Journal of the American Heart Association

ORIGINAL RESEARCH

Community-Acquired Pneumonia and Risk of Cardiovascular Events in People Living With HIV

Jerry S. Zifodya, MD; Meredith S. Duncan, PhD; Kaku A. So-Armah, PhD; Engi F. Attia, MD; Kathleen M. Akgün, MD; Maria C. Rodriguez-Barradas, MD; Vincent C. Marconi, MD; Matthew J. Budoff, MD; Roger J. Bedimo, MD; Charles W. Alcorn, MA; Guy W. Soo Hoo, MD; Adeel A. Butt, MD, MS; Joon W. Kim, MD; Jason J. Sico, MD, MHS; Hilary A. Tindle, MD; Laurence Huang, MD; Janet P. Tate, MPH; Amy C. Justice, MD; Matthew S. Freiberg, MD; Kristina Crothers, MD

BACKGROUND: Hospitalization with community-acquired pneumonia (CAP) is associated with an increased risk of cardiovascular disease (CVD) events in patients uninfected with HIV. We evaluated whether people living with HIV (PLWH) have a higher risk of CVD or mortality than individuals uninfected with HIV following hospitalization with CAP.

METHODS AND RESULTS: We analyzed data from the Veterans Aging Cohort Study on US veterans admitted with their first episode of CAP from April 2003 through December 2014. We used Cox regression analyses to determine whether HIV status was associated with incident CVD events and mortality from date of admission through 30 days after discharge (30-day mortality), adjusting for known CVD risk factors. We included 4384 patients (67% [n=2951] PLWH). PLWH admitted with CAP were younger, had less severe CAP, and had fewer CVD risk factors than patients with CAP who were uninfected with HIV. In multivariable-adjusted analyses, CVD risk was similar in PLWH compared with HIV-uninfected (hazard ratio [HR], 0.89; 95% CI, 0.70–1.12), but HIV infection was associated with higher mortality risk (HR, 1.49; 95% CI, 1.16–1.90). In models stratified by HIV status, CAP severity was significantly associated with incident CVD and 30-day mortality in PLWH and patients uninfected with HIV.

CONCLUSIONS: In this study, the risk of CVD events during or after hospitalization for CAP was similar in PLWH and patients uninfected with HIV, after adjusting for known CVD risk factors and CAP severity. HIV infection, however, was associated with increased 30-day mortality after CAP hospitalization in multivariable-adjusted models. PLWH should be included in future studies evaluating mechanisms and prevention of CVD events after CAP.

Key Words: AIDS ■ cardiovascular disease ■ community-acquired pneumonia ■ HIV

Community-acquired pneumonia (CAP) is a leading cause of infectious disease deaths[1] but the consequences of CAP extend beyond the lungs. Hospitalization with CAP from bacterial as well as viral causes is associated with increased risk of cardiovascular disease (CVD) including acute myocardial infarction, new onset or worsening congestive heart failure, and arrhythmias.[2–6] In those with CAP, subsequent CVD events are associated with increased mortality.[7] Older age, preexisting CVD, and CAP severity have been associated with an increased incidence of these events after CAP.[8,9] Among people uninfected with HIV, hospitalization with CAP is an independent risk factor for CVD events comparable to smoking, hypertension, and diabetes mellitus.[3] Up to one third of hospitalized patients with CAP have CVD events,[7] with most of the adverse CVD events occurring during the sentinel CAP hospitalization.[3,7–9] Importantly,

Correspondence to: Jerry S. Zifodya, MD, 1430 Tulane Avenue, #8509, New Orleans, LA 70112, USA. E-mail: jzifodya@tulane.edu

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.017645.

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In this cohort, people living with HIV were hospitalized with less severe pneumonia and had fewer cardiovascular disease (CVD) risk factors yet had a similar adjusted incidence of CVD events, during and after hospitalization with community-acquired pneumonia (CAP).
- HIV infection was associated with increased mortality after CAP hospitalization in fully adjusted models.
- Severe CAP was associated with an increased incidence of CVD events and mortality in both people living with HIV and patients uninfected with HIV.

What Are the Clinical Implications?

- People living with HIV should be recognized to be at risk for CVD events during and after hospitalization with CAP.
- People living with HIV should be included in future studies on the risk, mechanisms, and prevention of CVD events post-CAP.

Nonstandard Abbreviations and Acronyms

CAP	community-acquired pneumonia
PLWH	people living with HIV
VA	Veterans Affairs
VACS	Veterans Aging Cohort Study

increased CVD risk extends well past the hospitalization period of CAP, potentially up to 10 years, with a 4-fold increase in the first 30 days post-CAP.[3]

The risk for CVD events associated with CAP for people living with HIV (PLWH) compared with uninfected people is largely unknown. PLWH have at least a 4-fold higher incidence of CAP than patients uninfected with HIV,[10] and CAP is associated with an increased risk of longer-term mortality.[11] However other sequelae of CAP in PLWH, specifically risk of post-CAP CVD events, are poorly described. Notably, HIV infection itself has been associated with increased risk of CVD[12,13] possibly because of increased inflammation and immune activation.[14,15] CAP hospitalization has also been linked with increased inflammation[16] and platelet activation, which may result in a procoagulant state.[17] As both HIV infection and CAP are risk factors for CVD, there is a potential for synergism of the 2 in PLWH admitted with CAP, highlighting the importance of studying CVD after CAP in this vulnerable population.

We sought to determine whether the risk for CVD events and mortality post-CAP is different in PLWH compared with individuals without HIV. We used data on veterans infected and uninfected with HIV in the VACS (Veterans Aging Cohort Study), hospitalized with CAP, to assess rates and risk of CVD and mortality during and up to 30 days after CAP hospitalization. We hypothesized that PLWH would have an increased risk of CVD events and mortality associated with CAP compared with uninfected individuals, adjusting for potential confounders including age and severe CAP.

METHODS

We analyzed data from VACS, an observational, multisite, cohort study of PLWH and age-/race or ethnicity-/sex-/site-matched veterans uninfected with HIV (matched 1:2), in care within the US Veterans Affairs (VA) Healthcare System. VACS is described in detail elsewhere.[18,19] We included VACS participants who were hospitalized with a diagnosis of CAP between April 1, 2003 and December 31, 2014. The institutional review boards at Yale University (IRB #0309025943), and West Haven VA Medical Center (IRB #0001) approved this study. No informed consent was required. The data that support the findings of this study are available from the corresponding author upon reasonable request.

We determined the first CAP (including bacterial pneumonia, viral pneumonia, and unknown etiology) hospitalization in this time window using *International Classifications of Disease, Ninth Revision* (*ICD-9*) diagnosis codes present upon admission; we queried VA electronic health record, VA fee-for-service, and Medicare sources for these codes to capture all relevant admissions. Based on prior validation work within VACS,[20] we defined CAP admission by a CAP code as primary *ICD-9* for admission or as secondary to 1 of the following primary diagnoses: HIV,[19] respiratory failure, sepsis, or chronic bronchitis (Table S1). This algorithm identified 9205 patients admitted with CAP. We sequentially excluded 4199 patients with prior diagnoses of CVD, 74 individuals uninfected with HIV who seroconverted to HIV infected during follow-up, 21 individuals recorded as HIV uninfected but were found to be HIV infected, 444 patients with unclear follow-up time, and 83 with a hospital length of stay >45 days. After exclusions, our analytic sample comprised 4384 veterans.

We evaluated data on demographics, length of hospitalization, and laboratory results before and during hospitalization. We also determined tobacco use (current, past, never) from health factors data[21] and alcohol use disorder, illicit drug use[22] and existing comorbidities

from *ICD-9* codes. An outline of comorbidity extraction in the VACS cohort has previously been described.[12] In PLWH, we evaluated most recent CD4 cell counts and viral loads before hospitalization, and active antiretroviral therapy (ART) use at admission. Severe CAP was defined as the presence of any 1 of the following using VA administrative data: respiratory failure, mechanical ventilation (invasive or noninvasive), sepsis, and/or shock.

Similar to prior studies of CVD after CAP, our primary outcome of incident CVD during CAP hospitalization and up to 30 days after discharge was a composite of at least 1 of the following events defined by *ICD-9* codes: acute myocardial infarction, congestive heart failure, cardiomyopathy, unstable angina, acute ischemic stroke, revascularization, atrial fibrillation, and/or ventricular arrhythmia (30-day CVD incidence; Table S1).[3,5,8,13,23–25] We previously validated the *ICD-9* codes used for acute myocardial infarction events in this cohort.[12] Our secondary outcome was all-cause mortality during hospitalization and up to 30 days after discharge (30-day mortality).

Statistical Analysis

Summary statistics were stratified by HIV status and calculated as mean (SD) and median (25th percentile [Q1], 75th percentile [Q3]) for continuous variables or N (%) for categorical variables. Differences in baseline characteristics between groups were assessed via Wilcoxon rank-sum test or χ^2 test, respectively. Unadjusted CVD and mortality incidence rates were calculated per 10 000 person-days using Poisson regression by HIV status. We verified that the proportional hazards assumption held via interactions of HIV with the natural logarithm of follow-up time (CVD *P* value=0.43; mortality *P* value=0.22). We then performed Cox regression analyses to determine the association between HIV infection and incident CVD and mortality. With HIV as our exposure of interest, we generated 3 models: unadjusted, adjusted for age and severe CAP (minimally adjusted), and multivariable adjusted. In multivariable adjusted models, age, severe CAP, race/ethnicity, prior CAP, diabetes mellitus, hypertension, dyslipidemia, smoking status, alcohol use disorder, and illicit drug use served as confounders and covariates. In all models, we used a robust sandwich variance estimator to account for clustering among participants at the same site. Adjusted cumulative incidence plots were created for 30-day CVD incidence and mortality stratified by HIV status. In sensitivity analyses, we excluded those who died within 30 days of discharge, then evaluated CVD events. The associations in this model were similar; thus, we did not perform a competing risks analysis.

We stratified Cox proportional hazards regression models by HIV status to evaluate whether factors associated with 30-day incident CVD and mortality following CAP hospitalization differed between PLWH and individuals uninfected with HIV and to adjust for HIV-related variables (CD4 cell count, viral load, and ART usage) in models limited to PLWH. Risk factors considered were the same as previously described with the addition of the most recent CD4 cell count (PLWH only), HIV viral load (PLWH only), and ART usage (PLWH only).

Finally, we examined CVD and mortality incidence rates by increasing CAP severity in 3 groups: CAP alone (with no severity indicators); CAP and respiratory failure, noninvasive mechanical ventilation, and/or sepsis; and CAP with invasive mechanical ventilation and/or shock. Incidence rates were estimated using Poisson regression.

In supplemental analyses, all 30-day outcomes were reassessed at 90 days. Further, because use of macrolides and less commonly fluoroquinolones have been shown to be associated with cardiovascular outcomes,[26–29] additional supplemental analyses adjusted for use of one or both antibiotics between admission and end of follow-up to assess the robustness of our results.

We handled missing data via multiple imputation by chained equation techniques that generated 5 complete data sets. Regression-based predictive mean matching was used to produce biologically plausible imputed values. Results were combined across imputed data sets according to Rubin's rules.[30] Before imputation, all variables had complete data except the following: smoking data (16% missing for PLWH and 9% missing for HIV uninfected), CD4 cell count (20% missing), and HIV viral load (20% missing; Table 1). A 2-sided *P* value of <0.05 was used to determine statistical significance, and all analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

We included a total of 2951 PLWH and 1433 patients uninfected with HIV admitted with CAP in our analytic sample. PLWH were younger than people uninfected with HIV (mean [SD]: 52 [9] versus 56 [9] years) and more likely to be Black (55% versus 50%), both *P*<0.05 (Table 1). Regardless of HIV status, nearly all patients were men (>97%), and 21% were never smokers. Although illicit drug use was similarly high in both groups (PLWH: 44%; HIV uninfected: 46%, *P*=0.22), PLWH had a lower proportion of alcohol use compared with patients uninfected with HIV (38% versus 49%, *P*<0.05). Twenty-six percent of PLWH

Table 1. Baseline Characteristics Stratified by HIV Status

Baseline Characteristic*	PLWH (n=2951)	HIV-Uninfected (n=1433)
Age, y; mean (SD)	52 (9.0)	56 (9.1)
Male sex, n (%)	2867 (97)	1404 (98)
Race/ethnicity, n (%)		
Black	1634 (55)	713 (50)
White	988 (34)	583 (41)
Hispanic	268 (9.1)	106 (7.4)
Other	61 (2.1)	31 (2.2)
Before CAP hospitalization		
Prior CAP, n (%)	389 (13)	220 (15)
Hypertension, n (%)	1121 (38)	1830 (62)
Diabetes mellitus, n (%)	384 (13)	415 (29)
Dyslipidemia, n (%)	1687 (69)	680 (54)
Estimated glomerular filtration rate, mL/minute per 1.73 m^2; mean (SD)	93 (32)	95 (39)
Smoking, n (%)†		
Current	1567 (64)	776 (60)
Former	372 (15)	245 (19)
Never	526 (21)	276 (21)
History of alcohol use, n (%)	1125 (38)	704 (49)
History of illicit drug use, n (%)	1301 (44)	660 (46)
Chronic obstructive pulmonary disease, n (%)	1129 (38)	732 (51)
Antiretroviral therapy usage, n (%)		
Nucleoside reverse transcriptase inhibitor	1551 (53)	…
Nonnucleoside reverse transcriptase inhibitor	555 (19)	
Protease inhibitor	1121 (38)	
CD4 cell count, cells/mm^3†; median (Q1, Q3)	311 (140, 540)	…
CD4 cell count<200 cells/mm^3,† n (%)	774 (33)	…
HIV viral load, copies/mL †; median (Q1, Q3)	609 (50, 40 125)	…
HIV viral load<400 copies/mL, † n (%)	999 (42)	…
During CAP hospitalization		
Length of stay, days; median (Q1, Q3)	5.0 (3.0, 8.0)	4.0 (2.0, 8.0)
Severe CAP,‡ n (%)	294 (10)	248 (17)
Mechanical ventilation, n (%)		
Invasive	159 (5.4)	109 (7.6)
Noninvasive	67 (2.3)	50 (3.5)
Respiratory failure, n (%)	38 (1.3)	64 (4.5)
Sepsis, n (%)	117 (4.0)	103 (7.2)
Shock, n (%)	51 (1.7)	33 (2.3)
Cardiopulmonary resuscitation, n (%)	26 (0.9)	20 (1.4)
Antibiotics, n (%)		
Macrolides	751 (26)	214 (15)
Fluoroquinolone	980 (33)	525 (37)

CAP indicates community-acquired pneumonia; and PLWH, people living with HIV.

*All characteristics were statistically different between PLWH and HIV-uninfected Veterans ($P<0.05$) using χ^2 test or Wilcoxon test except sex ($P=0.11$), prior CAP ($P=0.05$), illicit drug use ($P=0.22$), estimated glomerular filtration rate ($P=0.99$), shock ($P=0.19$), and cardiopulmonary resuscitation ($P=0.12$).

†All variables had complete data except the following: smoking data were available on 2465 (PLWH), 1297 (HIV uninfected); CD4 cell count data were available on 2357 (PLWH); HIV viral load data were available on 2356 (PLWH).

‡Severe CAP is defined by the presence of any 1 of the following: respiratory failure, mechanical ventilation (invasive or noninvasive), sepsis, and/or shock.

received macrolides compared with 15% of patients uninfected with HIV. A total of 33% and 37% of PLWH and patients uninfected with HIV, respectively, received fluoroquinolones. Among PLWH, 88% were on at least 1 class of ART, 42% had an undetectable viral load, median (Q1, Q3) CD4 cell count was

311 (140, 540) cells/mm^3, and median (Q1, Q3) viral load was 609 (50, 40 125) copies/mL before CAP hospitalization.

PLWH had fewer risk factors for CVD including hypertension (38% versus 62%, $P<0.05$) and diabetes mellitus (13% versus 29%, $P<0.05$) than uninfected patients. Median (Q1, Q3) length of stay was higher in PLWH compared with patients uninfected with HIV (5.0 [3.0, 8.0] versus 4.0 [2.0, 8.0] days, $P<0.05$; Table 1). However, PLWH were less likely to have at least 1 indication for severe CAP (10% versus 17%, $P<0.05$). Use of invasive and noninvasive mechanical ventilation was lower in PLWH compared with patients uninfected with HIV (5.4% versus 7.6% and 2.3% versus 3.5% respectively, both $P<0.05$). PLWH were also less likely to have diagnoses of respiratory failure (1.3% versus 4.5%, $P<0.05$) or sepsis (4.0% versus 7.2%, $P<0.05$). Shock and cardiopulmonary resuscitation administration were similar (1.7% versus 2.3%, $P=0.19$; and 0.9% versus 1.4%, $P=0.12$ respectively).

Incident CVD

Overall, 5.4% (n=160) of PLWH and 8.6% (n=123; $P<0.0001$) of uninfected patients had an incident CVD event during CAP hospitalization or within 30 days of CAP discharge. Correspondingly, in unadjusted analyses, HIV was associated with lower CVD risk (Table 2, Hazard ratio [HR], 0.62; 95% CI, 0.50–0.77). When adjusted for age and severe CAP, HIV was no longer associated with lower CVD risk (HR, 0.80; 95% CI, 0.63–1.01). In the full multivariable model, there was no significant difference in CVD risk by HIV status (HR, 0.89; 95% CI, 0.70–1.12). Accordingly, adjusted cumulative CVD incidence was similar among PLWH compared with individuals uninfected with HIV (Figure 1A).

When stratified by HIV status to evaluate differences in CVD risk factors between PLWH and patients uninfected with HIV, severe CAP was highly associated with incident CVD in both PLWH (HR, 3.93; 95% CI, 2.71–5.70) and patients uninfected with HIV (HR, 2.43; 95% CI, 1.64–3.60; Table 3). Among PLWH, age was also associated with CVD incidence, but CD4, viral load, and ART regimen were not. Hypertension was associated with CVD incidence among PLWH and individuals uninfected with HIV. When evaluating all patients, CVD incidence rates were higher with increasing CAP severity; rates (95% CI) per 10 000 person-days: CAP alone 17.15 (14.83, 19.83); CAP and respiratory failure, noninvasive mechanical ventilation, and/or sepsis 28.48 (18.56, 43.71); and CAP with invasive mechanical ventilation and/or shock 85.90 (66.12, 111.61).

Mortality

Overall, 7.4% (n=218) of PLWH and 7.2% (n=103) of uninfected patients died during hospitalization or within 30 days after discharge from a CAP hospitalization ($P=0.80$). The majority (85%; n=273) died during hospitalization and 15% (n=48) died within the 30 days after discharge. HIV status was not associated with 30-day all-cause mortality in unadjusted analyses (Table 2). However, in models adjusted for age and severe CAP (HR, 1.53; 95% CI, 1.20–1.96) as well as in multivariable-adjusted models (HR, 1.49; 95% CI, 1.16–1.90; Figure 1B), HIV was associated with higher mortality risk.

In models stratified by HIV status, increasing age and severe CAP during hospitalization were both associated with increased mortality risk (Table 3). Among PLWH, higher CD4 cell count was associated with decreased mortality risk. Alcohol use was associated with increased mortality risk in individuals uninfected with HIV. Mortality incidence rates were higher with increasing CAP severity; rates (95% CI) per 10 000 person-days: CAP alone 13.54 (11.55, 15.86); CAP and intensive care unit admission, respiratory failure, noninvasive mechanical ventilation, and/or sepsis 58.72 (43.05, 80.09); and CAP with invasive mechanical ventilation and/or shock 168.10 (139.16, 203.06).

Supplemental Analyses

Outcomes at 90-days were largely similar to those at 30-days post-discharge (Tables S2 and S3). Further adjustment for receipt of macrolides or fluoroquinolones did not change overall results: HIV remained unassociated with 30-day incident CVD but increased risk of 30-day mortality (Table S4).

DISCUSSION

In this study, incident CVD risk during and 30 days after CAP hospitalization was similar in those with and without HIV infection in fully adjusted models (adjusted for age, severe CAP, and traditional CVD risk factors). Of note, PLWH who were admitted for CAP were significantly younger, less likely to have traditional CVD risk factors, and less likely to have severe CAP. In fully adjusted models, HIV infection was associated with increased mortality during and 30 days after CAP hospitalization. Severe CAP was also associated with increased risk of 30-day CVD incidence and mortality in both PLWH and veterans uninfected with HIV (Table 3). These associations were all similar when outcomes were assessed at 90 days and also when models adjusted for receipt of macrolides or fluoroquinolones. We found that of HIV-related variables in PLWH, only lower CD4 cell count was statistically significantly associated with increased mortality but not with CVD events, whereas HIV viral load and ART class were not associated with either incident CVD or mortality.

Table 2. Multivariable Analysis of Incident CVD and Mortality at 30 Days Following CAP Hospitalization*

30-Day CVD Incidence						
Group	N	CVD Events	Rate/10 000 PD [95% CI]	Unadjusted Risk [95% CI]	Minimally Adjusted Risk [95% CI]†	Multivariable Adjusted Risk [95% CI]‡
HIV uninfected	1433	123	30 [25, 36]	1.00	1.00	1.00
PLWH	2951	160	19 [16, 22]	0.62 [0.50, 0.77]	0.80 [0.63, 1.01]	0.89 [0.70, 1.12]
30-Day Mortality						
Group	N	Deaths	Rate/10 000 PD [95% CI]	Unadjusted Risk [95% CI]	Minimally Adjusted Risk [95% CI]†	Multivariable Adjusted Risk [95% CI]‡
HIV uninfected	1433	103	24 [20, 30]	1.00	1.00	1.00
PLWH	2951	218	25 [22, 29]	1.03 [0.81, 1.31]	1.53 [1.20, 1.96]	1.49 [1.16, 1.90]

*CAP, community-acquired pneumonia; CVD, cardiovascular disease; HIV, human immunodeficiency virus; PD, person-days; PLWH, people living with HIV.
†Adjusted for age and severe CAP.
‡Adjusted for age, severe CAP, race/ethnicity, prior CAP, diabetes mellitus, hypertension, dyslipidemia, smoking status, alcohol abuse, and illicit drug use.

Our findings are consistent with studies showing an increase in CVD events after CAP in patients uninfected with HIV.[2–7] However, the occurrence of CVD events in patients uninfected with HIV in our study (8.6%) is lower than previously reported (10%–32%). This may be due in part to exclusion of patients with prior CVD in our study. Corrales-Medina et al found CAP to be associated with an increased risk of subsequent CVD events with 11.5% of those with CAP having CVD events within 30 days of CAP hospitalization. This association was stronger with increasing CAP severity. Their study, however, excluded PLWH, a potentially key at-risk population.[8] Mesquita et al, in a prospective longitudinal cohort study of PLWH hospitalized with severe infections (of varying microbiological etiologies), showed a time-associated increased risk of CVD events, with the highest risk being proximal to the severe infection. Markers of HIV control, including higher CD4 count and ART use were protective against CVD events. This study focused on general severe infections and did not examine risk specifically associated with pneumonia.[31] To our knowledge, ours is the first study focusing on CVD events after admission for CAP in PLWH compared with patients uninfected with HIV.

The mechanism of increased CVD risk in patients with CAP is unclear. Several mechanisms have been proposed including increased inflammation as evidenced by elevated inflammatory markers that persist post-hospitalization,[16] endothelial dysfunction, procoagulant changes,[17,32] and direct invasion of cardiac myocytes by bacteria.[33] Inflammatory cells activated during acute infection upregulate host response proteins leading to destabilization of existing coronary plaques; the procoagulant changes increase the risk of coronary thrombosis.[34] CAP and CVD also share common risk factors such as smoking and age, thus potentially increasing the risk for CVD post CAP. Another mechanism that can contribute to acute myocardial infarction is demand ischemia.[35] Severe CAP often leads to hypoxemia, which may be exacerbated by increased metabolic demands, tachycardia, and hypotension leading to reduced coronary filling and cardiac myocyte hypoperfusion.

Because HIV is a recognized independent risk factor for CVD events, we anticipated finding a greater risk of CVD events following CAP in PLWH.[12,13] Notably, in our cohort, PLWH hospitalized with CAP were younger, had fewer CVD risk factors, and had less severe CAP compared with patients uninfected with HIV. These differences may be because of a lower threshold for hospitalization of PLWH with less severe CAP compared with uninfected individuals.[36,37] Additionally, the health of veterans uninfected with HIV, before hospitalization, may have been worse than that of veterans infected with HIV as evidenced by a higher prevalence of comorbidities including hypertension, diabetes mellitus, and chronic obstructive pulmonary disease among veterans uninfected with HIV in this analysis. These differences likely account for the lower unadjusted incidence rates of CVD events in PLWH. Indeed, in fully adjusted multivariable models that included age, traditional CVD risk factors, and CAP severity as well as other confounders, rates of CVD events were no longer significantly different in PLWH compared with uninfected patients.

Notably, HIV infection was associated with increased 30-day all-cause mortality despite a younger age and fewer comorbidities among PLWH compared with uninfected patients. This increased mortality in PLWH may also account for the lack of association of HIV infection with CVD events as death due to HIV infection may be a competing risk in this cohort with a high rate of nonsuppressed viremia on admission. In sensitivity analyses, we excluded those who died within 30 days of discharge, then evaluated CVD events. The associations in this model were similar;

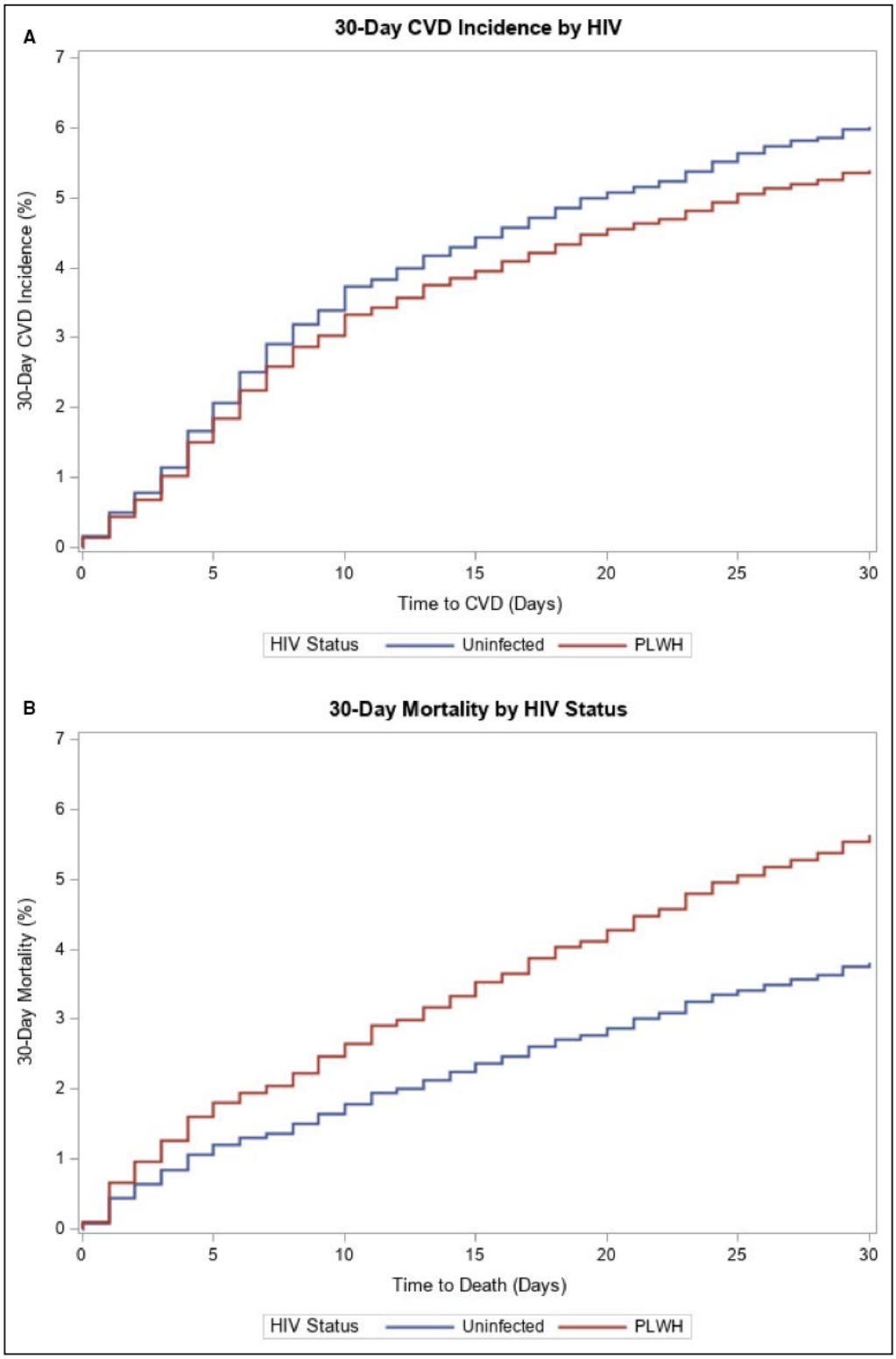

Figure 1. Adjusted* cumulative incidence plots for CVD events and mortality; from hospitalization through 30 days post-discharge.

A, Cumulative incidence plot showing similar adjusted CVD incidence in PLWH compared with uninfected patients following CAP hospitalization (*P*=0.33).* adjusted for age, severe CAP, race/ethnicity, prior CAP, diabetes mellitus, hypertension, dyslipidemia, smoking status, alcohol abuse, and illicit drug use. **B**, Cumulative incidence plot showing higher adjusted 30-day mortality in PLWH compared with uninfected patients following CAP hospitalization (*P*=0.002). CAP indicates community-acquired pneumonia; CVD, cardiovascular disease; and PLWH, people living with HIV.

Table 3. 30-Day CVD Incidence Rates and Mortality by HIV Status in Multivariable Cox Proportional Hazards Model

Characteristic	Incident CVD Hazard Ratio [95% CI]*		Mortality Hazard Ratio [95% CI]*	
	PLWH	HIV Uninfected	PLWH	HIV Uninfected
Age, 10 y	1.34 [1.14, 1.58]	1.14 [0.93, 1.39]	1.35 [1.17, 1.56]	1.30 [1.02, 1.66]
Severe CAP†	3.93 [2.71, 5.70]	2.43 [1.64, 3.60]	8.45 [6.39, 11.17]	6.57 [4.51, 9.56]
Race/ethnicity				
Black vs White	0.85 [0.62, 1.17]	0.83 [0.58, 1.20]	0.83 [0.57, 1.21]	1.74 [1.19, 2.54]
Hispanic vs White	0.83 [0.43, 1.59]	0.58 [0.29, 1.16]	1.24 [0.87, 1.75]	0.95 [0.48, 1.89]
Other vs White	1.52 [0.64, 3.60]	1.59 [0.67, 3.79]	1.90 [0.97, 3.74]	1.80 [0.46, 7.11]
Prior CAP	0.68 [0.36, 1.29]	1.03 [0.62, 1.73]	0.55 [0.34, 0.89]	0.17 [0.05, 0.57]
Diabetes mellitus	1.25 [0.77, 2.03]	1.00 [0.68, 1.47]	1.25 [0.81, 1.93]	1.07 [0.71, 1.62]
Hypertension	1.38 [1.02, 1.87]	2.20 [1.42, 3.42]	1.00 [0.76, 1.31]	0.79 [0.52, 1.18]
Dyslipidemia	0.99 [0.65, 1.51]	1.16 [0.76, 1.76]	1.33 [0.87, 2.04]	1.10 [0.73, 1.64]
Smoking				
Current vs never	1.54 [0.94, 2.54]	0.86 [0.53, 1.40]	1.09 [0.72, 1.66]	1.27 [0.63, 2.55]
Former vs never	1.20 [0.62, 2.34]	0.48 [0.26, 0.88]	0.83 [0.47, 1.48]	1.00 [0.47, 2.14]
Alcohol abuse	0.93 [0.63, 1.38]	1.39 [0.85, 2.27]	1.14 [0.79, 1.66]	1.98 [1.22, 3.23]
Illicit drug use	0.95 [0.63, 1.43]	0.61 [0.38, 0.98]	0.67 [0.46, 0.97]	0.55 [0.36, 0.84]
CD4 cell count, per 200 cells/mm^3 increase	0.93 [0.82, 1.03]	…	0.78 [0.67, 0.91]	…
HIV viral load, per 10 000 copies/mL increase	0.99 [0.98, 1.01]	…	1.00 [0.99, 1.00]	…
Receipt of nucleoside reverse transcriptase inhibitor	1.35 [0.86, 2.14]	…	1.02 [0.65, 1.60]	…
Receipt of nonnucleoside reverse transcriptase inhibitor	0.88 [0.60, 1.29]	…	0.81 [0.50, 1.32]	…
Receipt of protease inhibitor	0.86 [0.57, 1.31]	…	0.88 [0.60, 1.29]	…

CAP indicates community-acquired pneumonia; CVD, cardiovascular disease; and PLWH, people living with HIV.
*Adjusted for all listed characteristics.
†Severe CAP defined by the presence of any 1 of the following: respiratory failure, mechanical ventilation (invasive or noninvasive), sepsis, and/or shock.

thus, we did not perform a competing risks analysis. Some of the deaths could have been due to CVD events; unfortunately, we did not have cause of death data to assess this hypothesis. All-cause mortality, 7.4% among PLWH in our study, is similar to prior studies that have reported mortality rates ranging from 7% to 10%.[36,38] In contrast to our findings, recent investigations show similar mortality outcomes post-CAP in PLWH and adults uninfected with HIV.[36,39,40] However, as in our study, Cohen et al. showed increased pneumonia- and influenza-related mortality in PLWH (aged 25–54 years).[41]

This study has a number of limitations. First, use of *ICD-9* codes may not capture all CVD events and may overestimate some events such as atrial fibrillation that may have been present before admission but were not assigned *ICD-9* diagnosis codes; however, we used previously validated *ICD-9* codes and excluded patients with documented CVD diagnoses before hospitalization. These choices would result in nondifferential misclassification and are therefore unlikely to bias our results. Second, CVD events and hospitalizations that occurred outside the VA may have been missed. We incorporated Medicare and VA fee-for-service data and would therefore only miss hospitalizations covered by Medicaid or private insurance, which is unlikely to result in differential bias in PLWH compared with individuals uninfected with HIV. Third, as this is an observational study, we are unable to infer causality, but there is an established body of literature linking increased CVD events in individuals uninfected with HIV with increasing pneumonia severity. Fourth, only 42% of PLWH in our cohort had undetectable viral load. Results may differ in a cohort with a higher percentage of PLWH with controlled viremia. Finally, the cohort evaluated is a predominantly male cohort of US veterans so these results may not be generalizable to the other populations, particularly women.

CONCLUSIONS

In conclusion, the incidence of CVD events during and after hospitalization for CAP was similar in PLWH and uninfected patients, after adjusting for age, CVD risk

factors, and CAP severity. Notably, PLWH in this cohort were hospitalized with less severe pneumonia and had fewer CVD risk factors yet had a similar adjusted incidence of CVD events. HIV infection was associated with increased mortality after CAP hospitalization in fully adjusted models. Finally, severe CAP is associated with an increased incidence of CVD events and mortality in both PLWH and patients uninfected with HIV. PLWH should be included in future studies on the risk, mechanisms, and prevention of CVD events post-CAP.

ARTICLE INFORMATION

Received May 17, 2020; accepted October 16, 2020.

Affiliations

From the Department of Medicine, Section of Pulmonary Diseases, Critical Care, and Environmental Medicine, Tulane University School of Medicine, New Orleans, LA (J.S.Z.); Department of Medicine, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN (M.S.D., M.S.F.); Department of Biostatistics, College of Public Health, University of Kentucky, Lexington, KY (M.S.D.); Section of General Internal Medicine, Boston University School of Medicine, Boston, MA (K.A.S.-A.); Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle, WA (E.F.A., K.C.); Department of Medicine, Section of Pulmonary, Critical Care and Sleep Medicine, Veterans Affairs Connecticut Healthcare System, West Haven, CT (K.M.A., J.P.T.); Yale University School of Medicine, New Haven, CT (K.M.A., J.P.T., A.C.J.); Infectious Diseases Section, Michael E. DeBakey Veterans Affairs Medical Center, Baylor College of Medicine, Houston, TX (M.C.R.-B.); Atlanta Veterans Affairs Medical Center, Division of Infectious Diseases, Department of Global Health, Rollins School of Public Health and Department of Medicine, Emory University School of Medicine, Atlanta, GA (V.C.M.); Department of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA, Los Angeles, CA (M.J.B.); Department of Medicine, VA North Texas Health Care System and University of Texas Southwestern Medical Center, Dallas, TX (R.J.B.); Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, PA (C.W.A.); Department of Medicine, Pulmonary, Critical Care and Sleep Section, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA (G.W.S.H.); Veterans Affairs, Pittsburgh Healthcare System, Pittsburgh, PA (A.A.B.); Weill Cornell Medical College, New York, NY (A.A.B.) and Weill Cornell Medical College, Doha, Qatar (A.A.B.); Critical Care Medicine, James J. Peters Veterans Affairs Medical Center, Bronx, NY (J.W.K.); Neurology Service and Clinical Epidemiology Research Center (CERC), Veterans Affairs Connecticut Healthcare System, West Haven, CT (J.J.S.); Departments of Internal Medicine, Section of Internal Medicine, Neurology, Sections of Vascular Neurology and General Neurology, Center for NeuroEpidemiological and Clinical Research, Yale School of Medicine, New Haven, CT (J.J.S.); Geriatric Research Education and Clinical Centers (GRECC), Veterans Affairs Tennessee Valley Healthcare System, Nashville, TN (H.A.T.); Department of Medicine, Division of General Internal Medicine and Public Health, Vanderbilt University Medical Center, Nashville, TN (H.A.T., M.S.F.); Department of Medicine, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, CA (L.H.); Department of Medicine, Veterans Affairs Connecticut Healthcare System, West Haven, CT (A.C.J.); and Veterans Affairs Puget Sound Health Care System, Seattle, WA (K.C.).

Acknowledgments

JSZ is the guarantor for this work. Author contributions: JSZ and MSD had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JSZ, MSD, MSF, KC; Drafting of the manuscript: JSZ, MSD, JPT, ACJ, MSF, KC, LH. All included authors contributed substantially to the acquisition, analysis, or interpretation of data for the work; revised the manuscript critically for important intellectual content; approved the final version of the manuscript; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sources of Funding

This work was supported by the National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health [Grants U24 AA020794, U01 AA020790, U024 AA022001, and U10 AA013566] and in kind by the United States Department of Veterans Affairs. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs. The Emory Center for AIDS Research [P30AI050409]. KA was funded by National Institutes of Health [K01 HL134147]. KC was funded by National Institutes of Health [HL1U01HL142103]. LH was partly funded by National Institutes of Health [K24087713]. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures

None.

Supplementary Material

Tables S1–S4

REFERENCES

1. WHO. The top 10 causes of death. 2018. https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed June 12, 2020.
2. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, Katz K, Ko DT, McGeer AJ, McNally D, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378:345–353.
3. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang CC, Newman A, Loehr L, Folsom AR, Elkind MS, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA*. 2015;313:264–274.
4. Perry TW, Pugh MJ, Waterer GW, Nakashima B, Orihuela CJ, Copeland LA, Restrepo MI, Anzueto A, Mortensen EM. Incidence of cardiovascular events after hospital admission for pneumonia. *Am J Med*. 2011;124:244–251.
5. Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *ClinInfect Dis*. 2007;45:158–165.
6. Corrales-Medina VF, Serpa J, Rueda AM, Giordano TP, Bozkurt B, Madjid M, Tweardy D, Musher DM. Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. *Medicine*. 2009;88:154–159.
7. Violi F, Cangemi R, Falcone M, Taliani G, Pieralli F, Vannucchi V, Nozzoli C, Venditti M, Chirinos JA, Corrales-Medina VF. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. *Clin Infect Dis*. 2017;64:1486–1493.
8. Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ. Cardiac complications in patients with community-acquired pneumonia. *Circulation*. 2012;125:773–781.
9. Ramirez J, Aliberti S, Mirsaeidi M, Peyrani P, Filardo G, Amir A, Moffett B, Gordon J, Blasi F, Bordon J. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. *Clin Infect Dis*. 2008;47:182–187.
10. Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, Oursler KK, Rimland D, Gibert CL, Butt AA, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med*. 2011;183:388–395.
11. Sogaard OS, Lohse N, Gerstoft J, Kronborg G, Ostergaard L, Pedersen C, Pedersen G, Sorensen HT, Obel N. Mortality after hospitalization for pneumonia among individuals with HIV, 1995–2008: a danish cohort study. *PLoS One*. 2009;4:e7022.
12. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622.
13. Freiberg MS, Chang CH, Skanderson M, Patterson OV, DuVall SL, Brandt CA, So-Armah KA, Vasan RS, Oursler KA, Gottdiener J, et al. 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;2:536–546.
14. Stein JH, Hsue PY. Inflammation, immune activation, and CVD risk in individuals with HIV infection. *JAMA*. 2012;308:405–406.
15. Madjid M, Vela D, Khalili-Tabrizi H, Casscells SW, Litovsky S. Systemic infections cause exaggerated local inflammation in atherosclerotic coronary arteries: clues to the triggering effect of acute infections on acute coronary syndromes. *Tex Heart Inst J*. 2007;34:11–18.
16. Yende S, D'Angelo G, Kellum JA, Weissfeld L, Fine J, Welch RD, Kong L, Carter M, Angus DC. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med*. 2008;177:1242–1247.
17. Cangemi R, Pignatelli P, Carnevale R, Bartimoccia S, Nocella C, Falcone M, Taliani G, Violi F. Low-grade endotoxemia, gut permeability and platelet activation in community-acquired pneumonia. *J Infect*. 2016;73:107–114.
18. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, Goulet J, Simberkoff M, Butt AA, Rimland D, et al. Veterans aging cohort study (VACS): overview and description. *Med Care*. 2006;44:S13–S24.
19. 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–S30.
20. C. Rodriguez-Barradas M, Akgün K, Brown S, Butt A, J. Fine M, Goetz M, Graber C, Huang L, McGinnis K, Rimland D, et al. Community acquired pneumonia (CAP) requiring hospitalization in HIV infected (HIV+) and un-infected (HIV–) patients: evaluation of patients identified by ICD-9 codes. *Open ForumInfect Dis*. 2015;2(Suppl 1):1583.
21. McGinnis KA, Brandt CA, Skanderson M, Justice AC, Shahrir S, Butt AA, Brown ST, Freiberg MS, Gibert CL, Goetz MB, et al. Validating smoking data from the veteran's affairs health factors dataset, an electronic data source. *Nicotine & Tob Res*. 2011;13:1233–1239.
22. 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–S51.
23. Marconi VC, Duncan MS, So-Armah K, Re VL III, Lim JK, Butt AA, Goetz MB, Rodriguez-Barradas MC, Alcorn CW, Lennox J, et al. Bilirubin is inversely associated with cardiovascular disease among HIV-positive and HIV-negative individuals in VACS (veterans aging cohort study). *J Am Heart Assoc*. 2018;7:e007792. 10.1161/JAHA.117.007792
24. Beckman JA, Duncan MS, Alcorn CW, So-Armah K, Butt AA, Goetz MB, Tindle HA, Sico JJ, Tracy RP, Justice AC, et al. Association of human immunodeficiency virus infection and risk of peripheral artery disease. *Circulation*. 2018;138:255–265.
25. Griffin AT, Wiemken TL, Arnold FW. Risk factors for cardiovascular events in hospitalized patients with community-acquired pneumonia. *Int J Infect Dis*. 2013;17:e1125–e1129.
26. Polgreen LA, Riedle BN, Cavanaugh JE, Girotra S, London B, Schroeder MC, Polgreen PM. Estimated cardiac risk associated with macrolides and fluoroquinolones decreases substantially when adjusting for patient characteristics and comorbidities. *J Am Heart Assoc*. 2018;7:e008074. 10.1161/JAHA.117.008074
27. Cheng Y-J, Nie X-Y, Chen X-M, Lin X-X, Tang K, Zeng W-T, Mei W-Y, Liu L-J, Long M, Yao F-J, et al. The role of macrolide antibiotics in increasing cardiovascular risk. *J Am Coll Cardiol*. 2015;66:2173–2184.
28. Lu ZK, Yuan J, Li M, Sutton SS, Rao GA, Jacob S, Bennett CL. Cardiac risks associated with antibiotics: azithromycin and levofloxacin. *Expert Opin Drug Saf*. 2015;14:295–303.
29. Albert RK, Schuller JL. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med*. 2014;189:1173–1180.
30. Rubin DB. Multiple imputation for nonresponse in surveys. *Biom J*. 1989;31:131–132.
31. Mesquita EC, Coelho LE, Amancio RT, Veloso V, Grinsztejn B, Luz P, Bozza FA. Severe infection increases cardiovascular risk among HIV-infected individuals. *BMC Infect Dis*. 2019;19:319.
32. Rose JJ, Voora D, Cyr DD, Lucas JE, Zaas AK, Woods CW, Newby LK, Kraus WE, Ginsburg GS. Gene expression profiles link respiratory viral infection, platelet response to aspirin, and acute myocardial infarction. *PLoS One*. 2015;10:e0132259.
33. Brown AO, Mann B, Gao G, Hankins JS, Humann J, Giardina J, Faverio P, Restrepo MI, Halade GV, Mortensen EM, et al. Streptococcus pneumoniae translocates into the myocardium and forms unique microlesions that disrupt cardiac function. *PLoS Pathog*. 2014;10:e1004383.
34. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. *N Engl J Med*. 2019;380:171–176.
35. Stein GY, Herscovici G, Korenfeld R, Matetzky S, Gottlieb S, Alon D, Gevrielov-Yusim N, Iakobishvili Z, Fuchs S. Type-II myocardial infarction–patient characteristics, management and outcomes. *PLoS One*. 2014;9:e84285
36. Malinis M, Myers J, Bordon J, Peyrani P, Kapoor R, Nakamatzu R, Lopardo G, Torres A, Feldman C, Allen M, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. 2010;14:e22–e27.
37. Christensen D, Feldman C, Rossi P, Marrie T, Blasi F, Luna C, Fernandez P, Porras J, Martinez J, Weiss K, et al. HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. *Clin Infect Dis*. 2005;41:554–556.
38. Cilloniz C, Torres A, Polverino E, Gabarrus A, Amaro R, Moreno E, Villegas S, Ortega M, Mensa J, Marcos MA, et al. Community-acquired lung respiratory infections in HIV-infected patients: microbial aetiology and outcome. *Eur Respir J*. 2014;43:1698–1708.
39. Cilloniz C, Torres A, Manzardo C, Gabarrus A, Ambrosioni J, Salazar A, Garcia F, Ceccato A, Mensa J, de la Bella Casa JP, et al. Community-acquired pneumococcal pneumonia in virologically suppressed HIV-infected adult patients: a matched case-control study. *Chest*. 2017;152:295–303.
40. Barakat LA, Juthani-Mehta M, Allore H, Trentalange M, Tate J, Rimland D, Pisani M, Akgun KM, Goetz MB, Butt AA, et al. Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia. *HIV Med*. 2015;16:421–430.
41. Cohen C, Simonsen L, Sample J, Kang JW, Miller M, Madhi SA, Campsmith M, Viboud C. Influenza-related mortality among adults aged 25–54 years with AIDS in South Africa and the United States of America. *Clin Infect Dis*. 2012;55:996–1003.

SUPPLEMENTAL MATERIAL

Table S1. ICD-9 diagnosis codes.

Admission Diagnoses

CAP ICD-9: 480.x, 481.x, 482.x, 483.x, 484.x, 485.x, 486.x, 487.x, 507.x
*Chronic bronchitis ICD-9***:** 491.2
*HIV ICD-9***:** 042-044, V08
*Respiratory failure ICD-9***:** 518.81, 518.82, 518.84
*Sepsis ICD-9***:** 038.x, 995.91, 995.92, 790.7

CVD Event Diagnoses

Acute myocardial infarction ICD-9: 410.x (inpatient only)
Atrial fibrillation/flutter ICD-9: 427.31 and 427.32
Cardiomyopathy ICD-9: 425.1, 425.2, 425.3, 425.4, 425.5, 425.7, 425.8, 425.9, 425.0, 425.11, 425.18
CHF ICD-9: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.21, 428.22, 428.23, 428.31, 428.32, 428.33, 428.41, 428.42, 428.43, 428.9, 428.20, 428.30, 428.40
Ischemic Stroke ICD-9: 436 (inpatient only), 438.x (outpatient only), 433.x1, 434.x1
Revascularization Procedure ICD-9 Codes: 00.66, 36.00, 36.01, 36.02, 36.03, 36.04, 36.05, 36.06, 36.07, 36.08, 36.09; *CPT Codes*: 33510, 33511, 33512, 33513, 33514, 33515, 33516, 33517, 33518, 33519, 33520, 33521, 33522, 33523, 33530, 33531, 33532, 33533, 33534, 33535, 33536, 92973, 92974, 92975, 92976, 92977, 92978, 92979, 92980, 92981, 92982, 92983, 92984, 92995, 92996, 92997, 92998
Unstable angina ICD-9: 411.x (inpatient only)
Unspecified arrythmia ICD-9: 427, 427.2, 427.5, 427.8, 427.89, 427.9, 429.4, 997.1, V12.53
Ventricular arrythmia ICD-9: 427.1, 427.4

CAP, community acquired pneumonia; CHF, congestive heart failure; CVD, cardiovascular disease; HIV, human immunodeficiency virus; ICD-9, International Classifications of Disease Ninth Revision.

Table S2. Multivariable analysis of Incident CVD and Mortality at 90 days following CAP hospitalization*

90-Day CVD Incidence

Group	N	CVD Events	Rate/10,000 PD [95% CI]	Unadjusted Risk [95% CI]	Minimally Adjusted Risk [95% CI] †	Multivariable Adjusted Risk [95% CI] ‡
HIV-uninfected	1433	160	14 [12, 17]	1.00	1.00	1.00
PLWH	2951	207	9 [8, 10]	0.62 [0.51, 0.75]	0.81 [0.66, 0.99]	0.89 [0.72, 1.09]

90-Day Mortality

Group	N	Deaths	Rate/10,000 PD [95% CI]	Unadjusted Risk [95% CI]	Minimally Adjusted Risk [95% CI] †	Multivariable Adjusted Risk [95% CI] ‡
HIV-uninfected	1433	154	13 [11, 15]	1.00	1.00	1.00
PLWH	2951	329	13 [12, 15]	1.04 [0.86, 1.26]	1.50 [1.22, 1.84]	1.40 [1.14, 1.71]

* CAP, community-acquired pneumonia; CI, confidence interval; CVD, cardiovascular disease; HIV, human immunodeficiency virus; PD, person days; PLWH, people living with HIV.

† adjusted for age and severe CAP.

‡ adjusted for age, severe CAP, race/ethnicity, prior CAP, diabetes mellitus, hypertension, dyslipidemia, smoking status, alcohol abuse, and illicit drug use.

Table S3. 90-day CVD incidence rates and mortality by HIV status in multivariable Cox proportional hazards model

Characteristic	Incident CVD Hazard Ratio [95% CI]*		Mortality Hazard Ratio [95% CI]*	
	PLWH	HIV-uninfected	PLWH	HIV-uninfected
Age, 10 years	1.45 [1.25, 1.68]	1.25 [1.03, 1.48]	1.38 [1.22, 1.56]	1.49 [1.23, 1.79]
Severe CAP †	3.93 [2.85, 5.42]	2.50 [1.74, 3.59]	6.85 [5.52, 8.51]	4.57 [3.35, 6.24]
Race/ethnicity				
African American vs. White	0.93 [0.70, 1.23]	0.94 [0.68, 1.30]	0.88 [0.67, 1.16]	1.31 [0.93, 1.84]
Hispanic vs. White	0.92 [0.50, 1.71]	0.53 [0.29, 0.96]	1.15 [0.67, 1.66]	0.71 [0.38, 1.34]
Other vs. White	1.54 [0.74, 3.20]	1.34 [0.54, 3.31]	1.73 [0.99, 3.00]	1.87 [0.69, 5.08]
Prior CAP	0.78 [0.48, 1.28]	0.89 [0.54, 1.47]	0.66 [0.44, 1.01]	0.16 [0.06, 0.44]
Diabetes Mellitus	1.23 [0.81, 1.87]	1.07 [0.79, 1.46]	1.18 [0.84, 1.67]	1.00 [0.68, 1.46]
Hypertension	1.21 [0.95, 1.54]	1.99 [1.32, 3.00]	0.84 [0.66, 1.07]	0.75 [0.51, 1.11]
Dyslipidemia	0.98 [0.68, 1.41]	1.28 [0.89, 1.84]	1.13 [0.83, 1.52]	1.26 [0.91, 1.75]
Smoking				
Current vs. Never	1.41 [0.92, 2.17]	0.87 [0.56, 1.37]	1.12 [0.78, 1.60]	1.23 [0.66, 2.27]
Former vs. Never	1.13 [0.63, 2.03]	0.58 [0.35, 0.97]	0.98 [0.60, 1.60]	1.12 [0.61, 2.07]
Alcohol Abuse	1.02 [0.74, 1.42]	1.46 [0.98, 2.19]	1.07 [0.78, 1.47]	1.82 [1.21, 2.73]
Illicit Drug Use	1.00 [0.69, 1.45]	0.66 [0.43, 1.01]	0.72 [0.54, 0.96]	0.71 [0.49,1.02]
CD4 Cell Count, per 200 cells/mm^3 increase	0.97 [0.86, 1.09]	---	0.76 [0.66, 0.87]	---
HIV Viral Load, per 10,000 copies/mL increase	1.00 [0.99, 1.01]	---	1.00 [0.99, 1.00]	---
Receipt of NRTI	0.96 [0.62, 1.48]	---	0.98 [0.68, 1.41]	---
Receipt of NNRTI	0.96 [0.66, 1.39]	---	0.80 [0.54, 1.18]	---
Receipt of PI	1.19 [0.77, 1.83]	---	0.93 [0.67, 1.28]	---

* adjusted for all listed characteristics.

† Severe CAP defined by the presence of any one of the following: respiratory failure, mechanical ventilation (invasive or non-invasive), sepsis, and/or shock.

CAP, community-acquired pneumonia; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV.

Table S4. Multivariable analysis of Incident CVD and Mortality at 30 days following CAP hospitalization additionally adjusted for antibiotic usage*

30-Day CVD Incidence				
Group	**N**	**CVD Events**	**Rate/10,000 PD [95% CI]**	**Multivariable Adjusted Risk [95% CI]** †
HIV-uninfected	1433	123	30 [25, 36]	1.00
PLWH	2951	160	19 [16, 22]	0.92 [0.73, 1.17]
30-Day Mortality				
Group	**N**	**Deaths**	**Rate/10,000 PD [95% CI]**	**Multivariable Adjusted Risk [95% CI]** †
HIV-uninfected	1433	103	24 [20, 30]	1.00
PLWH	2951	218	25 [22, 29]	1.59 [1.22, 2.07]

* CAP, community-acquired pneumonia; CI, confidence interval; CVD, cardiovascular disease; HIV, human immunodeficiency virus; PD, person days; PLWH, people living with HIV.

† adjusted for age, severe CAP, race/ethnicity, prior CAP, diabetes mellitus, hypertension, dyslipidemia, smoking status, alcohol abuse, illicit drug use, macrolide use, and fluoroquinolone use.