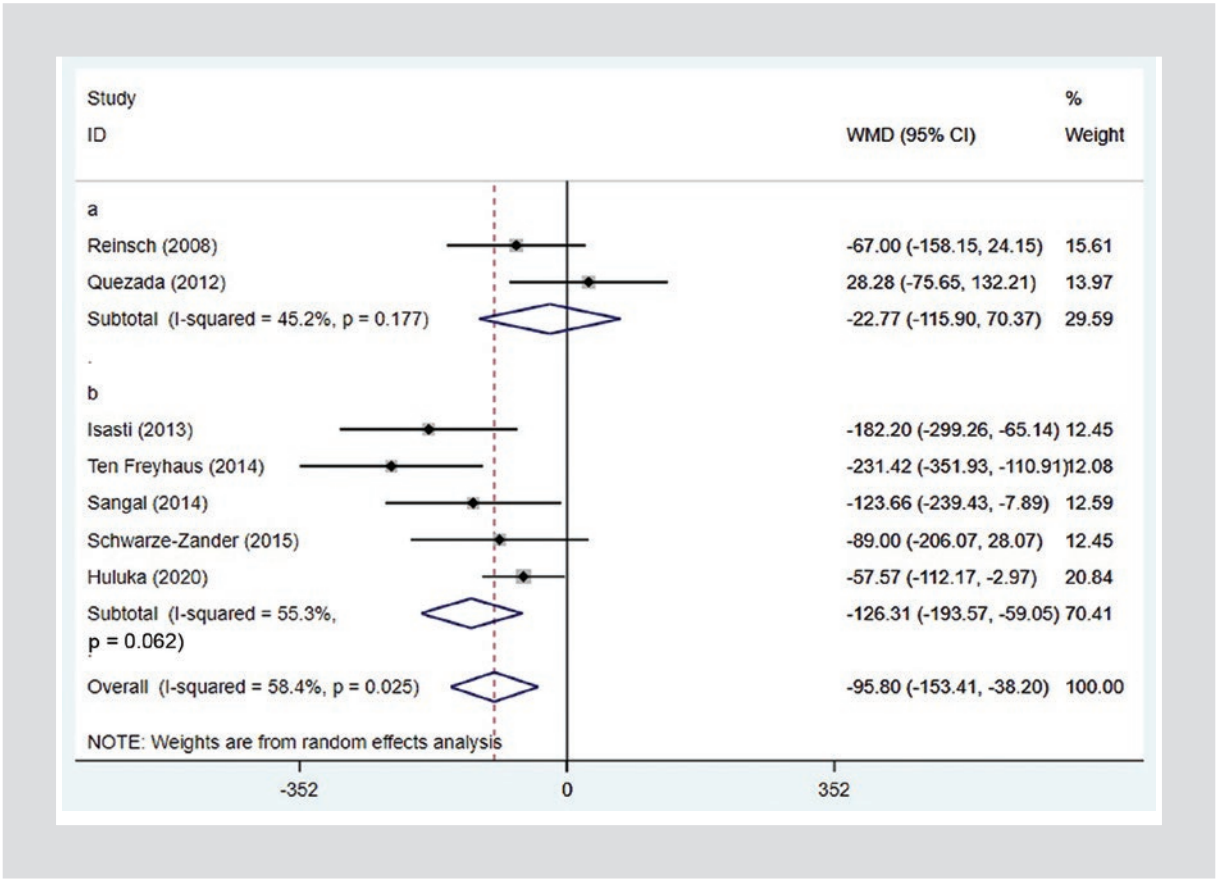

Figure 5. *Forest plot of subgroup analysis for different CD4 cell counts (group a: ≥ 500 cells/μL, group b: < 500 cells/μL).*

induce endothelial dysfunction in the ***in vitro*** and animal models, resulting in increased endothelin-1 production and endothelial proliferation and thus potentially contributing to or exacerbating underlying HIV-related PAH[31,32]. Nevertheless, our analysis suggested that people exposed to ART have a decreased risk of PAH, reflecting the fact that the risk of HIV-related PAH can be lowered by reducing chronic inflammation and viral suppression could not be overtaken by the consequences of ART-induced cardiovascular toxicity.

Previous studies have reported no statistically significant differences in CD4 cell counts between patients with and without PAH[33]. However, Sibton et al. found that the proportion of patients with a CD4 cell counts < 200/mm^3 was significantly higher among those having PAH[20]. Morris et al. demonstrated that the patients with an elevated tricuspid regurgitant jet velocity were more likely to have lower CD4 counts and higher HIV-RNA levels[34]. Our analysis suggested that PLWH with PAH were more likely to have lower CD4 cell counts in < 500 cells/L group. However, no significant difference was found between patients with and without PAH in the CD4 cell count ≥ 500 cells/μL group (WMD = −22.77, 95% CI −115.90 ~ 70.37, p = 0.632). This finding suggested that PAH is probably related to the degree of immune reconstitution, and those who achieve complete immune reconstitution are less likely to develop PAH.

Overall, 5 studies reported the proportion of patients with detectable viral load by PAH status. In these studies, 72-94% of patients received ART, and the mean ART duration ranged from 120 to 156 months. We found that the OR of PAH for PLWH with detectable viral load was 1.36 (95% CI 1.16 ~ 1.60, p < 0.001), which suggested that in the cohorts having received ART widely, HIV-positive people with detectable viral load were more likely to develop PAH than those with suppressed viral load. To data, no evidence of direct infection of vascular endothelium with HIV is available[35]. Kanmogne et al. reported that HIV-1 gp120 proteins could induce apoptosis and injury in primary human lung microvascular endothelial cells[10]. A study conducted by Almodovar et al. reported that Nef sequences from HIV-related PAH in-

dividuals displayed polymorphisms, which was not impacted by ART and the duration of HIV infection in functional domains[11].

In addition, it is suggested that IVDU plays a vital role in PAH. In most of the included studies, the percentage of patients with a history of IVDU was higher in the PAH group than in the non-PAH group. In addition, other studies have found a high prevalence of PAH in patients who acquired HIV infection by IVDU[20,21,26,30,36], which is consistent with our result (OR = 2.25, 95% CI 1.51 ~ 3.33, p < 0.001). In total, 8-64% of PAH cases were reported in individuals who also used intravenous drugs[19,20,37]. Dalvi et al. demonstrated that cocaine and opioid use contributed to enhance HIV-1-related pulmonary vascular remodeling by autopsy of patients with HIV[38]. In addition, the authors found that cocaine and the HIV protein Tat disrupted tight junction protein and induced related endothelial dysfunction *in vitro* via the ROS-dependent Ras/ERK signaling pathway[39].

The risk of PAH occurrence in patients with HIV is influenced both by specific features of this disease and by traditional cardiovascular factors. As shown in previous studies, left ventricular diastolic dysfunction is increased in HIV-positive individuals, which is consistent with the report suggesting that left heart disease is one of the most common causes of elevated PASP[22,40,41]. The primary risk factor for diastolic dysfunction is arterial hypertension, and this factor is associated with the presence of echocardiographic PAH[42]. Consistent with this observation, the prevalence of arterial hypertension appeared to be higher in HIV-positive individuals with PAH in our study (OR = 2.02, 95% CI 1.51 ~ 2.71, p < 0.001).

HIV-related PAH is more frequently seen in male patients, with a ratio of 1.5:1, in contrast to primary PAH, which is more common in women[27,28,43]. In addition, patients with PAH tended to be older than those without PAH. In the further subgroup analysis, patients with PAH tended to be older in the > 45-year-old group but we did not observe the same outcome in the ≤ 45-year-old group. This finding suggested that PAH is more likely to occur in the senior patients, especially in the middle- and old-age populations.

The exact mechanism by which smoking increases the risk of cardiovascular events in HIV-positive patients has not been determined to data[27,28,44]. Endothelial damage appears to be the cornerstone of heart disease in HIV[45]. However, in our study, no association of smoking with the presence of PAH was observed (OR = 0.95, 95% CI 0.51 ~ 1.76, p = 0.870). In addition, African descent and other common traditional risk factors for cardiovascular diseases, such as hyperlipidemia, diabetes, and HCV coinfection, had no noticeable contribution to PAH[6,7,21,26].

There are several limitations in study. Above all, the imperfect correlation between Doppler PASP estimates and invasive hemodynamics may have lead to the misclassification of PAH states, especially overestimating the incidence of PAH. Unfortunately, hemodynamic data in the HIV-positive population are limited. Secondly, because of the characteristics of a cross-sectional study, the HIV-associated PAH could not be distinguished from PAH developed before the diagnosis of HIV. Thirdly, the heterogeneity among studies may have affected the robustness of our results. Finally, as reported by Freyhaus et al., asymptomatic HIV-positive individuals with mildly elevated PASP illustrated no progress after 2 years[22]. Most of the included studies did not consider the clinical endpoints of PAH but focussed only at the functional changes in the heart.

Conclusion

Despite the aforementioned limitations, to the best of our knowledge, this study is the first to provide comprehensive and precise estimates for quantifying the associations of specific features of HIV infection and traditional risk factors for cardiovascular diseases with PAH in PLWH. This meta-analysis illustrated that the unsatisfactory immunovirological status, intravenous drug use, older age, and arterial hypertension were associated with increased PAH prevalence. We stress the protective role of ART in preventing PAH and suggest screening and monitoring for PAH in the high risk population.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.21000056. 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.

References

1. Thienemann F, Sliwa K, Rockstroh JK. HIV and the heart: the impact of antiretroviral therapy: a global perspective. EUR HEART J. 2013;34:3538-46.
2. Trickey A, May MT, Vehreschild J, Obel N, Gill MJ, Crane HM, et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV. 2017;4:e349-56.

3. Alonso A, Barnes AE, Guest JL, Shah A, Shao IY, Marconi V. HIV infection and incidence of cardiovascular diseases: an analysis of a large healthcare database. J Am Heart Assoc. 2019;8:e12241.
4. Shah AS, Stelzle D, Lee KK, Beck EJ, Alam S, Clifford S, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV. Circulation. 2018;138:1100-12.
5. Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. Chest. 1991;100:1268-71.
6. Isasti G, Moreno T, Pérez I, Cabrera F, Palacios R, Santos J. High prevalence of pulmonary arterial hypertension in a cohort of asymptomatic HIV-infected patients. AIDS Res Hum Retroviruses. 2013;29:231-4.
7. Brittain EL, Duncan MS, Chang J, Patterson OV, DuVall SL, Brandt CA, et al. Increased echocardiographic pulmonary pressure in HIV-infected and uninfected individuals in the veterans aging cohort study. Am J Res Crit Care. 2018;197:923-32.
8. Opravil M, Sereni D. Natural history of HIV-associated pulmonary arterial hypertension: trends in the HAART era. AIDS. 2008;22 Suppl 3:S35-40.
9. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis. 2012;205:S375-82.
10. Kanmogne GD, Primeaux C, Grammas P. Induction of apoptosis and endothelin-1 secretion in primary human lung endothelial cells by HIV-1 gp120 proteins. Biochem Biophys Res Commun. 2005;333:1107-15.
11. Almodovar S, Knight R, Allshouse AA, Roemer S, Lozupone C, McDonald D, et al. Human immunodeficiency virus nef signature sequences are associated with pulmonary hypertension. AIDS Res Hum Retroviruses. 2012;28:607-18.
12. Spikes L, Dalvi P, Tawfik O, Gu H, Voelkel NF, Cheney P, et al. Enhanced pulmonary arteriopathy in simian immunodeficiency virus-infected macaques exposed to morphine. Am J Respir Crit Care Med. 2012;185:1235-43.
13. Cool CD, Rai PR, Yeager ME, Hernandez-Saavedra D, Serls AE, Bull TM, et al. Expression of human herpesvirus 8 in primary pulmonary hypertension. N Engl J Med. 2003;349:1113-22.
14. Rostom A, Dube C, Cranney A, Saloojee N, Sy R, Garritty C, et al. Celiac Disease. Rockville, MD: Agency for Healthcare Research and Quality, US; 2004.
15. Newcastle-Ottawa Quality Assessment Scale Cohort Studies. Available from: http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf [Last accessed on 2016 Jun].
16. Cochran GW. The combination of estimates from different experiments. Biometrics. 1954;10:101-29.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
19. Reinsch N, Buhr C, Krings P, Kaelsch H, Kahlert P, Konorza T, et al. Effect of gender and highly active antiretroviral therapy on HIV-related pulmonary arterial hypertension: results of the HIV-HEART study. HIV Med. 2008;9:550-6.
20. Sitbon O, Lascoux-Combe C, Delfraissy JF, Yeni PG, Raffi F, De Zuttere D, et al. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med. 2008;177:108-13.
21. Quezada M, Martin-Carbonero L, Soriano V, Vispo E, Valencia E, Moreno V, et al. Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. AIDS. 2012;26:1387-92.
22. Ten Freyhaus H, Vogel D, Lehmann C, Kümmerle T, Wyen C, Fätkenheuer G, et al. Echocardiographic screening for pulmonary arterial hypertension in HIV-positive patients. Infection. 2014;42:737-41.
23. Schwarze-Zander C, Pabst S, Hammerstingl C, Ohlig J, Wasmuth JC, Boesecke C, et al. Pulmonary hypertension in HIV infection: a prospective echocardiographic study. HIV Med. 2015;16:578-82.
24. Sliwa K, Carrington MJ, Becker A, Thienemann F, Ntsekhe M, Stewart S. Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort. Eur Heart J. 2012;33:866-74.
25. Huluka DK, Mekonnen D, Abebe S, Meshesha A, Mekonnen D, Deyessa N, et al. Prevalence and risk factors of pulmonary hypertension among adult patients with HIV infection in Ethiopia. Pulm Circ. 2020;10:765576194.
26. Sangal RB, Taylor LE, Gillani F, Poppas A, Klinger JR, Ventetuolo CE. Risk of echocardiographic pulmonary hypertension in individuals with human immunodeficiency virus-hepatitis c virus coinfection. Ann Am Thorac Soc. 2014;11:1553-9.
27. Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA. HIV-Related pulmonary hypertension: analytic review of 131 cases. Chest. 2000;118:1133-41.
28. Nunes H, Humbert M, Sitbon O, Morse JH, Deng Z, Knowles JA, et al. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2003;167:1433-9.
29. Opravil M, Pechere M, Speich R, Joller-Jemelka HI, Jenni R, Russi EW, et al. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV cohort study. Am J Respir Crit Care Med. 1997;155:990-5.
30. Degano B, Guillaume M, Savale L, Montani D, Jaïs X, Yaici A, et al. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. AIDS. 2010;24:67-75.
31. Hebert VY, Crenshaw BL, Romanoff RL, Ekshyyan VP, Dugas TR. Effects of HIV drug combinations on endothelin-1 and vascular cell proliferation. Cardiovasc Toxicol. 2004;4:117-31.
32. Wang X, Chai H, Yao Q, Chen C. Molecular mechanisms of HIV protease inhibitor-induced endothelial dysfunction. J Acquir Immune Defic Syndr. 2007;44:493-9.
33. Petitpretz P, Brenot F, Azarian R, Parent F, Rain B, Herve P, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation. 1994;89:2722-7.
34. Morris A, Gingo MR, George MP, Lucht L, Kessinger C, Singh V, et al. Cardiopulmonary function in individuals with HIV infection in the antiretroviral therapy era. AIDS. 2012;26:731-40.
35. Mette SA, Palevsky HI, Pietra GG, Williams TM, Bruder E, Prestipino Aj, et al. Primary pulmonary hypertension in association with human immunodeficiency virus infection. A possible viral etiology for some forms of hypertensive pulmonary arteriopathy. Am Rev Respir Dis 1992;145:1196-200.
36. Zuber JP, Calmy A, Evison JM, Hasse B, Schiffer V, Wagels T, et al. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. Clin Infect Dis. 2004;38:1178-85.
37. Lederman MM, Sereni D, Simonneau G, Voelkel NF. Pulmonary arterial hypertension and its association with HIV infection: an overview. AIDS. 2008;22 Suppl 3:S1-6.
38. Dhillon NK, Li F, Xue B, Tawfik O, Morgello S, Buch S. Effect of cocaine on human immunodeficiency virus-mediated pulmonary endothelial and smooth muscle dysfunction. Am J Respir Cell Mol Biol. 2011;45:40-52.
39. Dalvi P, Wang K, Mermis J, Zeng R, Sanderson M, Johnson S, et al. HIV-1/cocaine induced oxidative stress disrupts tight junction protein-1 in human pulmonary microvascular endothelial cells: role of Ras/ERK1/2 pathway. PLoS One. 2014;9:e85246.
40. Reinsch N, Neuhaus K, Esser S, Potthoff A, Hower M, Brockmeyer NH, et al. Prevalence of cardiac diastolic dysfunction in HIV-infected patients: results of the HIV-HEART study. HIV Clin Trials. 2010;11:156-62.
41. Schuster IM, Thöni GJ, Edérhy SM, Walther G, Nottin S, Vinet A, et al. Subclinical cardiac abnormalities in human immunodeficiency virus-infected men receiving antiretroviral therapy. Am J Cardiol 2008;101:1213-7.
42. Seaberg EC, Munoz A, Lu M, Detels R, Margolick JB, Riddler SA, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. AIDS. 2005;19:953-60.
43. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023-30.
44. Sen S, Rabinstein AA, Elkind MS, Powers WJ. Recent developments regarding human immunodeficiency virus infection and stroke. Cerebrovasc Dis. 2012;33:209-18.
45. López M, Vispo E, San Román J, Herrero D, Peris A, Corral A, et al. Short communication high risk of endothelial dysfunction in HIV individuals may result from deregulation of circulating endothelial cells and endothelial progenitor cells. AIDS Res Hum Retroviruses. 2012;28:656-9.