# Protease Inhibitors and Cardiovascular Outcomes in Patients With HIV and Heart Failure

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## ABSTRACT

**BACKGROUND** Incident heart failure (HF) is increased in persons with human immunodeficiency virus (PHIV). Protease inhibitors (PIs) are associated with adverse cardiac remodeling and vascular events; however, there are no data on the use of PIs in PHIV with HF.

**OBJECTIVES** This study sought to compare characteristics, cardiac structure, and outcomes in PHIV with HF who were receiving PI-based versus non-PI (NPI) therapy.

**METHODS** This was a retrospective single-center study of all 394 antiretroviral therapy–treated PHIV who were hospitalized with HF in 2011, stratified by PI and NPI. The primary outcome was cardiovascular (CV) mortality, and the secondary outcome was 30-day HF readmission rate.

**RESULTS** Of the 394 PHIV with HF (47% female, mean age $60 \pm 9.5$ years, CD4 count $292 \pm 206$ cells/mm$^3$), 145 (37%) were prescribed a PI, whereas 249 (63%) were prescribed NPI regimens. All PI-based antiretroviral therapy contained boosted-dose ritonavir. PHIV who were receiving a PI had higher rates of hyperlipidemia, diabetes mellitus, and coronary artery disease (CAD); higher pulmonary artery systolic pressure (PASP); and lower left ventricular ejection fraction. In follow-up, PI use was associated with increased CV mortality (35% vs. 17%; $p < 0.001$) and 30-day HF readmission (68% vs. 34%; $p < 0.001$), effects seen in all HF types. Predictors of CV mortality included PI use, CAD, PASP, and immunosuppression. Overall, PIs were associated with a 2-fold increased risk of CV mortality.

**CONCLUSIONS** PI-based regimens in PHIV with HF are associated with dyslipidemia, diabetes, CAD, a lower left ventricular ejection fraction, and a higher PASP. In follow-up, PHIV with HF who are receiving a PI have increased CV mortality and 30-day HF readmission. (J Am Coll Cardiol 2018;72:518–30) © 2018 by the American College of Cardiology Foundation.

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The long-term survival of persons with human immunodeficiency virus (HIV) (PHIV) has improved (1). This improved survival in large part reflects the use of effective and tolerable antiretroviral therapy (ART) (1,2). Classes of ART include nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors (PIs), integrase inhibitors, and fusion inhibitors (3). Previous analyses have demonstrated associations between the use of some PIs and vascular events such as stroke and myocardial infarction (4-6).

In animal models, PIs are associated with an increase in transforming growth factor beta-1, leading to myocardial fibrosis and impaired cardiac function (7,8). Furthermore, echocardiographic studies in PHIV without known cardiovascular (CV) disease have shown that PIs are associated with left ventricular hypertrophy (9). It is therefore plausible that the use of PI-based ART may be associated with adverse outcomes in PHIV with heart failure (HF). Determination of whether PI-based ART regimens affect HF outcomes may be important for the following reasons: 1) the risk of incident HF is increased more than 2-fold among PHIV (10,11) and, as the group of PHIV ages, rates of incident HF are projected to increase dramatically (12); and 2) once HF is established in HIV

infection, there is a 4-fold increased risk of being admitted for decompensated HF and a 3-fold increase in CV mortality (13). Therefore, we aimed to study the association between PI use and CV outcomes in PHIV with HF. We hypothesized that PI-based therapy would be associated with adverse CV changes and adverse outcomes in HF.

## METHODS

**STUDY DESIGN AND PATIENT GROUP.** After obtaining Institutional Board Review approval, we retrospectively analyzed the data on 2,578 patients admitted to a U.S. tertiary care hospital (Bronx-Lebanon Hospital Center of Icahn School of Medicine at Mount Sinai, Bronx, New York) in 2011 with a primary diagnosis of acute decompensated HF. HF admission was defined according to the American College of Cardiology and American Heart Association key data elements and definitions for CV endpoint events: a hospital admission with a primary diagnosis of HF and length of stay of at least 24 h, with new or worsening symptoms of HF on presentation, objective evidence of new or worsening HF, and initiation or intensification of treatment specifically for HF (14).

**FIGURE 1  Consort Diagram for the Study**
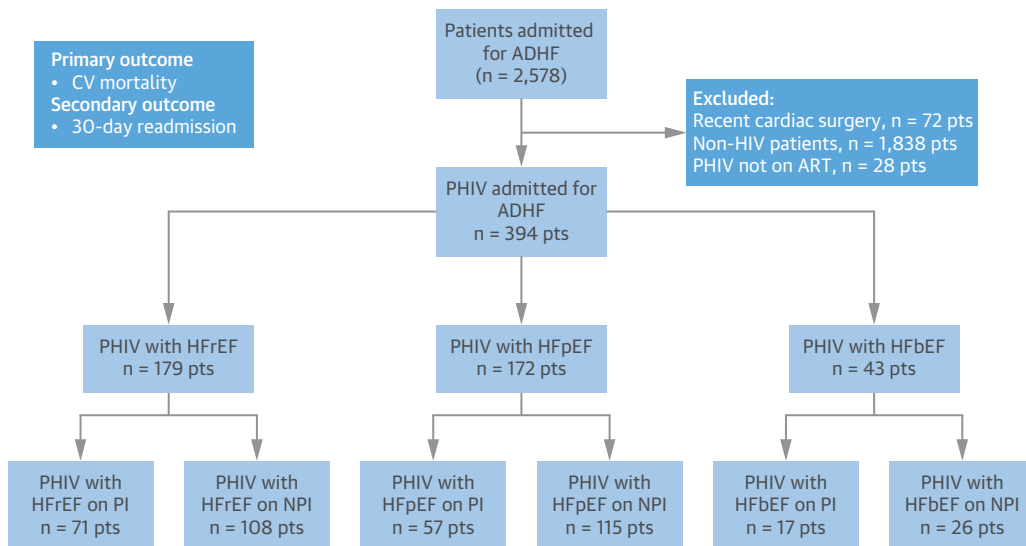
ADHF = acute decompensated heart failure; CV = cardiovascular; HFbEF = heart failure with borderline ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HIV = human immunodeficiency virus; NPI = non-protease inhibitor antiretroviral therapy; PHIV = persons with human immunodeficiency virus; PI = protease inhibitor (ritonavir boosted); Pts = patients.

| TABLE 1   Baseline Characteristics | | | | |
|---|---|---|---|---|
| | PHIV (n = 394) | PI (n = 145) | NPI (n = 249) | p Value |
| Female | 185 (47) | 65 (45) | 120 (48) | 0.519 |
| BMI, kg/m$^2$ | 27.0 ± 5.8 | 28.0 ± 5.8 | 26.0 ± 5.8 | **0.011** |
| Age, yrs | 60.0 ± 9.5 | 59.0 ± 10.0 | 60.0 ± 9.2 | 0.314 |
| Race | | | | |
|    Hispanic | 126 (32) | 51 (35) | 77 (31) | 0.572 |
|    African American | 169 (43) | 62 (43) | 107 (43) | |
|    Others | 99 (25) | 32 (22) | 65 (26) | |
| CV risk factors | | | | |
|    Diabetes | 142 (36) | 64 (44) | 78 (31) | **0.012** |
|    Hypertension | 241 (61) | 101 (69) | 140 (56) | **0.008** |
|    Hyperlipidemia | 162 (41) | 76 (52) | 86 (35) | **<0.001** |
|    Smoking | 193 (49) | 69 (47) | 124 (50) | 0.671 |
| CAD | 158 (40) | 75 (52) | 83 (33) | **<0.001** |
| Myocarditis | 47 (12) | 19 (13) | 28 (11) | 0.583 |
| ICD | 40 (10) | 22 (15) | 18 (7) | **0.011** |
| Cocaine use | 131 (33) | 52 (36) | 79 (32) | 0.400 |
| SBP, mm Hg | 143.0 ± 27.7 | 144.0 ± 28.2 | 142.0 ± 27.8 | 0.494 |
| DBP, mmHg | 77.0 ± 18.2 | 79.0 ± 19.6 | 76.0 ± 20.1 | 0.150 |
| Heart rate, beats/min | 84.0 ± 21.4 | 82.0 ± 23.2 | 85.0 ± 22.4 | 0.207 |
| PASP, mm Hg | 45.0 ± 9.5 | 48.0 ± 9.8 | 43.0 ± 9.0 | **<0.001** |
| LVEF, % | 47.0 ± 12.7 | 44.0 ± 14.3 | 48.0 ± 12.0 | **0.003** |
| SA | 113 (29) | 39 (27) | 74 (30) | 0.550 |
| HCV | 87 (22) | 35 (24) | 52 (21) | 0.452 |
| HIV parameters | | | | |
|    CD4 count at 1st HF admission, cells/mm$^3$ | 295 ± 207 | 284 ± 213 | 295 ± 201 | 0.609 |
|    Nadir CD4 count, cells/mm$^3$ | 245 ± 197 | 213 ± 184 | 276 ± 212 | **0.003** |
|    VL <200 copies/ml | 244 (62) | 87 (60) | 157 (63) | 0.547 |
|    Duration of ART, yrs | 8 (4–16) | 8 (4–16) | 9 (4–16) | 0.217 |
|    Duration of PI, yrs | — | 6 (4–11) | — | — |
|    Duration of HIV* | 8 (4–16) | 8 (4–16) | 9 (4–16) | 0.217 |
|    Duration of untreated HIV† | 75 (48–107) | 76 (48–107) | 74 (47–104) | 0.659 |
| Socioeconomic parameters | | | | |
|    High school or GED completion | 252 (64) | 96 (66) | 156 (62) | 0.478 |
|    Unemployment | 47 (12) | 19 (13) | 28 (11) | 0.583 |
| ART medications | | | | |
|    NRTIs | 394 (100) | 145 (100) | 249 (100) | >0.05 |
|    INSTIs | 106 (27) | 6 (4) | 92 (37) | **<0.001** |
|    NNRTIs | 165 (42) | 6 (4) | 157 (63) | **<0.001** |
| HF medications | | | | |
|    Beta-blocker | 351 (89) | 128 (88) | 223 (89) | 0.738 |
|    ACE inhibitor or ARB | 302 (86) | 108 (85) | 194 (87) | 0.437 |
|    Spironolactone | 36 (9) | 17 (12) | 19 (8) | 0.174 |
|    Furosemide | 311 (79) | 105 (72) | 206 (83) | **0.015** |

Values are n (%), mean ± SD, or median (interquartile range). **Bold** p values are statistically significant. *Duration of HIV is in years. †Duration of untreated HIV is the duration before starting ART after the diagnosis in days.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ART = antiretroviral therapy; BMI = body mass index; CAD = coronary artery disease; CV = cardiovascular; DBP = diastolic blood pressure; GED = general equivalency diploma; HCV = hepatitis C virus infection; HIV = human immunodeficiency virus; ICD = implantable cardioverter-defibrillator; INSTI = integrase inhibitor; LVEF = left ventricular ejection fraction; NNRTI = non-nucleoside reverse transcriptase inhibitor; NPI = non-protease inhibitor antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; PASP = pulmonary artery systolic pressure; PHIV = persons with human immunodeficiency virus; PI = ritonavir-based protease inhibitor; SA = sleep apnea; SBP = systolic blood pressure; VL = viral load.

Individuals who had a recent (≤3 months) history of cardiac surgery (n = 72), were excluded from the study. We further excluded patients without HIV infection (n = 1,838) and PHIV who were not prescribed ART (n = 24) (**Figure 1**), thus resulting in a final study group of 394 PHIV with HF. The cohort was further stratified by HF with reduced ejection fraction (HFrEF) (left ventricular ejection fraction [LVEF] <40%), HF with borderline ejection fraction (HFbEF) (LVEF 40% to 49%), and HF with preserved ejection fraction (HFpEF) (LVEF ≥50%) (**Figure 1**). The diagnoses of HIV infection and HF, as well as other clinically relevant variables, were ascertained in each patient through manual review of each of individual electronic health record (EHR).

**COVARIATES.** Through EHR review, data were collected on traditional HF risk factors (including hypertension, dyslipidemia, diabetes mellitus, coronary artery disease [CAD], family history of CAD, body mass index, previous or active cigarette smoking, and previous or active cocaine use). During EHR review, data were collected on LVEF and medication use at the time of discharge from the index HF hospitalization. Additional data included information on socioeconomic status (education level and employment status). For the purposes of this study, assignment to a PI regimen was made by reviewing the medications at the time of discharge. Details on HIV-specific parameters (CD4, viral load [VL]) were recorded from those available closest to the time of discharge from the index HF hospitalization (all were within 1 month of the date of discharge).

**OUTCOMES.** Our primary outcome was CV mortality, defined as death resulting from HF, sudden cardiac death, arrhythmias, and/or acute ischemic events (15). Death was determined through the Social Security Death Index (SSDI), and cause of death was confirmed by physician-adjudicated individual EHR review. The secondary outcome was 30-day HF hospital readmission rate, defined as described earlier and ascertained through physician-adjudicated individual EHR review. All outcomes were adjudicated by a physician blinded to all other variables including HIV drug class. The follow-up period began on the date of discharge from the first HF hospitalization in 2011.

**STATISTICAL ANALYSIS.** Continuous variables are presented as mean ± SD or median (interquartile range [IQR]), as appropriate on the basis of normality, and categorical variables are presented as percentages. Continuous data were compared with the use

**TABLE 2  Baseline Characteristics (PHIV With HFrEF)**

| | HFrEF on PIs (n = 71) | HFrEF on NPI (n = 108) | p Value |
|---|---|---|---|
| Female | 32 (45) | 54 (50) | 0.518 |
| BMI, kg/m$^2$ | 27.0 ± 6.0 | 26.0 ± 5.6 | 0.257 |
| Age, yrs | 58.0 ± 10.0 | 60.0 ± 8.3 | 0.148 |
| Race | | | |
| Hispanic | 26 (37) | 36 (33) | 0.899 |
| African American | 29 (41) | 47 (43) | |
| Others | 16 (22) | 25 (23) | |
| CV risk factors | | | |
| Diabetes | 29 (41) | 30 (28) | 0.070 |
| Hypertension | 50 (70) | 61 (57) | 0.060 |
| Hyperlipidemia | 34 (48) | 33 (31) | **0.020** |
| Smoking | 39 (54) | 48 (45) | 0.169 |
| CAD | 41 (57) | 35 (34) | **<0.001** |
| Myocarditis | 9 (12) | 14 (13) | 0.956 |
| ICD | 24 (34) | 16 (15) | **0.003** |
| Cocaine | 21 (30) | 39 (36) | 0.365 |
| SBP, mm Hg | 143.0 ± 26.2 | 141.0 ± 27.4 | 0.628 |
| DBP, mm Hg | 80.0 ± 19.2 | 78.0 ± 19.8 | 0.504 |
| Heart rate, beats/min | 83.0 ± 22.0 | 81.0 ± 21.1 | 0.542 |
| PASP, mm Hg | 50.0 ± 9.5 | 46.0 ± 8.4 | **0.003** |
| LVEF, % | 31.0 ± 7.1 | 39.0 ± 7.8 | **<0.001** |
| SA | 18 (25) | 30 (28) | 0.720 |
| HCV | 20 (29) | 24 (23) | 0.366 |
| HIV parameters | | | |
| CD4 count at 1st HF admission, cells/mm$^3$ | 288 ± 215 | 310 ± 213 | 0.502 |
| Nadir CD4 count, cells/mm$^3$ | 215 ± 182 | 281 ± 241 | **0.050** |
| VL <200 copies/ml | 42 (59) | 66 (63) | 0.793 |
| Duration of ART, yrs | 8 (4–16) | 9 (4–16) | 0.111 |
| Duration of PI, yrs | 6 (4–11) | — | — |
| Duration of HIV* | 8 (4–16) | 9 (4–16) | 0.111 |
| Duration of untreated HIV† | 76 (48–107) | 74 (46–106) | 0.689 |
| Socioeconomic parameters | | | |
| High school or GED completion | 43 (60) | 68 (63) | 0.746 |
| Unemployment | 11 (16) | 15 (14) | 0.765 |
| ART medications | | | |
| NRTIs | 71 (100) | 108 (100) | >0.05 |
| INSTIs | 3 (4) | 42 (39) | **<0.001** |
| NNRTIs | 2 (3) | 64 (59) | **<0.001** |
| HF medications | | | |
| Beta-blocker | 64 (90) | 95 (88) | 0.809 |
| ACE inhibitor or ARB | 63 (89) | 94 (87) | 0.818 |
| Spironolactone | 18 (25) | 18 (17) | 0.156 |
| Furosemide | 55 (78) | 93 (86) | 0.135 |

Values are n (%), mean ± SD, or median (interquartile range). **Bold** p values are statistically significant. *Duration of HIV is in years. †Duration of untreated HIV is the duration before starting ART after the diagnosis in days.

HFrEF = heart failure with reduced ejection fraction; other abbreviations as in Table 1.

**TABLE 3  Baseline Characteristics (PHIV With HFpEF)**

| | HfpEF on PI (n = 57) | HfpEF on NPI (n = 115) | p Value |
|---|---|---|---|
| Female | 24 (43) | 56 (49) | 0.415 |
| BMI, kg/m$^2$ | 28.0 ± 5.6 | 27.0 ± 5.6 | 0.272 |
| Age, yrs | 60.0 ± 9.0 | 60.0 ± 9.4 | 0.994 |
| Race | | | |
| Hispanic | 19 (34) | 35 (30) | 0.701 |
| African American | 26 (46) | 49 (43) | |
| Others | 12 (21) | 31 (27) | |
| CV risk factors | | | |
| Diabetes | 26 (45) | 40 (35) | 0.169 |
| Hypertension | 36 (64) | 64 (56) | 0.348 |
| Hyperlipidemia | 31 (54) | 40 (35) | **0.014** |
| Smoking | 20 (35) | 59 (51) | **0.044** |
| CAD | 28 (49) | 33 (29) | **0.008** |
| Myocarditis | 8 (14) | 13 (11) | 0.626 |
| Cocaine | 26 (46) | 32 (28) | **0.020** |
| SBP, mm Hg | 144.0 ± 25.8 | 141.0 ± 26.6 | 0.483 |
| DBP, mm Hg | 78 ± 18.8 | 79 ± 18.2 | 0.737 |
| Heart rate, beats/min | 80.0 ± 23.2 | 82.0 ± 22.7 | **0.590** |
| PASP, mm Hg | 47.0 ± 9.9 | 40.0 ± 8.1 | **<0.001** |
| LVEF, % | 57.0 ± 5.3 | 56.0 ± 5.0 | 0.231 |
| SA | 16 (28) | 36 (31) | 0.663 |
| HCV | 11 (20) | 25 (22) | 0.711 |
| HIV parameters | | | |
| CD4 count at 1st HF admission, cells/mm$^3$ | 276 ± 215 | 291 ± 193 | 0.645 |
| Nadir CD4 count, cells/mm$^3$ | 218 ± 185 | 272 ± 191 | 0.080 |
| VL <200 copies/ml | 34 (60) | 72 (63) | 0.707 |
| Duration of ART, yrs | 8 (4–14) | 9 (4–14) | 0.842 |
| Duration of PI, yrs | 6 (4–11) | — | — |
| Duration of HIV* | 8 (4–14) | 9 (4–14) | 0.842 |
| Duration of untreated HIV† | 75 (46–104) | 74 (46–106) | 0.632 |
| Socioeconomic parameters | | | |
| High school or GED completion | 38 (66) | 72 (63) | 0.601 |
| Unemployment | 7 (13) | 14 (12) | 0.983 |
| ART medications | | | |
| NRTIs | 57 (100) | 115 (100) | >0.05 |
| INSTIs | 3 (5) | 44 (38) | **<0.001** |
| NNRTIs | 4 (7) | 71 (62) | **<0.001** |
| HF medications | | | |
| Beta-blocker | 48 (85) | 102 (89) | 0.468 |
| ACE inhibitor or ARB | 47 (83) | 99 (86) | 0.651 |
| Spironolactone | 0 (0) | 0 (0) | |
| Furosemide | 39 (69) | 92 (80) | 0.093 |

Values are n (%), mean ± SD, or median (interquartile range). **Bold** p values are statistically significant. *Duration of HIV is in years. †Duration of untreated HIV is the duration before starting ART after the diagnosis in days.

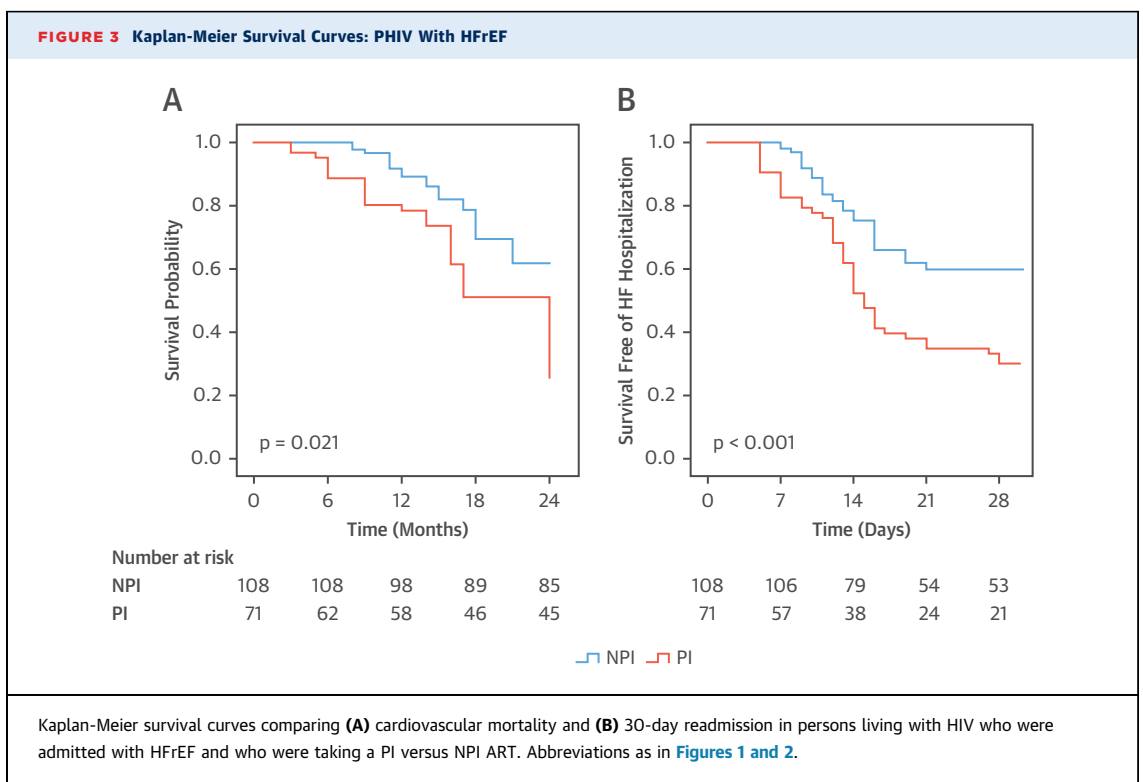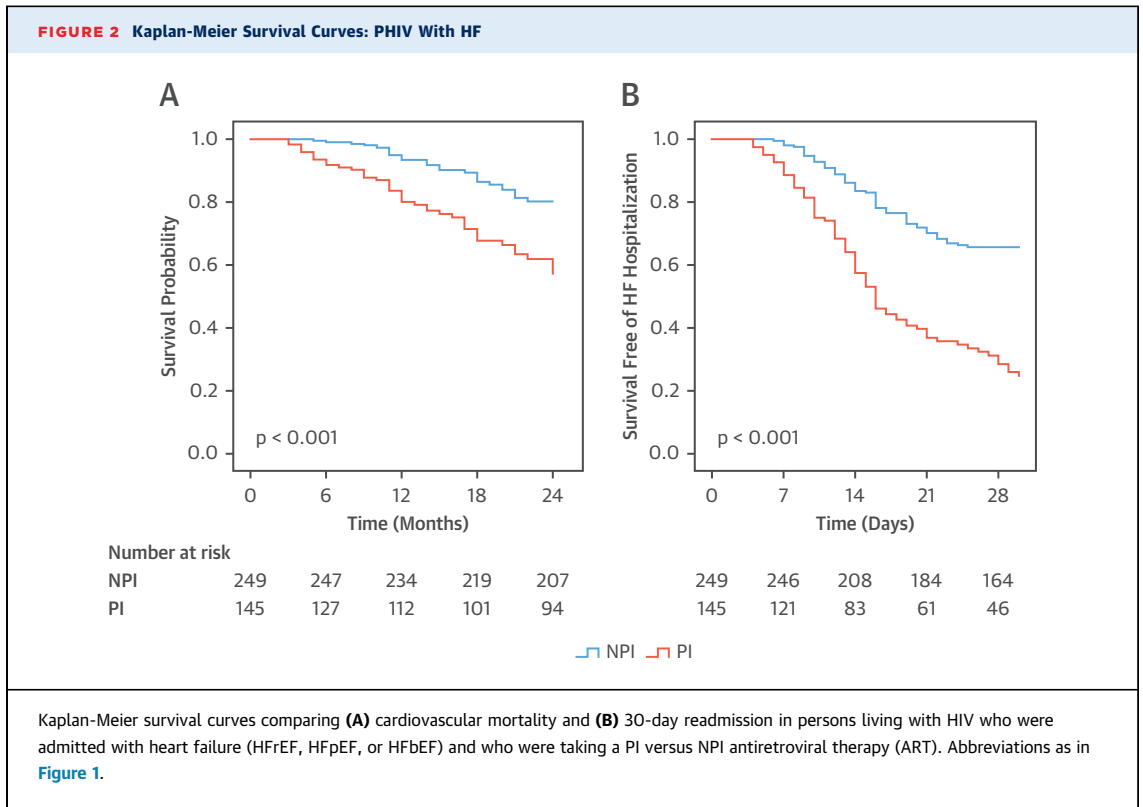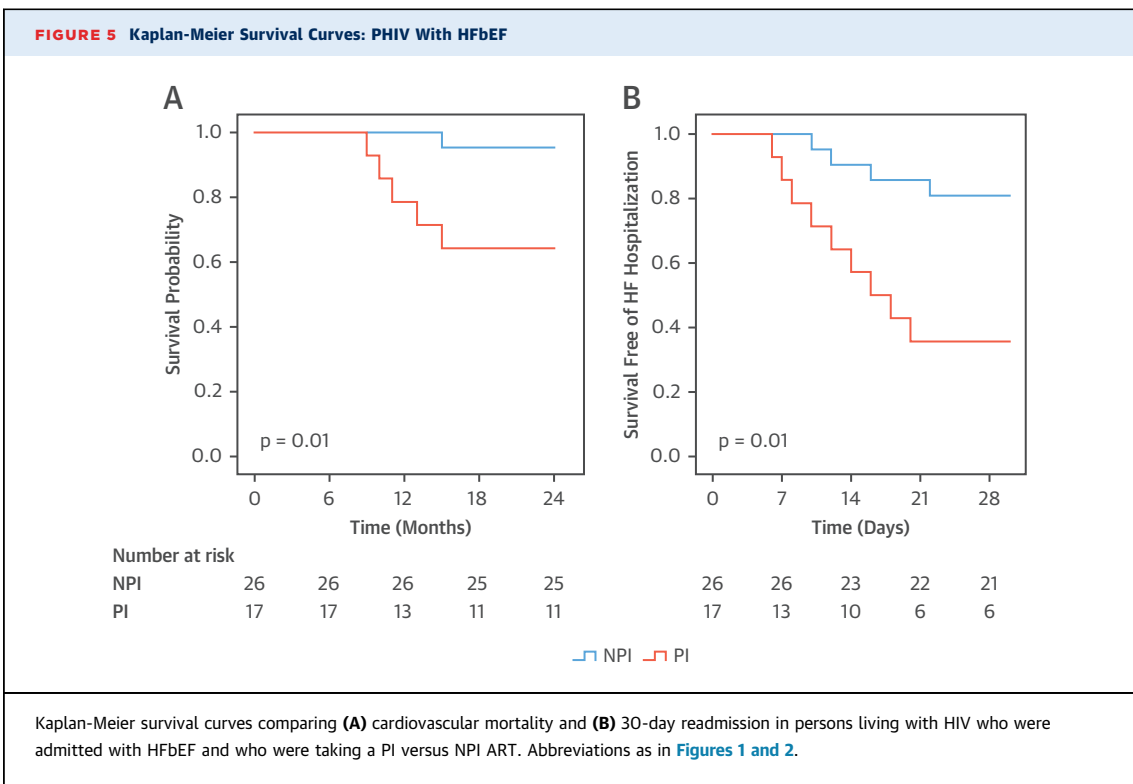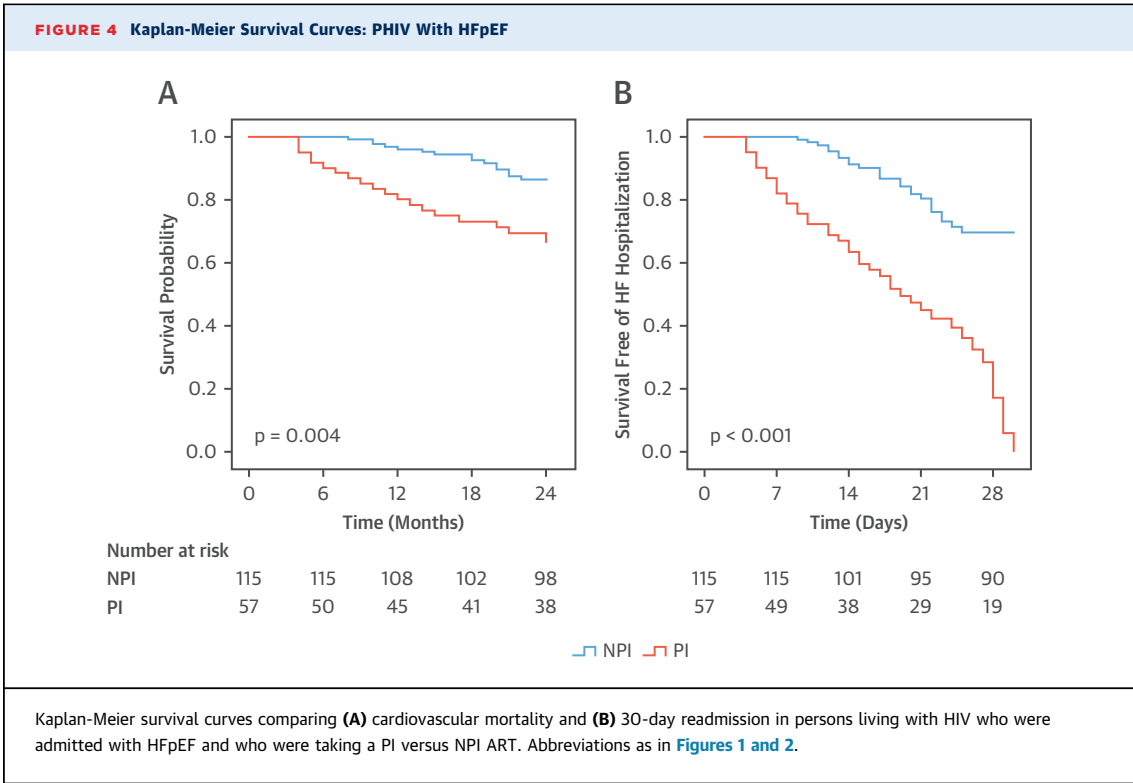HFpEF = heart failure with preserved ejection fraction; other abbreviations as in Table 1.

of unpaired Student's *t*-tests or Wilcoxon rank sum tests, as appropriate. Categorical data were compared using the chi-square or the Fisher exact test. Clinical parameters at index HF hospitalization and subsequent outcomes were compared among the following

groups: 1) PHIV with HF stratified by PI versus NPI; 2) PHIV with HFrEF stratified by PI versus NPI; 3) PHIV with HFpEF stratified by PI versus NPI; and 4) PHIV with HFbEF stratified by PI versus NPI. Survival curves were plotted using Kaplan-Meier curves.

**FIGURE 2  Kaplan-Meier Survival Curves: PHIV With HF**



Kaplan-Meier survival curves comparing **(A)** cardiovascular mortality and **(B)** 30-day readmission in persons living with HIV who were admitted with heart failure (HFrEF, HFpEF, or HFbEF) and who were taking a PI versus NPI antiretroviral therapy (ART). Abbreviations as in **Figure 1**.

**FIGURE 3  Kaplan-Meier Survival Curves: PHIV With HFrEF**



Kaplan-Meier survival curves comparing **(A)** cardiovascular mortality and **(B)** 30-day readmission in persons living with HIV who were admitted with HFrEF and who were taking a PI versus NPI ART. Abbreviations as in **Figures 1 and 2**.

**FIGURE 4  Kaplan-Meier Survival Curves: PHIV With HFpEF**



Kaplan-Meier survival curves comparing **(A)** cardiovascular mortality and **(B)** 30-day readmission in persons living with HIV who were admitted with HFpEF and who were taking a PI versus NPI ART. Abbreviations as in **Figures 1 and 2**.

**FIGURE 5  Kaplan-Meier Survival Curves: PHIV With HFbEF**



Kaplan-Meier survival curves comparing **(A)** cardiovascular mortality and **(B)** 30-day readmission in persons living with HIV who were admitted with HFbEF and who were taking a PI versus NPI ART. Abbreviations as in **Figures 1 and 2**.

Univariate and multivariate regression analyses were performed to determine the association between baseline covariates and the CV mortality rate. Multivariate Cox proportional hazard regression analyses for CV mortality rate were constructed using a p <0.01 on the univariate analysis for entry. Otherwise, statistical significance was defined using a 2-tailed p value ≤0.05. Both VL and CD4 count were not included in the multivariate model together because of the overlap between those individuals with a low CD4 count and those with a high VL. Statistical analyses were performed using SPSS software version 24 (IBM Corp., Armonk, New York).

## RESULTS

**BASELINE CHARACTERISTICS. PHIV with HF.** Among PHIV receiving ART and hospitalized with HF, the median duration of prescribed ART was 8.5 years (IQR: 4 to 16 years), the mean CD4 count was 295 cells/mm$^3$, and the median VL was 274 copies/ml (range <50 to 3,000,457 copies/ml). A total of 58% (228 of 394) of patients had a CD4 count of ≥200 cells/mm$^3$, and 62% (244 of 394) had a VL <200 copies/ml. Of the 394 PHIV taking ART, 145 patients (37%) had a PI-based regimen, whereas 249 patients (63%) had an NPI-based regimen. All PI-based regimens were ritonavir boosted. PI regimens prescribed in our cohort are listed in Online Table 1. When groups were stratified by a PI-based ART regimen versus a NPI-based regimen, those patients with a PI-based ART regimen were more likely to have hyperlipidemia (52% vs. 35%; p < 0.001), diabetes mellitus (44% vs. 31%; p = 0.012), CAD (52% vs. 33%; p < 0.001), higher pulmonary artery pressure (PASP) (48 ± 9.8 mm Hg vs. 43 ± 9.0 mm Hg; p < 0.001), and lower LVEF (44 ± 14.0% vs. 49 ± 12.0%; p = 0.003) (**Table 1**).

**PHIV with HFrEF.** There were 179 PHIV with HFrEF who were receiving ART (median duration 8.5 years [IQR: 4 to 16 years]). Among PHIV with HFrEF and ART, the mean CD4 count was 299 cells/mm$^3$, and the median VL was 273 copies/ml (range <50 to 3,000,457 copies/ml). A total of 57% (102 of 179) of patients had a CD4 count of ≥200 cells/mm$^3$, and 60% (108 of 179) had VL <200 copies/ml. Of the 179 PHIV with HFrEF, 71 patients (40%) had a PI-based ART regimen, whereas 108 (60%) had an NPI-based regimen. When PHIV with HFrEF were stratified by PI-based ART versus NPI, findings were similar to those in the overall cohort (**Table 2**).

**PHIV with HFpEF.** There were 172 PHIV with HFpEF who were receiving ART (median duration 8 years [IQR: 4 to 14 years]). In this group, the mean CD4 count was 291 cells/mm$^3$, and the median VL was 307

**TABLE 4** Univariate Analysis (PHIV Total Cohort, N = 394): Outcome CV Mortality

| | Hazard Ratio | 95% CI Lower | 95% CI Upper | p Value |
|---|---|---|---|---|
| Sex | 1.017 | 0.761 | 1.276 | 0.913 |
| Age | 0.954 | 0.920 | 1.017 | 0.324 |
| BMI | 0.946 | 0.902 | 1.012 | 0.112 |
| Diabetes | 1.234 | 1.015 | 1.579 | 0.037 |
| Hypertension | 1.078 | 0.842 | 1.329 | 0.591 |
| Hyperlipidemia | 1.202 | 0.955 | 1.583 | 0.080 |
| Smoking | 1.142 | 0.875 | 1.527 | 0.235 |
| History of CAD | 1.735 | 1.311 | 2.329 | **<0.001*** |
| ICD | 1.171 | 1.042 | 1.343 | **<0.001*** |
| Cocaine | 1.165 | 0.963 | 1.493 | 0.063 |
| PASP | 1.142 | 1.068 | 1.172 | **<0.001*** |
| LVEF | 0.953 | 0.934 | 0.973 | **<0.001*** |
| OSA | 1.014 | 0.679 | 1.518 | 0.963 |
| CD4 count ≥200 | 0.993 | 0.991 | 0.995 | **<0.001*** |
| Nadir CD4 count | 0.897 | 0.871 | 0.951 | **<0.001*** |
| VL >200 | 3.212 | 1.911 | 5.861 | **<0.001*** |
| ART duration | 0.973 | 0.919 | 1.054 | 0.658 |
| HIV duration | 1.011 | 0.928 | 1.098 | 0.682 |
| Untreated HIV duration | 1.171 | 0.883 | 1.361 | 0.731 |
| Education† | 0.721 | 0.521 | 0.977 | **0.006*** |
| Unemployment | 1.027 | 0.953 | 1.657 | 0.341 |
| Abacavir | 0.761 | 0.581 | 1.057 | 0.657 |
| Beta blocker | 0.608 | 0.335 | 1.105 | 0.106 |
| ACE inhibitor or ARB | 0.580 | 0.333 | 1.008 | 0.056 |
| Spironolactone | 1.216 | 1.074 | 1.377 | **0.001*** |
| Furosemide | 0.725 | 0.466 | 1.128 | 0.162 |
| PI | 1.598 | 1.219 | 2.095 | **<0.001*** |

**Bold** p values are statistically significant. *p < 0.01. †High school diploma, GED, or higher.

CI = confidence interval; other abbreviations as in **Table 1**.

**TABLE 5** Multivariate Analysis (PHIV Total Cohort, N = 394): Outcome CV Mortality*

| | Hazard Ratio | 95% CI Lower | 95% CI Upper | p Value |
|---|---|---|---|---|
| PI | 1.797 | 1.257 | 2.567 | **0.001** |
| CD4 count | 0.991 | 0.987 | 0.995 | **<0.001** |
| History of CAD | 2.113 | 1.512 | 2.971 | **<0.001** |
| ICD | 1.125 | 0.737 | 2.433 | 0.513 |
| PASP | 1.083 | 1.053 | 1.179 | **<0.001** |
| LVEF | 1.016 | 0.971 | 1.074 | 0.568 |
| Spironolactone | 1.632 | 0.956 | 3.048 | 0.110 |
| Education† | 0.763 | 0.531 | 0.877 | **0.023** |

**Bold** p values are statistically significant. *Cox proportional hazard regression for multivariate analysis for primary outcome (CV mortality). This model included all the covariates with p < 0.01 on univariate analysis (**Table 4**) except for VL. Both VL and CD4 count were not included in the multivariate model together because of the overlap between those individuals with a low CD4 count and a high VL. VL was included in the multivariate model (Online Table 3). †High school diploma, GED, or higher.

Abbreviations as in **Tables 1 and 4**.

**TABLE 6** Univariate Analysis (PHIV With HFrEF, n = 179): Outcome CV Mortality

| | Hazard Ratio | 95% CI Lower | 95% CI Upper | p Value |
|---|---|---|---|---|
| Sex | 1.219 | 0.821 | 1.842 | 0.288 |
| Age | 0.972 | 0.934 | 1.024 | 0.264 |
| BMI | 0.934 | 0.879 | 1.018 | 0.138 |
| Diabetes | 1.278 | 0.956 | 1.703 | 0.095 |
| Hypertension | 1.147 | 0.843 | 1.560 | 0.326 |
| Hyperlipidemia | 1.271 | 0.826 | 1.742 | 0.116 |
| Smoking | 1.344 | 0.869 | 2.076 | 0.143 |
| History of CAD | 1.644 | 1.122 | 2.344 | **0.002*** |
| ICD | 1.419 | 1.078 | 1.866 | **0.001*** |
| Cocaine | 1.163 | 0.542 | 2.421 | 0.632 |
| PASP | 1.062 | 1.014 | 1.133 | **0.003*** |
| LVEF | 0.882 | 0.842 | 0.924 | **<0.001*** |
| OSA | 1.032 | 0.827 | 1.242 | 0.847 |
| CD4 count ≥200 | 0.996 | 0.994 | 0.998 | **0.002*** |
| Nadir CD4 count | 0.868 | 0.764 | 0.878 | **0.004*** |
| VL >200 | 1.852 | 1.265 | 3.402 | **0.005*** |
| ART duration | 0.932 | 0.823 | 1.068 | 0.327 |
| HIV duration | 1.023 | 0.801 | 1.174 | 0.561 |
| Untreated HIV duration | 1.186 | 0.762 | 1.414 | 0.672 |
| Education† | 0.677 | 0.539 | 0.934 | **0.007*** |
| Unemployment | 1.056 | 0.857 | 1.341 | 0.341 |
| Abacavir | 0.801 | 0.573 | 1.135 | 0.523 |
| Beta blocker | 0.864 | 0.782 | 0.946 | 0.031 |
| ACE inhibitor or ARB | 0.833 | 0.747 | 0.921 | 0.021 |
| Spironolactone | 1.477 | 1.135 | 1.983 | **0.002*** |
| Furosemide | 0.915 | 0.781 | 1.167 | 0.436 |
| PI | 1.521 | 1.019 | 2.126 | **0.006*** |

**Bold** p values are statistically significant. *p < 0.01. †High school diploma, GED, or higher.

Abbreviations as in **Tables 1, 2, and 4**.

copies/ml (range <50 to 3,000,457 copies/ml). A total of 60% (98 of 172) of patients had a CD4 count of ≥200 cells/mm³, and 63% (106 of 172) had VL <200 copies/ml. Of the 172 PHIV with HFpEF, 57

**TABLE 7** Multivariate Analysis (PHIV With HFrEF, n = 179): Outcome CV Mortality*

| | Hazard Ratio | 95% CI Lower | 95% CI Upper | p Value |
|---|---|---|---|---|
| PI | 1.755 | 1.063 | 2.741 | **0.009** |
| CD4 count | 0.992 | 0.990 | 0.995 | **<0.001** |
| History of CAD | 1.565 | 1.248 | 1.762 | **0.005** |
| ICD | 1.615 | 0.758 | 3.246 | 0.235 |
| PASP | 1.126 | 1.012 | 1.316 | **0.021** |
| LVEF | 0.941 | 0.912 | 0.978 | **0.003** |
| Spironolactone | 1.286 | 0.343 | 2.217 | 0.681 |
| Education† | 0.725 | 0.643 | 0.976 | **0.012** |

**Bold** p values are statistically significant. *Cox proportional hazard regression for multivariate analysis for primary outcome (CV mortality). This model included all the covariates with p < 0.01 on univariate analysis (**Table 6**) except for VL. †High school diploma, GED, or higher.

Abbreviations as in **Tables 1, 2, and 4**.

patients (33%) had a PI-based ART regimen, whereas 115 patients (67%) had an NPI. When PHIV with HFpEF were stratified by PI-based ART regimen versus NPI, findings were comparable with those of the overall cohort and the HFrEF group (**Table 3**).

**PHIV with HFbEF.** There were 43 PHIV with HFbEF who were receiving ART (median duration 9.0 years [IQR: 4 to 16 years]). In this group, the mean CD4 count was 281 cells/mm³, and the median VL was 296 copies/ml (range <50 to 3,000,457 copies/ml). A total of 53% (23 of 43) of patients had a CD4 count of ≥200 cells/mm³, and 63% (33 of 43) had VL <200 copies/ml. Of the 43 PHIV with HFbEF, 17 patients (40%) had a PI, whereas 26 patients (60%) had an NPI.

**OUTCOMES. CV mortality.** In the entire cohort of 394 patients, there were 93 CV deaths (23%) over 2 years of follow-up. The CV mortality rate was higher among PHIV hospitalized with HF who were taking a PI versus an NPI (35% vs. 17%; p < 0.001) (**Figure 2A**). Similar findings of increased CV mortality were noted when the cohort was stratified by the type of HF (HFrEF, HFpEF, and HFbEF). Specifically, among the PHIV hospitalized with HFrEF, the CV mortality rate was higher among the individuals who were taking a PI versus an NPI (36% vs. 21%; p = 0.021) (**Figure 3A**); among the PHIV hospitalized with HFpEF, the CV mortality rate was higher in the individuals taking a PI versus an NPI (33% vs. 15%; p = 0.004) (**Figure 4A**); and among the PHIV hospitalized with HFbEF, the CV mortality rate was also higher in the individuals who were taking a PI versus an NPI (35% vs. 4%; p = 0.01) (**Figure 5A**). There was an interaction present between the type of HF and the use of a PI-based regimen; however, PI use remained an independent predictor of CV mortality (Online Table 2). There was also no difference in CV mortality when different types of PIs were compared (Online Table 3). Saquinavir causes QT and PR interval prolongation and is no longer recommended as first-line for ART (16); therefore, the association between PI use and adverse outcomes was retested after the exclusion of patients taking saquinavir, and the finding remained unchanged (Online Tables 4 and 5). Among PHIV with HF, factors associated with CV mortality on univariate analysis included the following: the use of a PI-based regimen; traditional HF risk factors or measures of CV disease (a history of CAD, increased PASP, and low LVEF); HIV-specific parameters (low nadir CD4 count or at index hospitalization and high VL); and low education level (**Table 4**). In a multivariable model, the following parameters remained independently associated with CV mortality rate: use of a PI-based

regimen; history of CAD; increased PASP; low nadir CD4 count or at index hospitalization (or high VL); and low education level (**Table 5,** Online Tables 6 and 7). Similar findings were noted when analogous analyses were performed among groups stratified by HFpEF and HFrEF (**Tables 6 to 9**). For example, in PHIV hospitalized with HFrEF, factors associated with CV mortality on univariate analysis included use of a PI-based regimen, traditional HF risk factors or measures of CV disease (a history of CAD, increased PASP, and low LVEF), HIV-specific parameters (low CD4 count and high VL), and low education level (**Table 6**). In a multivariable model among PHIV hospitalized with HFrEF, the following parameters remained independently associated with CV mortality rate: use of a PI-based regimen; history of CAD; increased PASP; decreased LVEF; low CD4 count (or high VL); and low education level (**Table 7**).

**30-day HF readmission rates.** In the entire cohort of 394 patients, 46% were readmitted with decompensated HF within 30 days of discharge from the incident HF hospitalization. The use of a PI-based regimen was associated with a 2-fold increased risk of readmission for HF. Specifically, the 30-day hospital readmission rate was higher among PHIV with HF who were taking a PI versus an NPI (68% vs. 34%; p < 0.001) (**Figure 2B**). Similar findings of an increased 30-day HF readmission rate with PIs were noted when groups were analyzed according to the type of HF: HFrEF with a PI versus HFrEF not with a PI; (70% vs. 55%; p < 0.001) (**Figure 3B**); HFpEF with a PI versus HFpEF with an NPI (66% vs 22%; p < 0.001) (**Figure 4B**); and HFbEF with a PI versus HFbEF with an NPI (65% vs. 23%; p = 0.01) (**Figure 5B**). Additionally, no difference in 30-day readmission rate was noted among the different types of PIs (data not shown). Factors associated with 30-day HF readmission on univariate analysis included use of a PI-based regimen, traditional HF risk factors or measures of CV disease (a history of CAD, cocaine use, increased PASP), HIV-specific parameters (low CD4 count and high VL), and socioeconomic parameters (low education level and unemployment) (Online Table 8). In a multivariable model in PHIV hospitalized with HFrEF, the following parameters remained independently associated with CV mortality rate: use of a PI-based regimen; history of CAD; cocaine use; increased PASP; low CD4 count (or high VL); low education level; and unemployment (Online Table 9).

## DISCUSSION

We tested the associations between ritonavir-boosted PI regimens and cardiac structure and outcomes

**TABLE 8** Univariate Analysis (PHIV With HFpEF, n = 172): Outcome CV Mortality

| | Hazard Ratio | 95% CI Lower | 95% CI Upper | p Value |
|---|---|---|---|---|
| Sex | 1.232 | 0.824 | 1.863 | 0.264 |
| Age | 0.965 | 0.947 | 1.024 | 0.812 |
| BMI | 0.952 | 0.879 | 1.062 | 0.438 |
| Diabetes | 1.201 | 0.863 | 1.782 | 0.217 |
| Hypertension | 1.057 | 0.581 | 1.548 | 0.942 |
| Hyperlipidemia | 1.182 | 0.812 | 1.737 | 0.331 |
| Smoking | 1.013 | 0.711 | 1.437 | 0.968 |
| History of CAD | 1.824 | 1.167 | 2.835 | **<0.001*** |
| Cocaine | 1.322 | 1.003 | 1.983 | 0.031 |
| PASP | 1.215 | 1.123 | 1.311 | **<0.001*** |
| LVEF | 0.975 | 0.924 | 1.025 | 0.862 |
| OSA | 1.042 | 0.571 | 1.823 | 0.883 |
| CD4 count ≥200 | 0.968 | 0.955 | 0.987 | **<0.001*** |
| Nadir CD4 count | 0.801 | 0.628 | 0.966 | **0.002*** |
| VL >200 | 1.332 | 1.121 | 1.635 | **<0.001*** |
| ART duration | 1.031 | 0.910 | 1.241 | 0.543 |
| HIV duration | 1.104 | 0.817 | 1.305 | 0.621 |
| Untreated HIV duration | 1.117 | 0.786 | 1.422 | 0.672 |
| Education† | 0.701 | 0.523 | 0.961 | **0.005*** |
| Unemployment | 1.211 | 0.765 | 1.451 | 0.681 |
| Abacavir | 0.671 | 0.374 | 1.058 | 0.764 |
| Beta blocker | 0.236 | 0.113 | 0.473 | **<0.001*** |
| ACE inhibitor or ARB | 0.248 | 0.127 | 0.524 | **<0.001*** |
| Furosemide | 0.485 | 0.263 | 0.746 | **0.003*** |
| PI | 1.642 | 1.143 | 2.321 | **0.002*** |

**Bold** p values are statistically significant. *p < 0.01. †High school diploma, GED, or higher.
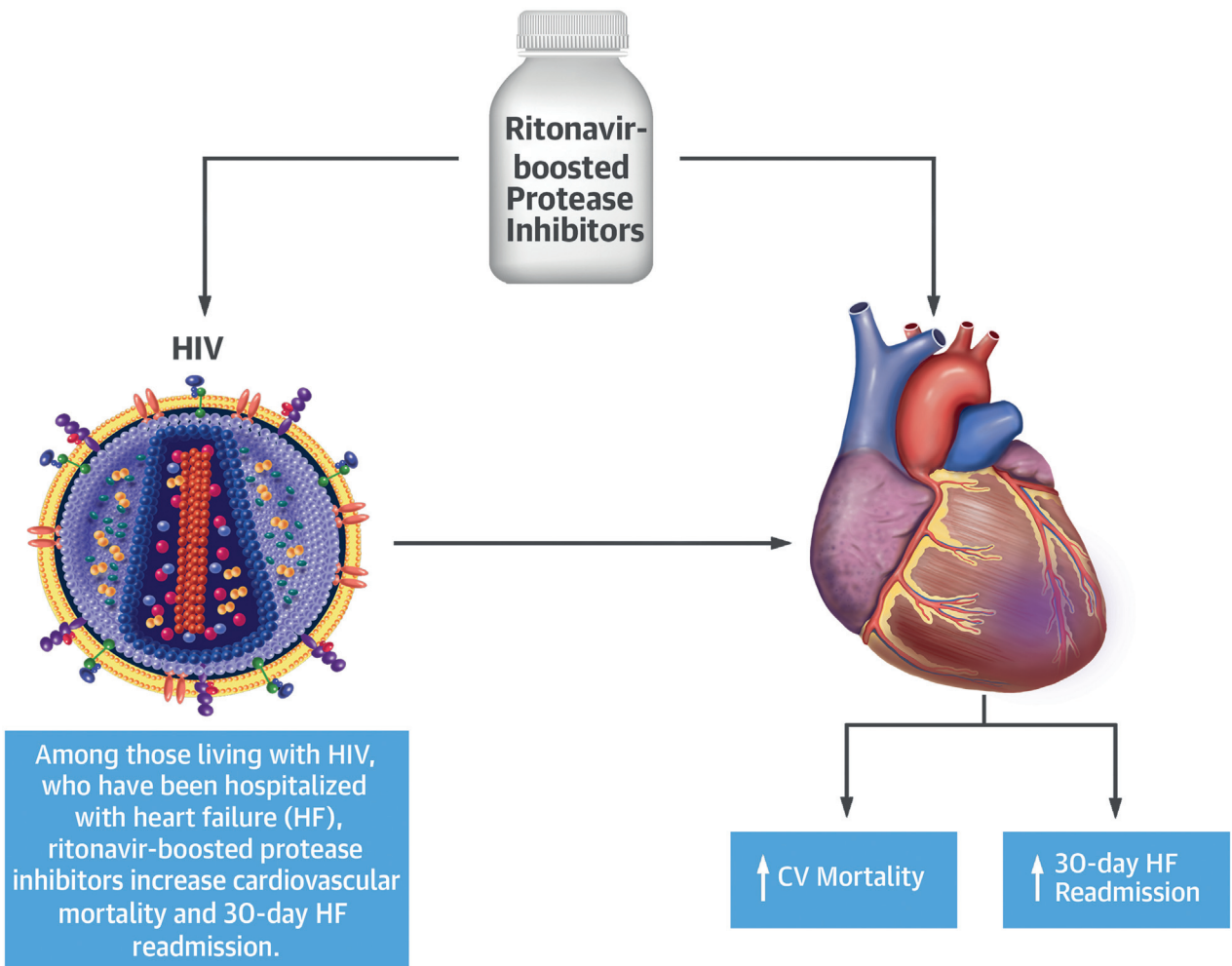Abbreviations as in **Tables 1, 3, and 4**.

among PHIV with HF (**Central Illustration**). We report 4 key findings of broad clinical relevance to the care of patients with HIV and HF in our study: 1) 36% of the cohort of PHIV were receiving a PI-based regimen,

**TABLE 9** Multivariate Analysis (PHIV With HFpEF, n = 172): Outcome CV Mortality*

| | Hazard Ratio | 95% CI Lower | 95% CI Upper | p Value |
|---|---|---|---|---|
| PI | 2.013 | 1.107 | 3.234 | **0.009** |
| CD4 count | 0.972 | 0.964 | 0.986 | **<0.001** |
| History of CAD | 2.176 | 1.263 | 3.548 | **0.003** |
| Cocaine use | 1.234 | 0.676 | 2.316 | 0.548 |
| PASP | 1.112 | 1.053 | 1.236 | **<0.001** |
| Beta blocker | 0.622 | 0.234 | 2.821 | 0.552 |
| ACE inhibitor or ARB | 0.372 | 0.114 | 1.381 | 0.118 |
| Furosemide | 0.834 | 0.351 | 1.824 | 0.671 |
| Education† | 0.545 | 0.342 | 0.823 | **0.023** |

**Bold** p values are statistically significant. *Cox proportional hazard regression for multivariate analysis for primary outcome (CV mortality). This model included all the covariates with p < 0.01 on univariate analysis (**Table 8**) except for VL. †High school diploma, GED, or higher.
Abbreviations as in **Tables 1, 3, and 4**.

**CENTRAL ILLUSTRATION** Cardiovascular Outcomes Associated With Protease Inhibitors



Among those living with HIV, who have been hospitalized with heart failure (HF), ritonavir-boosted protease inhibitors increase cardiovascular mortality and 30-day HF readmission.

↑ CV Mortality

↑ 30-day HF Readmission

Alvi, R.M. et al. J Am Coll Cardiol. 2018;72(5):518–30.

In this study, ritonavir-boosted protease inhibitors were associated with increased cardiovascular mortality and 30-day heart failure (HF) readmission rates among persons with human immunodeficiency virus (HIV) with HF.

as compared with a non–PI-based regimen, and these patients had higher rates of hyperlipidemia, diabetes mellitus, and CAD; 2) patients taking a PI had a higher PASP and lower LVEF; 3) in follow-up, PHIV with HF who had a PI-based regimen had higher rates of CV death; and 4) increased 30-day HF hospitalization for those patients who had PI-based ART compared with those who had NPI-based ART. To our knowledge, these findings are the first data linking PI-based ART to adverse cardiac structural changes and outcomes among PHIV with HF.

Previous studies have shown an association between some PI-based ART regimens and vascular events [6,17-19]; for example, data from the (DAD) Data Collection on Adverse Events of Anti-HIV Drugs Study) cohort from subjects enrolled from 1999 through 2005 and from 2009 through 2016 have shown that some PI-based regimens were associated with an increase in a composite vascular endpoint (death, stroke, myocardial infarction, and revascularization) [4,6]. There are no data on the association between PI-based regimens and outcomes specifically among PHIV with HF, a group at high risk of adverse events. Chen et al. [20], in a study involving 21,435 PHIV, demonstrated an association between current use of tenofovir (a nucleoside reverse transcriptase

inhibitor) and an approximately 30% to 40% lower risk of incident HF compared with past users or never users of this drug. In that study, patients with HF were excluded, and the effect of PI regimens was not the focus; however, a significant proportion of the comparator group was prescribed a PI-based ART regimen.

As compared with uninfected controls, there is a marked increase in CV death among PHIV (13,21,22). For instance, Tseng et al. (22) completed a study of >2,800 individuals with HIV that showed a 4.5-fold greater risk of sudden cardiac death among PHIV. In that cohort, those patients who died had a higher prevalence of CAD, cardiomyopathy, and HF. Indeed, the prevalence of HF in that group was 30% in patients who died as compared with 9% in those patients with HIV who did not die (22). There are limited data on CV mortality in PHIV with HF (10,13). Janjua et al. (13) reported increased CV mortality in women living with HIV; however, analyses testing the association of factors such as ART classes with CV outcomes were limited by the small sample and number of outcomes. We found that PI-based regimens were associated with an increase in CV mortality among PHIV with HF. The mechanism for this increase in CV mortality related to PI use is unclear, but several possibilities exist, including the following: 1) patients prescribed PIs had an increased 30-day HF readmission rate, which is closely linked to mortality in broad groups of patients with HF (23); 2) patients receiving ART had a higher PASP and a lower LVEF, both strong predictors of adverse outcomes, including mortality, in HF (24,25); and 3) PHIV with HF who were taking a PI had increased rates of diabetes and CAD, both independent risk factors for mortality in HF (26,27). Additionally, other factors not addressed in this study may have played a role. Specifically, among PHIV, the increased CV risk is, in part, independent of traditional CV risk factors and is probably related to a persistent and heightened state of inflammation (28-30). Inflammation is associated with worse outcomes in HF and CV disease, and the persistent inflammation in HIV may not be addressed using ART alone. For example, Zanni et al. (30) reported an increase in arterial inflammation after 6 months of ART treatment, a finding suggesting that additional therapies, beyond ART, may be needed to control inflammation among PHIV.

In this study, PHIV with HF who had a ritonavir-boosted PI had higher rates of hyperlipidemia and diabetes. The mechanisms involved in the increased rates of hyperlipidemia and diabetes seen with PI-based regimens and how the increase contributes to the heightened adverse outcomes noted in our cohort are active areas of research and may involve an increase in intramyocardial fat or cardiac steatosis (31-34). PHIV have a 3-fold elevation in intramyocardial fat and a relationship among the increase in intramyocardial fat, serum lipids, visceral fat, and impairment in measures of both diastolic and systolic function (34). In support of this, PHIV with HF who received PI-based ART in our study had a lower LVEF and a higher PASP as compared with patients who had NPI-based regimens. Additionally, the findings of a higher PASP and a lower LVEF were consistent across all types of HF. PI-based ARTs have been linked to an increase in PASP in other cohorts with HIV without HF (9). For example, in a prospective observational study of 322 PHIV without HF who underwent an echocardiogram, Mondy et al. (9) reported an elevated PASP in 23% and an association between PI use (ritonavir boosted) and the increased PASP. Additionally, emerging data suggest that ritonavir-boosted PIs may increase myocardial fibrosis, in turn reducing systolic and diastolic function (7,35,36). Another example, by Laurence et al. (7) in a mouse model using boosting doses of ritonavir, reported that PIs were associated with an increase expression of transforming growth factor beta-1, leading to an increase in myocardial fibrosis and a lower LVEF.

There was an association between socioeconomic parameters (e.g., education level and employment status) and CV outcomes among PHIV with HF. Lower education level (high school or GED status) and employment status have been shown to be associated with poor HF outcomes among HIV-uninfected individuals (37,38). However, there are few data linking socioeconomic parameters with HF outcomes among PHIV. The present study demonstrated an inverse association between lower education level and CV mortality and 30-day HF readmission and a positive association between unemployment and 30-day HF readmission. Future studies will need to focus on whether additional teaching and early post-discharge follow-up may have positive impacts on CV outcomes in this cohort.

**STUDY LIMITATIONS.** This was a retrospective cohort study in a single U.S. urban tertiary care center of PHIV hospitalized with HF and thus a high-risk group. We do not have a denominator for the number of patients seen with HF in an outpatient setting, with and without HIV, and it is unclear whether PI use is associated with a difference in outcomes among PHIV with HF who were not hospitalized. Despite an ART being prescribed in 90% of the cohort, viral suppression was noted in 62%. The level of viral suppression may be inferior to that noted in more updated

registries and clinical trials. However, this level of viral suppression is comparable to that reported in other contemporary observational clinical cohort studies (56% to 62%) (11,20,22), and the viral suppression reported in our study is similar to that reported in a study by Hanna et al. (39) involving more than 7,196 PHIV from the same geographic location during the same time period (66%). Therefore, a potential explanation for the worse outcomes in PHIV is poor adherence to treatment for either HIV or HF. In this retrospective study, adherence could not be assessed. However, we did test whether other surrogates of adherence were different between groups. In patients with HF who do not take HF medications, both heart rate and blood pressure are increased (40,41). In our study cohort, there was no difference in blood pressure and heart rate between the PHIV who had a PI as compared with the PHIV who had a non-PI-based regimen, a finding suggesting that compliance with HF medications may be similar between groups. Finally, even though we have applied the covariates in different multivariate models for independent prediction of outcomes, the possibility of residual confounding persists.

## CONCLUSIONS

Being prescribed a ritonavir-boosted PI-based ART regimen was associated with dyslipidemia, a higher prevalence of CAD, increased PASP, and lower LVEF. In follow-up, PHIV with HF who were prescribed a PI-based ART regimen were noted to be at twice the risk for 30-day HF admission and CV mortality, an effect independent of HIV control. Further research is needed to determine whether PI-based regimens, either individual regimens or as a class effect, contribute pathophysiologically to processes leading to worse outcomes in HF (e.g., myocardial fat and fibrosis) and whether these findings can be replicated in prospective cohorts.

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### PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Ritonavir-boosted PI therapy is associated with hyperlipidemia, diabetes, lower LVEF, higher PASP, and adverse CV outcomes in PHIV with HF.

**TRANSLATIONAL OUTLOOK:** Additional studies in this cohort are needed to determine the pathophysiological mechanisms responsible for these adverse effects.

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**KEY WORDS** antiretroviral therapy, heart failure, heart failure readmission, human immunodeficiency virus

**APPENDIX** For supplemental tables, please see the online version of this paper.