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Increased Echocardiographic Pulmonary Pressure in HIV-Infected and Uninfected Individuals in the Veterans Aging Cohort Study

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Clinical impact: This work demonstrates that HIV-infected individuals are at higher risk of adjusted mortality than uninfected individuals in the anti-retroviral therapy era and that mortality risk begins at pulmonary pressure values currently considered to be normal. These findings have implications for pulmonary hypertension screening, surveillance, and risk factor modification in HIV-infected individuals.

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At a Glance Commentary:

Little is known about the risk factors and impact of pulmonary pressure on outcomes in HIV, particularly in comparison with demographically and behaviorally similar uninfected people. Further, no data exist to guide risk-stratification or to inform the optimal threshold for recommending invasive hemodynamic evaluation in this population. This work provides a contemporary examination of the epidemiology of increased pulmonary pressure among a national sample of HIV-infected and uninfected individuals referred for echocardiography. HIV infection with unsuppressed viral control was independently

associated with increased pulmonary pressure. HIV-infected individuals are at higher risk of adjusted mortality than uninfected individuals and risk factors for pulmonary hypertension differ by HIV status. We observed that mortality risk in HIV-infected individuals was significantly increased at pulmonary pressure values currently considered normal and well below the threshold at which consideration of invasive evaluation is recommended. These findings have implications for pulmonary hypertension screening, surveillance, and risk factor modification in HIV-infected individuals.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Background: The epidemiology and prognostic impact of increased pulmonary pressure among HIV-infected individuals in the antiretroviral therapy era is not well described.

Methods: This study evaluated 8,296 veterans referred for echocardiography with reported pulmonary artery systolic pressure (PASP) estimates from the Veterans Aging Cohort study, an observational cohort of HIV-infected and uninfected veterans matched by age, sex, race/ethnicity, and clinical site. The primary outcome was adjusted mortality by HIV status.

Results: PASP was reported in 2,831 HIV-infected and 5,465 HIV-uninfected veterans (follow up 3.8±2.6 years). As compared to uninfected veterans, HIV infected veterans with HIV viral load >500 copies/ml (odds ratio (OR)=1.27, 95% CI=1.05-1.54) and those with CD4 cell count<200 cells/mm3 (OR=1.28, 95% CI=1.02-1.60) had a higher prevalence of PASP≥40 mmHg. As compared to uninfected veterans with a PASP<40mmHg, HIV-infected veterans with a PASP≥40 mmHg had an increased risk of death (adjusted HR=1.78, 95% CI=1.57-2.01). This risk persisted even among participants without prevalent comorbidities (adjusted HR 3.61 95%CI 2.17-6.01). The adjusted risk of mortality in HIV-infected veterans was higher at all PASP values compared with uninfected veterans, including at values currently considered to be normal.

Conclusions: HIV-infected people with high HIV viral loads or low CD4 cell counts have a higher prevalence of increased PASP compared to uninfected people. Mortality risk in HIV-infected veterans increases at lower values of PASP than previously recognized and is present even among those without prevalent comorbidties. These findings may inform clinical decision making regarding screening and surveillance of PH in HIV-infected individuals.

Abstract Word Count: 248/250

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INTRODUCTION

HIV-infected people have an increased risk of cardiovascular disease, including pulmonary hypertension (PH)(1-6). Important knowledge gaps remain in our understanding of PH in the HIV population, in part because most studies have focused on pulmonary arterial hypertension (PAH), which is rare. Little is known about the risk factors and impact of pulmonary pressure on outcomes in HIV. Presently, no data exist to guide risk-stratification or to inform the optimal threshold for recommending invasive hemodynamic evaluation in this population. These questions are important because the prevalence of HIV infection is increasing, especially among older and minority populations(7).

To address these knowledge gaps, we present data from the largest contemporary cohort of HIV-infected and uninfected individuals with PA pressure estimates, detailed comorbidity profiles, and mortality outcomes. We investigated mortality risk across a spectrum of echocardiographic PA pressure estimates in a large, nation-wide cohort of HIV-infected and uninfected veterans treated in a single health care system. This study builds on our prior work in the Veterans Aging Cohort Study (VACS) by using echocardiographic estimates of PA pressure rather than *International Classification of Diseases* codes for PH(8). Increased pulmonary pressures in this study refers to an estimated PASP >40mmHg on echocardiography, not a specific disease entity such as PAH. The aims of this study were to examine the prognostic impact of PA pressure, to identify clinical features associated with increased pulmonary pressure, and to ascertain the PA pressure threshold at which mortality risk increases in HIV-infected and

uninfected veterans. Some of the results of these studies have been previously reported in the form of an abstract(9).

METHODS

The VACS is a prospective observational longitudinal cohort of HIV-infected and uninfected veterans matched 1:2 for age, race/ethnicity, sex, and clinical site and enrolled in the same calendar year(10). Clinical and demographic data are extracted from the VA Corporate Data Warehouse and the VA electronic medical record Health Factor data set(10). The Vanderbilt University Medical Center, Yale University, and West Haven VA Medical Center institutional review boards approved this study. The VACS has a waiver of informed consent.

We included all VACS participants enrolled on or after April 1, 2003 who had been referred for a transthoracic echocardiogram and had a reported pulmonary artery systolic pressure (PASP). The baseline was a participant's first PASP measurement on or after April 1, 2003. The prevalence of all covariates and laboratory measurements were based on measures ascertained closest to the date of the baseline echocardiogram. All participants were followed from their baseline date to death or censored on September 30, 2012, if living.

A custom rule-based information extraction system was built using Leo framework to provide PASP and left ventricular ejection fraction (LVEF) data for the study(11, 12). On

manual validation, the accuracy of extracted PASP values across different report formats was 95-100%. PASP values less than 12mmHg or greater than 152mmHg were assumed to be non-physiologic or due to data entry errors (e.g. PASP of -10mmHg) and were excluded(13). Right atrial pressure estimation was non-standardized. PASP values were extracted directly from the echocardiogram reports, which integrated the interpreting physician's estimation of right atrial pressure. Increased PASP was defined as PASP >40mmHg(14, 15). For secondary analyses, we extracted left atrial size and left ventricular thickness to better understand drivers of elevated PASP. Left atrial enlargement was defined as anterior-posterior diameter >40mm and left ventricular hypertrophy was defined as interventricular septal thickness >11mm. As our data extraction tool was not designed apriori to extract data on LA and LV size; we were not able to completely capture these variables.

HIV status was determined based on a validated metric including at least 1 inpatient or 2 or more outpatient *International Classification of Diseases (ICD)-9* codes for HIV and if the participant was included in the VA Immunology Case Registry.(10) Our analyses included the following outcomes (1) all-cause mortality, (2) increased PASP, and (3) incident heart failure (HF). For the latter, we used the presence of 1 or more inpatient or 2 or more outpatient VA, VA fee for service, or Medicare *ICD-9* codes to identify HF events within and outside the VA health care system, as previously described(11, 16). Mortality was determined from the VA vital status file, which is compiled from combined sources including inpatient mortality, social security data, and national death benefits data, a method previously shown to provide excellent mortality ascertainment(17).

We determined age, sex, and race/ethnicity using administrative data. Comorbid hypertension, diabetes mellitus, dyslipidemia, renal disease, hepatitis C infection, chronic obstructive pulmonary disease (COPD), alcohol abuse, smoking status, coronary heart disease, stroke, atrial fibrillation, cancer, and anemia were ascertained using a combination of clinical, laboratory, and or ICD-9 code data collected closest to the date of the baseline echocardiogram, as previously described(18-22). We also calculated the VACS index, a score that assesses mortality risk using indicators of HIV disease and organ system injury(23). Hypertension was categorized as absent (blood pressure <140/90 mm Hg and no antihypertensive medication) or present (≥140/90 mm Hg or on antihypertensive medication)(24). We collected CD4+ lymphocyte counts (CD4 cell counts) and HIV viral load value closest to and within 180 days from the date of the baseline echocardiogram. Baseline ART was categorized by regimen of ART within 180 days prior to baseline: protease inhibitors (PI) plus nucleoside reverse transcriptase inhibitors (NRTI); non-nucleoside reverse transcriptase inhibitors (NNRTI) plus NRTI, other (i.e., use of PI, NRTI, or NNRTI medications but not in combination as described in other two categories), and no ART use (referent group). All ART medications that were on VA formulary during the study period were included. We have previously demonstrated in a nested sample that 98% of HIV-infected veterans obtain their ART medications from the VA(10).

STATISTICAL ANALYSIS

Descriptive statistics for all variables by HIV and increased pulmonary pressure were analyzed using Wilcoxon tests for continuous variables and the χ^2 test for categorical

variables. We used logistic regression models to identify clinical associations with increased pulmonary pressure. We used Cox proportional hazards models to estimate the hazard ratio (HR) and 95% CIs to examine mortality risk by HIV and increased pulmonary pressure in adjusted analyses. Secondary analyses were restricted to participants without significant comorbidities. Similar analyses were used to assess the risk of Incident HF except that the follow-up was through 12/31/2011 when we were last able to ascertain HF events from Medicare data. All models included age, sex, race/ethnicity, established cardiovascular risk factors and other relevant comorbidities selected *a priori*. For models involving only HIV-infected participants, we further adjusted for baseline HIV viral load, CD4 count, and ART regimen. To visually inspect the association between PASP and all-cause mortality, we stratified by HIV status and plotted the risk of all-cause mortality by PASP (modeled with restricted cubic splines). To assess whether the impact of HIV on mortality risk differed at various values of PASP, we included an interaction term between HIV status and PASP, and at each PASP value, plotted the mortality risk for an HIV-infected veteran versus an uninfected veteran. Missing covariate data were accounted for using multiple imputation techniques where continuous variables were imputed using predictive mean matching in order to produce biologically plausible values and categorical variables were imputed using a discriminate function with a non-informative Jeffrey's prior. Using multiple imputation, we created five complete datasets. Analyses were performed in each of the five datasets and results were combined across imputations according to Rubin's rules.

RESULTS

We identified 8,296 (2,831 HIV-infected and 5,465 uninfected veterans) with reported PASP values on echocardiography. Increased PASP was observed in 782 HIV-infected and 1,478 uninfected vetarans). PASP values were similar between HIV-infected and uninfected veterans (36±15mmHg vs. 36±14mmHg; p=0.99) as was the prevalence of increased PASP (28% vs. 27%, respectively; p=0.58). HIV-infected veterans with increased PASP had a lower CD4 cell count, higher HIV viral load, and were less likely to have been exposed to any ART compared with HIV-infected veterans without increased pulmonary pressure (**Table 1**). In addition to established PH risk factors (diabetes, COPD, HF), black race was associated with increased PASP in HIV-infected and uninfected veterans (**Table 2**). Current or former smoking status was associated with increased PASP among HIV-infected, but not uninfected veterans (p for interaction = 0.037). In contrast, male sex (p for interaction = 0.056) and obesity (p for interaction 0.10) were only associated with increased PASP among uninfected veterans. All ART regimens were associated with a protective point estimate in adjusted analyses, but did not reach statistical significance.

Veterans with HIV viral load ≥500 copies/mL and those with CD4 cell counts <200 cells/mm^3 were significantly more likely to have increased PASP compared to uninfected veterans (OR 1.27, 95%CI 1.05-1.54) and (OR 1.28, 95%CI 1.02-1.60, respectively, **Supplemental Table 1**).

In this study, 2,656 participants died (42% among HIV-infected veterans) during 3.8±2.6 years of follow-up. Mortality rates per 1000 person-years were highest in HIV-infected veterans with increased pulmonary pressure (**Table 3**). This finding persisted in secondary analyses adjusting for prevalent left atrial enlargement and left ventricular hypertrophy (**Supplemental Table 2**) As compared to uninfected veterans with normal PASP, veterans with increased PASP, regardless of HIV status, had at least a 50% higher mortality rate (**Table 3**). Among HIV-infected veterans, increased PASP was associated with a significant increased risk of death even after adjusting for demographics, comorbidities, viral load, CD4 count, and ART regimen (HR 1.30 95%CI 1.14-1.49, p<0.001). In veterans without prevalent stroke, heart failure, COPD, diabetes, or renal disease, increased PASP was associated with at least double the mortality risk, regardless of HIV status (**Table 3**) and was highest in HIV-infected veterans with increased PASP (HR 3.61 95%CI 2.17-6.01, p<0.001). Incident HF rates and risk increased among individuals with increased PASP regardless of HIV status (**Supplemental Table 3**).

When we modeled PASP as a continuous variable stratified by HIV status using a PASP value of 15mmHg as the reference, the adjusted risk of death in HIV-infected veterans began to increase at a lower PASP compared with uninfected veterans and with a larger effect size at all PASP values (**Figure 1**). For example, an HIV-infected individual with a PASP of 30mmHg has a HR of 1.40 (95%CI 1.18-1.67) for mortality, whereas the corresponding HR for uninfected individuals is 1.21 (95%CI 1.04-1.41). HIV-infected veterans had an increased risk of mortality as compared to uninfected

veterans across all PASP values (**Figure 2**). The difference in risk between HIV-infected and uninfected veterans was highest at values currently considered normal or modestly elevated.

DISCUSSION

In this national sample of veterans referred for echocardiography, HIV-infected people with unsuppressed HIV virus or low CD4 cell counts had a higher prevalence of increased PASP than uninfected people. As compared to participants with either HIV infection or increased PASP, participants with both conditions had the highest rates and risk of death. While mortality risk increased with increasing PASP, HIV-infected people had significantly increased mortality risk at PA pressure values currently considered normal and well below the threshold at which consideration of invasive evaluation is recommended(14). Although risk factor profiles for increased PASP varied by HIV status, black race was independently associated with increased PASP in both HIV-infected and uninfected veterans.

Increased PASP in individuals with HIV has been well-described, particularly in the pre-ART era(1, 2, 25, 26). Our study adds to this field by examining PASP in the ART era in a national sample that includes demographically and behaviorally similar uninfected individuals. Unlike prior studies that were limited by small sample sizes, missing covariate data, or lacked outcome data, this study was powered to examine how mortality risk changes across a wide distribution of PASP values. Although this study

was unable to discriminate pre-capillary PH from PH due to left heart disease because echocardiographic estimates of PASP do not inform on the etiology of increased pulmonary pressure, we presume that most of the increased PASP in VACS is due to left heart disease or parenchymal lung disease given the high prevalence of cardiovascular risk factors and COPD in our cohort.

Although the high burden of comorbid disease was undoubtedly a major driver of outcomes in our study, increased PASP was significantly associated with mortality even among those veterans without prevalent comorbidities (**Table 3**). Similarly, increased PASP was also associated with increased risk of incident HF regardless of HIV status. Interestingly, there was no increased risk of heart failure among HIV-infected individuals without PH, which is inconsistent with prior reports, including from VACS(11). This likely reflects an increased risk of heart failure in the reference population (uninfected individuals with normal pulmonary pressure) who were referred for echocardiograms, rather than a lack of an association between HIV and heart failure. Taken together, these data suggest that HIV confers risk for increased PASP and mortality beyond that expected from chronically elevated LV pressure. Differences in the ability of the right ventricle to adapt to elevated afterload may explain higher mortality in HIV-infected veterans, but these data are not available in our cohort. These findings are important because PH due to LV disease is far more common than PAH. Thus, studies investigating the mechanisms of HIV-associated PH should also focus on PH in patients with LV disease, not just PAH.

Understanding why the combination of HIV and increased PASP is associated with higher mortality may lead to mechanistic insights in pulmonary vascular disease in uninfected individuals. Some studies report an association between HIV-specific biomarkers and ART (e.g. higher viral load) and PH(5, 27-31). Reports for the latter association are conflicting and typically involve patients with confirmed or presumed PAH(32-34). In this study, high viral load and lower CD4 cell count were associated with increased PASP. This is consistent with our prior work in VACS linking high HIV viral loads and immunodeficiency with an increased risk of acute myocardial infarction and heart failure. (11, 16, 35, 36). ART exposure or specific regimen was not associated with adjusted risk of increased pulmonary pressure; however, our cross-sectional study does not account for the intensity of duration of ART use.

Consistent with prior studies(37), increased PASP was significantly associated with diabetes, COPD, and renal function. The magnitude of association between some clinical features (smoking, obesity, male gender) differed significantly by HIV status. Black veterans accounted for 61% of the HIV-infected subjects with increased PASP but only 51% of the total HIV-infected cohort. Black race was associated with a higher prevalence of PASP in uninfected veterans. These findings suggest that PASP risk factor profiles differ by HIV status and that black individuals are particularly vulnerable, which may aid clinician decision making regarding PH screening and surveillance intervals in this high risk population.

Our findings related to pulmonary pressure and mortality have important implications for HIV infected patients and their providers. The prevalence of elevated PASP in referral populations using echocardiographic estimates ranges from 6-57% (4, 5, 31, 38-41). Given this broad range, it is unclear whether a cutoff applied to the general population for recommending invasive evaluation (e.g. 40mmHg) is appropriate for HIV-infected individuals or others at risk for PH. Current recommendations are largely empiric, vary based on expert opinion, and do not specifically relate to risk in specific PH causes. In VACS participants, the adjusted risk of death increases at a lower PASP value in HIV-infected versus uninfected veterans. Moreover, lower PASP values were associated with a high risk of mortality in HIV-infected veterans. In contrast to uninfected veterans, the effect of PASP in HIV-infected veterans was non-linear with disproportionate risk occurring between values of roughly 30-50mmHg. Accordingly, these data should prompt reconsideration of the current approaches to PH diagnosis, screening, and surveillance in HIV infected individuals. Echocardiographic estimates of PASP are particularly relevant for HIV-infected individuals and their providers in endemic areas where catheterization laboratories are rare and risk projection is necessarily based on echocardiographic data. One speculation for the observation of increased mortality among HIV-infected individuals with PH is that HIV may lower the threshold for right ventricular decompensation due to effects on the immune system, HIV medications, or both. The relative hazard of mortality between HIV-infected and uninfected veterans declined at higher PASP estimates in our cohort (**Figure 2**). This may reflect the inability of the right ventricle to compensate at high afterload regardless of HIV status. These findings require validation, ideally in cohorts with a greater proportion of women, but

suggest that the spectrum and magnitude of risk may differ between infected and uninfected individuals.

Limitations

We studied an echocardiography referral population; therefore, we are unable to comment on the prevalence of PH in the general HIV community. PASP estimates were not collected according to a common protocol or interpreted by a central laboratory. Nonetheless, our study involves a large nationwide sample with clinically interpreted echocardiograms on which management decisions are made, making our findings highly generalizable. The correlation between Doppler PASP estimates and invasive hemodynamics is imperfect, which may lead to misclassification of PH status(42). Unfortunately, hemodynamic data in the HIV VA population are sparse(43). We do not have data on right ventricular function, which is an important mediator of mortality in the setting of increased pulmonary pressure. This is an important focus of future work as we refine our data extraction tool. Similarly, data on exposure to PAH-specific therapies is not currently available in VACS. We did not have access to data on self-reported substance use, including exposure to cocaine and methamphetamine, which are risk factors for PH. We were unable to ascertain the indication for echocardiography. Although indications may have differed between HIV-infected and uninfected veterans, the distribution of PASP between groups was nearly identical, suggesting lack of a systematic bias. Finally, an inherent limitation to a veteran population is the relative paucity of women.

Conclusion

HIV infected people with high HIV viral loads or low CD4 cell counts have a higher prevalence of elevated PASP compared to uninfected people. In HIV-infected people, mortality risk increases with increasing PASP values and is present even at lower values of PASP than previously recognized. These findings support the need for future work examining the mechanisms of developing increased PASP in HIV-infected people as well as the causes driving the associated mortality risk. Importantly, these findings may provide rationale for HIV-specific thresholds for invasive evaluation and inform future recommendations for screening and surveillance of HIV-infected individuals for PH.

Acknowledgements:

None

Table 1. Baseline Characteristics of Veterans Stratified by HIV and PASP Status

Baseline Characteristics *,†,‡	HIV-infected (n = 2831)		HIV-uninfected (n = 5465)	
	No PH: PASP ≤ 40 mmHg (n = 2049)	PH: PASP > 40 mmHg (n = 782)	No PH: PASP ≤ 40 mmHg (n = 3987)	PH: PASP > 40 mmHg (n = 1478)
Age, y				
Mean (SD)	56.7 (9.8)	57.9 (10.0)	57.5 (9.4)	59.2 (9.3)
Median	56.0	57.0	57.0	58.0
Age Category, %				
<40	3.5	2.3	2.4	0.8
40-64	77.7	76.0	78.9	75.1
65+	18.8	21.7	18.7	24.1
Male sex, %	97.3	98.1	96.2	98.9
Race/ethnicity, %				
African American	48.1	60.7	46.8	59.1
White	40.0	31.7	40.0	32.7
Hispanic	9.0	4.9	11.0	6.5
Other	2.8	2.7	2.2	1.7
Framingham Risk Factors, %				
Hypertension, %	89.2	94.6	95.8	97.4
Diabetes mellitus	33.0	44.3	41.7	55.9
Dyslipidemia, %	68.8	66.5	60.3	57.9
Smoking, %				
Current	46.7	52.3	42.6	42.3
Former	22.3	25.1	25.3	28.0
Never	31.0	22.6	32.2	29.7
Other risk factors, %				
VACS Index				
Mean (SD)	41.4 (24.7)	50.5 (27.0)	27.4 (18.9)	34.9 (20.7)

Median	37.0	47.0	22.0	33.0
HCV infection, %	40.8	43.4	19.5	21.2
Renal disease, mL/min/1.73m^2				
eGFR ≥60	78.7	66.7	81.7	65.9
eGFR 30-59	14.7	16.4	13.4	21.8
eGFR <30	6.6	16.9	4.9	12.4
BMI, kg/m^2				
BMI<18.5	5.1	7.0	2.0	2.7
18.5≤BMI<30	74.7	74.1	55.9	50.6
BMI≥30	20.1	18.8	42.1	46.7
Anemia, g/dL				
Hemoglobin ≥14	36.1	28.0	50.5	36.0
Hemoglobin 12-13.9	37.1	34.4	33.4	35.1
Hemoglobin 10-11.9	19.3	25.8	12.5	20.7
Hemoglobin <10	7.6	11.8	3.6	8.2
History of Alcohol Abuse, %	37.5	41.7	36.5	37.3
COPD, %	30.6	41.6	31.0	44.9
Heart Failure, %				
Ejection Fraction > 50%	3.1	8.6	3.7	9.1
Ejection Fraction ≤ 50%	7.7	17.1	6.9	13.1
No Ejection Fraction	10.9	24.3	14.7	35.2
No Heart Failure	78.3	50.0	74.7	42.6
Left Atrial Enlargement, %	30.7	53.5	41.7	63.0
Left Ventricular Hypertrophy, %	35.5	49.8	43.5	52.2
Stroke, %	6.2	6.7	7.5	8.3

Coronary Heart Disease, %	35.5	46.0	48.2	61.2
Atrial Fibrillation, %	11.4	15.9	16.3	25.4
Cancer, %	11.0	13.6	9.0	11.0
HIV-specific variables, §				
CD4 Cell count, mm				
CD4≥500	34.6	32.5	--	--
200≤CD4<500	45.4	43.0	--	--
CD4<200	19.9	24.5		
HIV-1 RNA, copies/mL				
HIV-1 RNA<500	68.6	61.0	--	--
500≤HIV-1 RNA<1000	3.0	4.4		
HIV-1 RNA≥1000	28.4	34.6		
ART regimen, %			--	--
NRTI + PI	40.7	36.7	--	--
NRTI + NNRTI	18.8	17.8	--	--
Other	6.2	6.1	--	--
No ART	34.4	39.4	--	--

Abbreviations: AMI, acute myocardial infarction; ART, antiretroviral therapy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PA, pulmonary artery; PI, protease inhibitor

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

* All characteristics were statistically different among HIV-infected veterans ($P<0.05$) using χ^2 test or Wilcoxon rank sum test except the following: age ($P=0.07$), sex ($P=0.22$), dyslipidemia ($P=0.25$), HCV infection ($P=0.21$), BMI ($P=0.13$), stroke ($P=0.62$), cancer ($P=0.06$) and ART regimen ($P=0.09$).

† All characteristics were statistically different among HIV-uninfected veterans ($P<.05$) using χ^2 test or Wilcoxon rank sum test except the following: dyslipidemia ($P=0.11$), smoking status ($P=0.09$), HCV infection ($P=0.16$), alcohol dependence ($P=0.59$), and stroke ($P=0.34$).

All variables had complete data except the following: Hypertension data were available on 2829 (HIV-infected) and 5462 (uninfected); dyslipidemia data were available on 2699 (HIV-infected) and 5244 (uninfected); smoking data were available on 2549 (HIV-infected) and 5023 (uninfected); VACS Index data were available on 2285 (HIV-infected) and 5396 (uninfected); eGFR data were available on 2818 (HIV-infected) and 5421 (uninfected); BMI data were available on 2824 (HIV-infected) and 5458 (uninfected); anemia data were available on 2817 (HIV-infected) and 5405 (uninfected); left atrial data were available on 1489(HIV-infected) and 2195 (uninfected); interventricular septum thickness data were

available on 995 (HIV-infected) and 1807 (uninfected);CD4 cell count data were available on 2374 (HIV-infected); and HIV-1 RNA data were available on 2376 (HIV-infected).

§ Because uninfected veterans do not have HIV-specific biomarkers or ART regimens, these cells contain only dashes.

Table 2. Clinical Features Associated with Increased PASP Stratified by HIV Status

Characteristic	HIV-infected (n = 2831)		HIV-uninfected (n = 5465)	
	Unadjusted OR [95% CI]	Adjusted OR [95% CI]	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
Age, 10 years	1.14 [1.05, 1.24]*	1.13 [1.01, 1.26]*	1.21 [1.13, 1.28]*	1.06 [0.98, 1.14]
Male Sex	1.44 [0.81, 2.56]	1.28 [0.66, 2.45]	3.59 [2.14, 6.04]*	3.16 [1.84, 5.44]*
Race/Ethnicity				
African American vs. White	1.59 [1.33, 1.91]*	1.38 [1.11, 1.71]*	1.55 [1.36, 1.76]*	1.48 [1.28, 1.72]*
Hispanic vs. White	0.68 [0.47, 0.99]	0.62 [0.41, 0.94]*	0.72 [0.57, 0.92]*	0.84 [0.65, 1.08]
Other vs. White	1.20 [0.71, 2.01]	1.52 [0.86, 2.69]	0.94 [0.60, 1.48]	1.27 [0.78, 2.06]
Hypertension	2.15 [1.53, 3.02]*	1.48 [0.98, 2.24]	1.69 [1.18, 2.41]*	0.73 [0.50, 1.07]
Diabetes mellitus	1.61 [1.36, 1.90]*	1.23 [1.01, 1.50]*	1.77 [1.57, 2.00]*	1.24 [1.08, 1.42]*
Dyslipidemia	0.89 [0.74, 1.07]	0.98 [0.80, 1.20]	0.90 [0.79, 1.02]	0.81 [0.71, 0.94]*
Smoking				
Current vs. Never	1.51 [1.22, 1.86]*	1.41 [1.11, 1.81]*	1.06 [0.91, 1.24]	1.02 [0.84, 1.23]
Former vs. Never	1.50 [1.15, 1.94]*	1.36 [1.04, 1.79]*	1.18 [1.00, 1.40]*	1.06 [0.88, 1.27]
VACS Index, 5 points	1.07 [1.05, 1.08]*	***	1.10 [1.08, 1.11]*	***
HCV infection	1.11 [0.94, 1.31]	0.91 [0.74, 1.12]	1.11 [0.96, 1.29]	1.04 [0.87, 1.23]
Renal Disease, mL/min/1.73m^2				
eGFR 30-59 vs. ≥60	1.31 [1.04, 1.65]*	1.08 [0.84, 1.41]	2.00 [1.71, 2.34]*	1.37 [1.15, 1.64]*

eGFR <30 vs. ≥60	3.02 [2.33, 3.92]*	2.04 [1.50, 2.79]*	3.13 [2.52, 3.88]*	1.65 [1.28, 2.13]*
BMI, kg/m^2				
BMI <18.5 vs. 18.5-29.9	1.37 [0.98, 1.93]	1.28 [0.86, 1.89]	1.48 [1.01, 2.18]*	1.32 [0.86, 2.01]
BMI ≥30 vs. 18.5-29.9	0.94 [0.76, 1.16]	0.94 [0.74, 1.20]	1.22 [1.08, 1.38]*	1.21 [1.05, 1.39]
Anemia, g/dL				
Hemoglobin 12-13.9 vs. ≥14	1.20 [0.98, 1.48]	0.97 [0.77, 1.22]	1.48 [1.28, 1.70]*	1.14 [0.98, 1.33]
Hemoglobin 10-11.9 vs. ≥14	1.73 [1.38, 2.17]*	1.05 [0.80, 1.38]	2.32 [1.95, 2.75]*	1.42 [1.17, 1.73]*
Hemoglobin <10 vs. ≥14	2.03 [1.51, 2.74]*	1.05 [0.72, 1.52]	3.15 [2.42, 4.08]*	1.69 [1.25, 2.29]*
Alcohol Dependence/Abuse	1.19 [1.01, 1.41]*	1.05 [0.86, 1.29]	1.03 [0.91, 1.17]	0.98 [0.85, 1.14]
COPD	1.61 [1.36, 1.91]*	1.28 [1.05, 1.56]*	1.81 [1.60, 2.05]*	1.40 [1.22, 1.61]*
Heart Failure				
EF>50 vs. No HF	4.30 [3.00, 6.16]*	3.32 [2.25, 4.88]*	4.38 [3.41, 5.62]*	2.96 [2.27, 3.85]*
EF≤50 vs. No HF	3.50 [2.71, 4.52]*	2.90 [2.19, 3.84]*	3.33 [2.72, 4.08]*	2.74 [2.21, 3.40]*
No EF vs. No HF	3.50 [2.80, 4.37]*	2.77 [2.14, 3.59]*	4.20 [3.63, 4.86]*	3.08 [2.61, 3.64]*
Stroke	1.09 [0.78, 1.52]	0.85 [0.58, 1.24]	1.11 [0.89, 1.39]	0.84 [0.66, 1.06]
Coronary Heart Disease	1.55 [1.31, 1.83]*	1.07 [0.88, 1.32]	1.70 [1.51, 1.92]*	1.03 [0.89, 1.19]
Atrial Fibrillation	1.46 [1.16,	0.97 [0.74, 1.29]	1.76 [1.52,	1.16 [0.98, 1.36]

	1.85]*		2.03]*	
Cancer	1.27 [0.99, 1.63]	1.30 [0.99, 1.71]	1.25 [1.03, 1.52]*	1.05 [0.85, 1.31]
CD4 Cell Count, mm				
200-499 vs. ≥500	1.03 [0.82, 1.28]	0.87 [0.69, 1.11]	---	---
<200 vs. ≥500	1.35 [1.06, 1.73]*	1.14 [0.85, 1.52]	---	---
HIV-1 RNA copies, mL				
500-999 vs. <500	1.51 [0.96, 2.37]	1.53 [0.93, 2.49]	---	---
≥1000 vs. <500	1.33 [1.06, 1.66]*	1.19 [0.89, 1.58]		
ART regimen				
NRTI + NNRTI vs. No ART	0.83 [0.65, 1.05]	0.83 [0.63, 1.10]	---	---
NRTI + PI vs. No ART	0.79 [0.65, 0.95]*	0.93 [0.74, 1.16]	---	---
Other vs. No ART	0.87 [0.61, 1.25]	0.98 [0.66, 1.46]	---	---

Adjusted analyses include age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, HCV (hepatitis C virus) infection, smoking status, renal disease, BMI, anemia, alcohol dependence or abuse, COPD (chronic obstructive pulmonary disease), CHF (congestive heart failure), stroke, CHD (coronary heart disease), atrial fibrillation, and cancer. Analyses in the HIV-infected group also include HIV-specific biomarkers and ART (antiretroviral therapy) regimens. Due to concerns regarding collinearity, VACS (Veterans Aging Cohort Study) Index was not included in the adjusted model. Statistically significant ($p<0.05$) associations are denoted with an asterisk

Table 3. Mortality Rates and Risk According to HIV and Increased PASP Status[*]

Group	N	Deaths	Rate/1000PY [95% CI]	Mortality Risk Fully adjusted [95% CI][†]	Mortality Risk VACS index adjusted [95% CI][‡]	Mortality Risk Fully Adjusted and FIB4 [95% CI][§]
HIV-, PASP ≤ 40	3987	887	54 [51, 58]	1.00	1.00	1.00
HIV-, PASP > 40	1478	645	127 [117, 137]	1.51 [1.36, 1.68]	1.88 [1.70, 2.08]	1.51 [1.36, 1.68]
HIV+, PASP ≤ 40	2049	698	92 [86, 99]	1.37 [1.24, 1.53]	1.14 [1.03, 1.27]	1.35 [1.21, 1.50]
HIV+, PASP > 40	782	426	178 [162, 196]	1.81 [1.60, 2.05]	1.70 [1.50, 1.93]	1.78 [1.57, 2.01]
Sub-analysis In Subset with No Prevalent Comorbidities[‖]						
HIV-, PASP ≤ 40	689	58	18 [14, 24]	1.00	1.00	1.00
HIV-, PASP > 40	79	15	43 [24, 70]	2.00 [1.12, 3.58]	1.66 [0.94, 2.93]	2.04 [1.14, 3.65]
HIV+, PASP ≤ 40	460	101	52 [42, 63]	2.10 [1.48, 2.98]	1.40 [0.99, 1.98]	2.06 [1.45, 2.94]
HIV+, PASP > 40	66	24	99 [64, 148]	3.49 [2.10, 5.80]	2.07 [1.25, 3.42]	3.61 [2.17, 6.01]

[*]CI = confidence interval; HIV = human immunodeficiency virus; PASP = pulmonary artery systolic pressure; PH = pulmonary hypertension; PY = patient years

[†]adjusted for age, sex, race/ethnicity, hypertension, diabetes, LDL and HDL cholesterol, triglycerides, HCV infection, smoking status, renal disease, BMI, anemia, alcohol dependence or abuse, COPD, CHF, stroke, CHD, atrial fibrillation, and cancer.

[‡]adjusted for VACS Index

[§]adjusted for everything in † as well as the Fibrosis 4 index (FIB4)

[‖]In these analyses, we removed individuals with prevalence of any of the following: diabetes, renal disease, COPD, CHF, stroke, or CHD, and thus, the mortality risk is not adjusted for these characteristics.

REFERENCES

1. Barnett CF, Hsue PY, Machado RF. Pulmonary hypertension: an increasingly recognized complication of hereditary hemolytic anemias and HIV infection. *JAMA* 2008;299:324–331.
2. Sitbon O, Lascoux-Combe C, Delfraissy J-F, Yeni PG, Raffi F, De Zuttere D, Gressin V, Clerson P, Sereni D, Simonneau G. Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. *American Journal of Respiratory and Critical Care Medicine* 2008;177:108–113.
3. Almodovar S, Cicalini S, Petrosillo N, Flores SC. Pulmonary hypertension associated with HIV infection: pulmonary vascular disease: the global perspective. *CHEST* 2010;137:6S–12S.
4. Mondy KE, Gottdiener J, Overton ET, Henry K, Bush T, Conley L, Hammer J, Carpenter CC, Kojic E, Patel P, Brooks JT, SUN Study Investigators. High Prevalence of Echocardiographic Abnormalities among HIV-infected Persons in the Era of Highly Active Antiretroviral Therapy. *Clin Infect Dis* 2011;52:378–386.
5. Morris A, Gingo MR, George MP, Lucht L, Kessinger C, Singh V, Hillenbrand M, Busch M, McMahon D, Norris KA, Champion HC, Gladwin MT, Zhang Y, Steele C, Sciurba FC. Cardiopulmonary function in individuals with HIV infection in the antiretroviral therapy era. *AIDS* 2012;26:731–740.
6. Hsue PY, Bolger AF, Martin JN. Pulmonary hypertension in HIV-infected individuals. *Clin Infect Dis* 2011;53:96–author reply 96–7.
7. Moore RD. Epidemiology of HIV infection in the United States: implications for linkage to care. *Clin Infect Dis* 2011;52 Suppl 2:S208–13.
8. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, Oursler KK, Rimland D, Gibert CL, Butt AA, Justice AC. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *American Journal of Respiratory and Critical Care Medicine* 2011;183:388–395.
9. Brittain EL, Chang J, Crothers K, Akgun K, Gibert CL, Goetz MB, Kim J, Pisani MA, So-Armah KA, Duncan MS, Justice AC, Freiberg MS. Pulmonary Hypertension in HIV: Prognostic Impact and Risk Factors in a Large National Sample. *Circulation* 2016;134:A19510.
10. Fultz SL, Skanderson M, Mole LA, Gandhi N, Bryant K, Crystal S, Justice AC. Development and verification of a “virtual” cohort using the National VA Health Information System. *Med Care* 2006;44:S25–30.
11. Freiberg MS, Chang C-CH, Skanderson M, Patterson OV, DuVall SL, Brandt CA, So-Armah KA, Vasan RS, Oursler KA, Gottdiener J, Gottlieb S, Leaf D, Rodriguez Barradas M, Tracy RP, Gibert CL, Rimland D, Bedimo RJ, Brown ST, Goetz MB, Warner A, Crothers K, Tindle HA, Alcorn C, Bachmann JM, Justice AC, Butt AA. Association Between HIV Infection and the Risk of Heart Failure With Reduced Ejection Fraction and Preserved Ejection Fraction in the Antiretroviral Therapy Era: Results From the Veterans Aging Cohort Study. *JAMA Cardiol* 2017;doi:10.1001/jamacardio.2017.0264.
12. Patterson OV, Freiberg MS, Skanderson M, J Fodeh S, Brandt CA, DuVall SL. Unlocking echocardiogram measurements for heart disease research through natural language processing. *BMC Cardiovasc Disord* 2017;17:151.
13. Assad TR, Brittain EL, Wells QS, Farber-Eger EH, Halliday SJ, Doss LN, Xu M,

Wang L, Harrell FE, Yu C, Robbins IM, Newman JH, Hemnes AR. Hemodynamic evidence of vascular remodeling in combined post- and precapillary pulmonary hypertension. *Pulm Circ* 2016;6:313–321.
14. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*, 2009 ed. 2009;53:1573–1619.
15. Jankowich MD, Wu W-C, Choudhary G. Association of Elevated Plasma Endothelin-1 Levels With Pulmonary Hypertension, Mortality, and Heart Failure in African American Individuals: The Jackson Heart Study. *JAMA Cardiol* 2016;1:461–469.
16. White JR, Chang C-CH, So-Armah KA, Stewart JC, Gupta SK, Butt AA, Gibert CL, Rimland D, Rodriguez-Barradas MC, Leaf DA, Bedimo RJ, Gottdiener JS, Kop WJ, Gottlieb SS, Budoff MJ, Khambaty T, Tindle HA, Justice AC, Freiberg MS. Depression and human immunodeficiency virus infection are risk factors for incident heart failure among veterans: Veterans Aging Cohort Study. *Circulation* 2015;132:1630–1638.
17. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Ann Epidemiol* 2002;12:462–468.
18. Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology* 2004;40:115–119.
19. McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, Brown ST, Freiberg MS, Gibert CL, Goetz MB, Kim JW, Pisani MA, Rimland D, Rodriguez-Barradas MC, Sico JJ, Tindle HA, Crothers K. Validating smoking data from the Veteran's Affairs Health Factors dataset, an electronic data source. *Nicotine Tob Res* 2011;13:1233–1239.
20. Goulet JL, Fultz SL, McGinnis KA, Justice AC. Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV/HCV-co-infected veterans. *AIDS* 2005;19 Suppl 3:S99–105.
21. Kraemer KL, McGinnis KA, Skanderson M, Cook R, Gordon A, Conigliaro J, Shen Y, Fiellin DA, Justice AC. Alcohol problems and health care services use in human immunodeficiency virus (HIV)-infected and HIV-uninfected veterans. *Med Care* 2006;44:S44–51.
22. Bedimo RJ, McGinnis KA, Dunlap M, Rodriguez-Barradas MC, Justice AC. Incidence of non-AIDS-defining malignancies in HIV-infected versus noninfected patients in the HAART era: impact of immunosuppression. *J Acquir Immune Defic Syndr* 2009;52:203–208.
23. Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, Nattermann J, Lampe FC, Bucher HC, Sterling TR, Crane HM, Kitahata MM, May M, Sterne JAC. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. *AIDS* 2013;27:563–572.

24. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;
25. Speich R, Jenni R, Opravil M, Pfab M, Russi EW. Primary pulmonary hypertension in HIV infection. *CHEST* 1991;100:1268–1271.
26. Opravil M, Sereni D. Natural history of HIV-associated pulmonary arterial hypertension: trends in the HAART era. *AIDS* 2008;22 Suppl 3:S35–40.
27. Nunes H, Humbert M, Sitbon O, Morse JH, Deng Z, Knowles JA, Le Gall C, Parent F, Garcia G, Hervé P, Barst RJ, Simonneau G. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. *American Journal of Respiratory and Critical Care Medicine* 2003;167:1433–1439.
28. Degano B, Guillaume M, Savale L, Montani D, Jaïs X, Yaici A, Le Pavec J, Humbert M, Simonneau G, Sitbon O. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. *AIDS* 2010;24:67–75.
29. Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA. HIV-Related pulmonary hypertension: analytic review of 131 cases. *CHEST* 2000;118:1133–1141.
30. Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dubé MP, Fichtenbaum CJ, Gerschenson M, Mitchell CKC, Murphy RL, Squires K, Stein JH, ACTG 5152s Study Team. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol* 2008;52:569–576.
31. Quezada M, Martin-Carbonero L, Soriano V, Vispo E, Valencia E, Moreno V, de Isla LP, Lennie V, Almería C, Zamorano JL. Prevalence and risk factors associated with pulmonary hypertension in HIV-infected patients on regular follow-up. *AIDS* 2012;26:1387–1392.
32. Opravil M, Pechère M, Speich R, Joller-Jemelka HI, Jenni R, Russi EW, Hirschel B, Lüthy R. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV Cohort Study. *American Journal of Respiratory and Critical Care Medicine* 1997;155:990–995.
33. Zuber J-P, Calmy A, Evison JM, Hasse B, Schiffer V, Wagels T, Nuesch R, Magenta L, Ledergerber B, Jenni R, Speich R, Opravil M, Swiss HIV Cohort Study Group. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. *Clin Infect Dis* 2004;38:1178–1185.
34. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect* 2000;40:282–284.
35. Sico JJ, Chang C-CH, So-Armah K, Justice AC, Hylek E, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, Rimland D, Bidwell Goetz M, Butt AA,

Rodriguez-Barradas MC, Gibert C, Leaf D, Brown ST, Samet J, Kazis L, Bryant K, Freiberg MS, Veterans Aging Cohort Study. HIV status and the risk of ischemic stroke among men. *Neurology* 2015;84:1933–1940.
36. Freiberg MS, Chang C-CH, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doebler D, Bryant K, Justice AC. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* 2013;173:614–622.
37. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. Clinical and Biological Insights Into Combined Post- and Pre-Capillary Pulmonary Hypertension. *J Am Coll Cardiol* 2016;68:2525–2536.
38. 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;29:231–234.
39. Hsue PY, Deeks SG, Farah HH, Palav S, Ahmed SY, Schnell A, Ellman AB, Huang L, Dollard SC, Martin JN. Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. *AIDS* 2008;22:825–833.
40. 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;11:1553–1559.
41. Selby VN, Scherzer R, Barnett CF, MacGregor JS, Morelli J, Donovan C, Deeks SG, Martin JN, Hsue PY. Doppler echocardiography does not accurately estimate pulmonary artery systolic pressure in HIV-infected patients. *AIDS* 2012;26:1967–1969.
42. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine*, 2009 ed. 2009;179:615–621.
43. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, Swenson ER, Goldstein RH, Leopold JA, Zamanian RT, Elwing JM, Plomondon ME, Grunwald GK, Barón AE, Rumsfeld J, Choudhary G. Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the VA-CART Program. *Circulation* 2016;doi:10.1161/CIRCULATIONAHA.115.020207.

Figure 1. Adjusted Risk of Mortality According to PASP value and HIV Status

Restricted cubic spline plots of all-cause mortality according to PASP value and HIV-infected (**Panel A**) and uninfected (**Panel B**) veterans. The reference group for HIV-infected individuals are HIV-infected subjects with a PASP value of 15mmHg and similar for uninfected individuals. There is a non-linear relationship between PASP and mortality in HIV-infected veterans and higher risk at lower values compared with uninfected veterans. Adjusted for age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, HCV infection, smoking status, renal disease, BMI, anemia, alcohol dependence or abuse, COPD, CHF, stroke, CHD, atrial fibrillation, and cancer.

Figure 2. Incremental Change in Adjusted Risk by PASP value

Point estimates and 95% confidence intervals represent the hazard ratios of death at each PASP comparing HIV-infected to uninfected veterans. Incremental risk is highest at lower values and remains higher in HIV-infected veterans at all values. This model includes PASP, HIV status, and the interaction between PASP and HIV status along with adjustment for age, sex, race/ethnicity, hypertension, diabetes, LDL and HDL cholesterol, triglycerides, HCV infection, smoking status, renal disease, BMI, anemia, alcohol dependence or abuse, COPD, CHF, stroke, CHD, atrial fibrillation, and cancer.