## Title
Clinical outcomes of HIV-infected men with CAP



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# Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia

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## Abstract

**Objectives—**Outcomes of community–acquired pneumonia (CAP) among HIV-infected older adults are unclear.

**Methods—**Associations between HIV infection and three CAP outcomes (30-day mortality, readmission within 30 days post-discharge, and hospital length of stay [LOS]) were examined in the Veterans Aging Cohort Study (VACS) of male Veterans, age ≥ 50 years, hospitalized for CAP from 10/1/2002 through 08/31/2010. Associations between the VACS Index and CAP outcomes were assessed in multivariable models.

**Results—**Among 117 557 Veterans (36 922 HIV-infected and 80 635 uninfected), 1203 met our eligibility criteria. The 30-day mortality rate was 5.3%, the mean LOS was 7.3 days, and 13.2% were readmitted within 30 days of discharge. In unadjusted analyses, there were no significant differences between HIV-infected and uninfected participants regarding the three CAP outcomes ($P > 0.2$). A higher VACS Index was associated with increased 30-day mortality, readmission, and LOS in both HIV-infected and uninfected groups. Generic organ system components of the VACS Index were associated with adverse CAP outcomes; HIV-specific components were not. Among HIV-infected participants, those not on antiretroviral therapy (ART) had a higher 30-day mortality

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(HR 2.94 [95% CI 1.51, 5.72]; $P = 0.002$) and a longer LOS (slope 2.69 days [95% CI 0.65, 4.73]; $P = 0.008$), after accounting for VACS Index. Readmission was not associated with ART use (OR 1.12 [95% CI 0.62, 2.00] $P = 0.714$).

**Conclusion—**Among HIV-infected and uninfected older adults hospitalized for CAP, organ system components of the VACS Index were associated with adverse CAP outcomes. Among HIV-infected individuals, ART was associated with decreased 30-day mortality and LOS.

### Keywords

HIV; outcomes; pneumonia

## Introduction

Adults aged 50 years or older represent 10.8% of new HIV infections, and it is estimated that they will constitute the majority of patients living with HIV in the USA by 2020 [1–3]. Opportunistic pneumonias were a major cause of morbidity and mortality in the pre-antiretroviral therapy (ART) era. Although rates of opportunistic pneumonias have declined markedly among HIV-infected individuals on ART, the rate of bacterial pneumonia has not decreased proportionately [4,5]. HIV-infected adults remain at increased risk of community-acquired pneumonia (CAP) compared with uninfected individuals, with an overall mortality estimated at 5–12% [6–9].

Although much has been learned about health outcomes of CAP in uninfected patients, CAP outcomes among HIV-infected adults are less clear. Some studies reported a higher incidence of CAP-related mortality and complications among HIV-infected compared with uninfected individuals; others suggested that HIV infection did not influence mortality or length of stay (LOS) among patients hospitalized for CAP [10–17]. Little is known about CAP prognosis among the growing population of HIV-infected older adults (i.e. age ≥ 50 years) in the post-ART era, and existing guidelines for the treatment of hospitalized patients with CAP do not specifically address the approach to patients with HIV infection, including the applicability of severity of illness scores such as CURB-65 (Confusion, Blood urea nitrogen >19 mg/dl, Respiratory rate =or>30 breaths/minute, Systolic blood pressure <90 mm Hg or Diastolic blood pressure < or = 60 mm Hg, and Age = or > 65 years) or the Pneumonia Severity Index (PSI) [18,19]. The Veterans Aging Cohort Study (VACS), a longitudinal observational cohort study, is an ideal framework in which to study health outcomes in HIV-infected and uninfected older adults with CAP [20]. The VACS Index is a composite quantitative measure of HIV-specific (i.e. CD4 count and HIV RNA) and general organ system components (i.e. haemoglobin concentration, platelet count, concentration of hepatic transaminases, estimated glomerular filtration rate and hepatitis C) as well as age (Table 1) [21]. The VACS Index is a validated predictor of all-cause mortality in HIV-infected patients [21,22] and also predicts 30-day mortality for both HIV-infected and uninfected patients admitted to the medical intensive care unit (ICU) [23]. The index is correlated with biomarkers of inflammation [24].

In this study, we examined the impact of HIV infection on clinical outcomes in older adults (age ≥ 50 years) hospitalized with CAP. We hypothesized that those with HIV infection have

a greater risk of adverse outcomes, including 30-day mortality, readmission within 30 days post-discharge, and hospital LOS, compared with uninfected patients. We explored factors associated with adverse CAP outcomes, including the VACS Index and its components as a measurement of severity of injury scores.

## Methods

The associations between HIV infection and three clinical outcomes following hospitalization for CAP were examined using data from the VACS virtual cohort [20]. The VACS virtual cohort study is an ongoing prospective, observational, virtual cohort study that includes more than 40 000 HIV-infected veterans and 80 000 age-, race-, and site-matched uninfected controls. The VACS cohort was established to investigate the overall impact of HIV infection, treatment, and comorbid conditions on morbidity and mortality. Patients eligible for the current study were those alive and under follow-up from 1 October 2002 to 31 August 2010. Our inclusion criteria were age ≥ 50 years on hospital admission and hospitalization with CAP during the study period. The diagnosis of CAP was based on International Classification of Diseases, 9th Revision (ICD-9) codes on hospital discharge with the diagnosis of pneumonia (Appendix S1) [25], either as a primary diagnosis or as a diagnosis secondary only to HIV diagnosis, in which intravenous antibiotics were administered within 72 hours of admission, and with no prior hospitalization within 90 days of admission. Those with pneumonia secondary to *Pneumocystis jiroveci*, *Mycobacterium tuberculosis*, or fungal infection were not included. Women, who represented < 2% of the cohort, those with undetermined HIV status, and those with incomplete covariate data were also excluded. Only the first episode of CAP during the study period was included in our analysis.

### Study variables

Age was measured in years at the date of admission. The VACS Index score was obtained at hospital admission, using the highest score on the day of, the day before, or the day after admission. Components of the VACS Index were categorized and assigned point values using a previously established system and summed to calculate a score [21]. The race/ethnicity category was collapsed to ‘white’ or ‘nonwhite’. Smoking status was characterized as ‘current’, ‘past’ or ‘never’. The presence of pulmonary comorbidities and alcohol- and drug-related diagnoses were all coded as yes/no. Pulmonary comorbidities were defined by ICD-9 codes related to the standard VACS pulmonary comorbidities defined by the VACS pulmonary working group and are attributed to the diagnosis for the period from 1 year before to 6 months after enrolment in the VACS cohort (Appendix S2). Alcohol- or drug-related diagnoses were ICD-9 codes attributed to alcohol or substance abuse-related diagnosis within 1 year of admission for CAP. For both alcohol- and drug-related diagnoses, ICD-9 codes indicating treatment for remission or rehabilitation were excluded. Finally, within the HIV-infected group, ART at the time of presentation with CAP was defined as receiving ART within 14 days prior to CAP admission. Three CAP outcomes were examined: 30-day mortality (defined as death from any cause within 30 days of admission), all-cause readmission within 30 days post-discharge and hospital LOS in days.

### Statistical analysis

We calculated descriptive statistics by HIV status, assessing the significance of differences in means with Student *t*-tests and differences among proportions with a $\chi^2$ test in the analytic sample. Multivariable regression models were used to assess the association between outcomes and the variables listed above (e.g. sociodemographic characteristics, smoking, comorbidities, ART use, VACS Index) using Cox regression for mortality, logistic regression for readmission and linear regression for LOS. For these three outcomes, five sets of models were run. The first model set (model 1) involved the entire sample (HIV-infected and uninfected individuals). The second set (model 2) was restricted to uninfected individuals only. The third to fifth sets (models 3−5) included only HIV-infected participants. All models were adjusted for race, smoking status, pulmonary comorbidity, and alcohol- and drug-related diagnoses within the year prior to admission. As age is included as an item in the VACS Index score, model set 5 (HIV-infected individuals only), which separated HIV-specific (i.e. CD4 count and HIV RNA) and organ system components (i.e. haemoglobin concentration, platelet count, concentration of hepatic transaminases, estimated glomerular filtration rate and hepatitis C), was additionally adjusted for age, dichotomized as < 65 or ≥ 65 years. In order to estimate the effect of ART, model set 5 investigated the association of VACS Index score components and ART (yes/no) on admission with the various outcomes. All statistical tests were two-tailed and results were considered statistically significant when $P < 0.05$. Analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC, USA).

## Results

Among the cohort of 117 557 veterans (36 922 HIV-infected and 80 635 uninfected demographically matched veterans), 2578 met the criteria for hospitalization because of CAP, and 1612 of those were aged 50 years or older. Among the subset of 1612 participants, 389 were excluded [four for undetermined HIV status and 385 (288 HIV-infected and 97 uninfected) for missing covariate data]. Twenty women were excluded (17 HIV-infected and three uninfected) as this represented an insufficient number to provide generalizability to women (< 2% of the cohort). Of the 1203 remaining in our study sample, 670 (55.7%) were HIV-infected and 533 (44.3%) were uninfected (Fig. 1). The median age was 56 years for HIV-infected participants [lower quartile (LQ)–upper quartile (UQ) 53–60 years] and 57 years for uninfected participants (LQ–UQ 54–63 years).

There were several differences in patient characteristics by HIV status (Table 2). Compared with uninfected participants, the HIV-infected participants were less likely to be aged ≥ 65 years [70 (10.4%) HIV-infected individuals versus 112 (21.0%) uninfected individuals; $P < 0.001$], to be of white race [275 (41.0%) versus 249 (46.7%), respectively; $P = 0.049$], or to have a pulmonary comorbidity [64 (9.6%) versus 71 (13.3%), respectively; $P = 0.040$], but more likely to have a drug-use-related diagnosis [132 (19.7%) versus 78 (14.6%), respectively; $P = 0.021$]. There were no significant differences between HIV-infected and uninfected participants regarding smoking, alcohol-related diagnoses, type of pneumonia or any of the three clinical CAP outcomes (i.e. 30-day mortality, readmission within 30 days of discharge, or hospital LOS). Based on ICD-9 codes identified, the majority of participants

(84.5%) had an unspecified cause of CAP hospitalization, 13.6% were classified as having bacterial causes and 1.9% viral causes; the aetiology of CAP did not vary by HIV status. Among the subset of HIV-infected participants, 81.8% were on ART at the time of hospitalization and 53.4% had HIV RNA < 500 HIV-1 RNA copies/ml. Comparing HIV-infected participants on ART with those not on ART, there was no significant difference in mean CD4 count at the time of hospitalization (390.6 versus 413.3 cells/μL, respectively; $P = 0.484$). However, the mean HIV viral load at the time of hospitalization was lower in the participants on ART compared with those not on ART (34 698 versus 65 192 copies/mL, respectively; $P = 0.046$).

The majority of study participants (96.4%) received one or more groups of CAP-appropriate intravenous antibiotics, as defined by the Infectious Diseases Society of America guidelines [19], within 72 hours of admission. The five most commonly prescribed antimicrobial agents included one or a combination of the following antibiotic groups: respiratory tract-targeted beta lactams, 20.9% (e.g. amoxicillin/clavulanate, ampicillin/sulbactam, cefuroxime, cefaclor, cefamandole, cefpodoxime, cefotaxime or ceftriaxone); respiratory tract-targeted quinolones, 17.7% (e.g. gatifloxacin, levofloxacin, moxifloxacin or ofloxacin); macrolides, 17.0% (e.g. azithromycin, clarithromycin or erythromycin); anti-pseudomonal beta lactams, 12.5% (e.g. ticarcillin, piperacillin, cefepime, ceftazidime or imipenem); and anti-methicillin-resistant *Staphylococcus aureus* agents, 11.4% (e.g. vancomycin or linezolid). Overall, the 30-day mortality rate for study participants hospitalized for CAP was 5.3%; the mean LOS was 7.3 days [standard deviation (SD) 9.9 days], and 13.2% were readmitted within 30 days of discharge. In unadjusted analyses, HIV infection was not statistically significantly associated with any outcome ($P > 0.2$ for all). However, organ system components' score of the VACS Index score were significantly greater among the HIV-infected cohort compared with the uninfected cohort [mean 32.7 (SD 19.4) versus 27.2 (SD 17.5), respectively; $P < 0.001$], as was the total VACS Index score [mean 60.1 (SD 25.1) versus 42.3 (SD 19.6), respectively; $P < 0.001$]. The majority of the HIV-infected cohort had CD4 counts < 500 cells/μL and HIV viral loads < 500 copies/mL and were receiving ART.

The adjusted models 1 to 5 for the three CAP clinical outcomes (30-day mortality, readmission and LOS) are shown in Table 3. Model 1 used the entire cohort (HIV-infected and uninfected participants) and showed that the VACS Index (scaled in five-point increments) was significantly associated with 30-day mortality [hazard ratio (HR) 1.17; 95% confidence interval (CI) 1.12, 1.23; $P < 0.001$], readmission 30 days post-discharge [odds ratio (OR) 1.08; 95% CI 1.05, 1.12; $P < 0.001$] and hospital LOS (slope 0.24; 95% CI 0.12, 0.36; $P < 0.001$). For each five-point increment in VACS Index score there was a 17% increase in the risk of 30-day mortality, an 8% increase in the risk of readmission within 30 days post-discharge, and a 0.24-day incremental increase in LOS. These relationships remained, with approximately the same magnitudes, for both the uninfected group (model 2) and the HIV-infected group (model 3). Model 4 assessed the association with ART after adjusting for VACS Index in the HIV-infected participants only, and showed that the absence of ART on admission conferred a nearly three-fold increase in 30-day mortality (HR 2.94; 95% CI 1.51, 5.72; $P = 0.002$) and 2.7 additional days of hospitalization (slope 2.69; 95% CI 0.65, 4.73; $P = 0.008$); ART was not associated with readmission (HR 1.12; 95% CI 0.62, 2.00; $P = 0.714$). Model 5 (HIV-infected individuals only) examined the effects of the HIV-

specific and organ system components of the VACS Index and showed that organ system components were strongly associated with all three CAP outcomes. As with model 4, lack of ART on admission was associated with increased 30-day mortality and LOS.

Figure 2 illustrates the adjusted 30-day mortality rate by ART on admission and the median of the VACS Index score divided into tertiles. As shown, an increasing VACS Index score was associated with a greater mortality difference in those not taking ART compared with those taking ART. Specifically, for a VACS Index score median of 58, the adjusted mortality rate was 18.4 (95% CI 6.6, 51.3)/1000 person-months for those on ART versus 73.6 (95% CI 24.8, 218.5)/1000 person-months for those not on ART. Similarly, for a VACS Index score median of 86, the adjusted mortality rate was 39.6 (95% CI 16.3, 96.2)/1000 person-months for those on ART versus 128.5 (95% CI 55.2, 299.3)/1000 person-months for those not on ART.

## Discussion

This study demonstrated that, among older male veterans hospitalized for CAP, a higher VACS Index score was associated with a higher risk of 30-day mortality, readmission within 30 days post-discharge, and prolonged LOS. Outcomes did not differ overall by HIV status in this sample, but after adjustment for all the components of the VACS Index score, ART exposure was independently associated with decreased mortality and LOS among the HIV-infected group.

Previous publications that examined CAP outcomes among hospitalized HIV-infected patients reported conflicting results [4,5,10–14,16–17]. Some studies showed that HIV infection did not affect mortality or LOS [13,17]; others concluded the opposite [16]. HIV-infected patients were reported to have higher mortality and longer LOS in high-risk subgroups including injecting drug users, smokers and patients with pulmonary comorbidities. However, most of these cohort studies were carried out in the pre-ART era, had small sample sizes, did not adjust for HIV-specific covariates (e.g. CD4 count, viral load and ART use), or did not include substantial numbers of older adults [10–14, 16–17].

Our study involved the largest sample to date of HIV-infected older men hospitalized for CAP and assessed for multiple clinical outcomes, and it highlighted several important findings. First, it demonstrated the clinical significance of the VACS Index scoring system as a predictor of CAP outcomes among older adults with and without HIV infection. While outcomes did not differ statistically by HIV status, the wide variation in outcomes observed among both HIV-infected and uninfected groups was substantially explained by VACS Index score for both groups. The VACS Index has been validated to predict all-cause mortality in HIV-infected individuals [20–23], but this is the first study showing its value in predicting clinically relevant CAP outcomes including 30-day mortality, hospital LOS and readmission in both HIV-infected and uninfected participants. In our analysis, HIV viral loads, CD4 cell counts, race, smoking, pulmonary comorbidities, and substance abuse- and alcohol use-related diagnoses did not individually influence CAP adverse outcomes for HIV-infected participants compared with uninfected participants. Prior reports had utilized composite scoring systems in HIV-infected patients with CAP to predict mortality [10–12]. However,

our study not only demonstrated the association of the VACS Index score with adverse CAP outcomes, but showed that CAP clinical outcomes among older men were affected less by HIV-specific measures (e.g. CD4 count and viral load) than by organ system components of the VACS Index score. This may be explained by the chronic inflammatory state in HIV-infected patients, even in those with suppressed viral loads and preserved CD4 counts, which could potentially cause physiological injury reflected in the organ system components of the VACS Index (e.g. estimated glomerular filtration rate and haemoglobin concentration). Hence, the VACS Index could provide, based on routinely available clinical data, a valuable tool in guiding clinical decision making by identifying HIV-infected patients hospitalized with CAP who are at greater risk of adverse outcomes.

Secondly, although the VACS Index score was recognized as an important predictor of 30-day mortality and LOS, the lack of ART use in the HIV-infected cohort was independently associated with three-fold increase in mortality (HR 2.94; 95% CI 1.51, 5.72; $P = 0.002$) and a 2.7-day prolongation of hospitalization (slope 2.69; 95% CI 0.65, 4.73; $P = 0.008$). An increasing VACS Index score was associated with a greater increase in mortality in those not taking ART compared with those taking ART. While those in the first tertile of VACS Index scores had low and comparable mortality with or without ART, those with VACS Index scores above 80 and not taking ART had approximately 3 times the 30-day mortality rate of those taking ART on admission (Fig. 2). One can speculate that patients who are on ART might be more adherent to medical care and make better health lifestyle choices that affected short-term mortality. Alternatively, HIV-infected older adults on ART might have improved innate or adaptive immunity that was not reflected in CD4 counts or HIV viral loads [26].

Of note, despite there being only a modest difference in median age at CAP diagnosis (56 years for HIV-infected participants and 57 years for uninfected participants), the HIV-infected group included a significantly lower proportion of participants who were ≥ 65 years old compared with the uninfected group. Several studies reported the increased risk of comorbidities in HIV-infected individuals than in HIV-uninfected adults [26–32]. Chronic HIV infection, despite HIV viral suppression, might exacerbate pathophysiological processes such as endothelial or end organ damage which could increase the risk for aging and multiple morbidities, including pneumonia.

Important strengths of our study included a large sample size and the use of multivariate techniques to adjust for confounders. It also had limitations. First, the study population involved only male veterans who were hospitalized; therefore, the results are not generalizable to women or ambulatory patients with CAP. Secondly, participants treated or readmitted after discharge in a non-Veterans Administration Healthcare System were not captured. Thirdly, a large number of CAP diagnoses had unspecified pathogens possibly because of the limitations of using ICD-9 codes for microbiological CAP categorization, consistent with preceding reports concluding that identifying the microbiological pathogen in many patients with CAP continued to be problematic [33–39]. Although *S. pneumoniae* had been the most commonly identified aetiology of bacterial pneumonia among HIV-infected patients [9] and was found to be associated with a high rate of complications, approximately one-third of cases remained microbiologically undiagnosed despite significant efforts and the usage of the most reliable diagnostic testing [9,36–39]. In this

study, almost 85% of diagnoses were classified as unspecified, but more than 96.4% of the participants received appropriate respiratory tract-targeted antibiotics based on the classification adopted from the Infectious Diseases Society of America guidelines [19]. Although a prior study of pneumococcal vaccine suggested that it was protective against pneumonia among HIV-infected patients [40], the lack of data regarding pneumococcal and influenza vaccination in our data set during the study period prevented additional analyses of their impact on the clinical outcomes.

In summary, our findings highlighted the clinical value of the VACS Index score in prognostic evaluation of CAP adverse outcomes among older adults with or without HIV infection. We also showed the positive impact of ART among older HIV-infected adults hospitalized for CAP independent of its effect on CD4 count or HIV viral load. As the number of older adults with HIV infection increases, future efforts should be focused on strategies to reduce adverse clinical outcomes for pneumonia and other common nonopportunistic infections.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV infection and older Americans: the public perspective. Am J Public Health. 2012; 102:1516–1526. [PubMed: 22698038]
2. The CASCADE Collaboration. Survival after introduction of HAART in people with known duration of HIV-1 infection. Lancet. 2000; 355:1158–1159. [PubMed: 10791383]
3. Center of Disease Control and Prevention. HIV Surveillance Report. 2011; 23
4. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. Chest. 2001; 120:1888–1893. [PubMed: 11742918]
5. Crothers K, Thompson BW, Burkardt K, et al. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. Proc Am Thorac Soc. 2011; 8:275–281. [PubMed: 21653528]
6. Murray JF, Felton CP, Garay SM, et al. Pulmonary complications of the acquired immunodeficiency syndrome. N Engl J Med. 1984; 310:1682–1688. [PubMed: 6328301]
7. Bartlett JG. Pneumonia in the patient with HIV infection. Infect Dis Clin North Am. 1998; 12:807–820. [PubMed: 9779391]
8. Meduri GU, Stein DS. Pulmonary manifestations of acquired immunodeficiency syndrome. Clin Infect Dis. 1992; 14:98–113. [PubMed: 1571469]
9. Madeddu G, Porqueddo EM, Cambosu F, et al. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. Infection. 2008; 36:231–236. [PubMed: 18463787]
10. Curran A, Falco V, Crespo M, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. HIV Med. 2008; 9:609–615. [PubMed: 18557951]

11. Tumbarello M, Tacconelli E, de Gaetano K, et al. Bacterial pneumonia in HIV-infected patients: analysis of risk factors and prognostic indicators. J Acquir Immune Defic Syndr Hum Retrovirol. 1998; 18:39–45. [PubMed: 9593456]
12. Chew KW, Yen IH, Li JZ, Winston LG. Predictors of pneumonia severity in HIV-infected adults admitted to an urban public hospital. AIDS Patient Care STD. 2011; 25:273–277.
13. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. Int J Infect Dis. 2010; 14:e22–e27. [PubMed: 19586789]
14. Feldman C, Klugman KP, Yu VL, et al. Bacteremic pneumococcal pneumonia: impact of HIV on clinical presentation and outcome. J Infect. 2007; 55:125–135. [PubMed: 17524486]
15. Neiderman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2001; 163:1730–1754. [PubMed: 11401897]
16. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with human immunodeficiency virus. N Engl J Med. 1995; 333:845–851. [PubMed: 7651475]
17. Christensen D, Feldman C, Rossi P, 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. [PubMed: 16028168]
18. Bartlett JG, Breiman RF, Mandell LA, File TM. Community-acquired pneumonia in adults: guidelines for management. Clin Infect Dis. 1998; 26:811–838. [PubMed: 9564457]
19. Mandell LA, Wunderink RG, Azueto A, et al. Infectious Disease Society of America /American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007; 44(Suppl 2):S27–S72. [PubMed: 17278083]
20. Fultz SL, Skanderson M, Mole LA, et al. Development and verification of a ‘virtual’ cohort using the National VA Health Information System. Med Care. 2006; 44(8 Suppl 2):S25–S30. [PubMed: 16849965]
21. Tate JP, Justice AC, Hughes MD, et al. An internationally generalizable risk index for mortality after one year of antiretroviral therapy. AIDS. 2013; 27:563–572. [PubMed: 23095314]
22. Justice AC, Modur SP, Tate JP, et al. for the NA-ACCORD and VACS Project Teams. Predictive Accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. J Acquir Immune Defic Syndr. 2013; 62:149–163. [PubMed: 23187941]
23. Akgün KM, Tate JP, Pisani M, et al. Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era. Crit Care Med. 2013; 41:1458–1467. [PubMed: 23507717]
24. Justice AC, Freiberg MS, Tracy R, et al. Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? Clin Infect Dis. 2012; 54:984–994. [PubMed: 22337823]
25. Aronsky D, Haug PJ, Lagor C, Dean NC. Accuracy of administrative data for identifying patients with pneumonia. Am J Med Qual. 2005; 20:319–328. [PubMed: 16280395]
26. Perez JL, Moore RD. Greater effect of highly active antiretroviral therapy on survival in people aged >or =50 years compared with younger people in an urban observational cohort. Clin Infect Dis. 2003; 36:212–218. [PubMed: 12522755]
27. Shah S, Mildvan D. HIV and aging. Curr Infect Dis Rep. 2006; 8:241–247. [PubMed: 16643776]
28. Effros RB, Fletcher CV, Gebo K, et al. Workshop on HIV infection and aging: what is known and future research directions. Clin Infect Dis. 2008; 47:542–553. [PubMed: 18627268]
29. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary disease in the combination antiretroviral therapy era. Am J Respir Crit Care Med. 2011; 183:388–395. [PubMed: 20851926]
30. Goulet JL, Fultz S, Rimland D, et al. Do patterns of comorbidity vary by HIV status, age, and HIV severity? Clin Infect Dis. 2007; 45:1593–1601. [PubMed: 18190322]
31. Backus LI, Boothroyd DB, Phillips BR, et al. National Quality Forum performance measures for HIV/AIDS care: the Department of Veterans Affairs’ experience. Arch Intern Med. 2010; 170:1239–1246. [PubMed: 20660844]

32. Justice AC. HIV and aging: time for a new paradigm. Curr HIV/AIDS Rep. 2010; 7:69–76. [PubMed: 20425560]
33. Polsky B, Gold JWM, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. Ann Intern Med. 1986; 104:38–41. [PubMed: 3484420]
34. Frankel RE, Virata M, Hardalo C, Altice FL, Friedland G. Invasive pneumococcal disease: clinical features, serotypes, and antimicrobial resistance patterns in cases involving patients with and without Human Immunodeficiency Virus Infection. Clin Infect Dis. 1996; 23:577–584. [PubMed: 8879783]
35. Baril L, Astagneau P, Nguyen J, et al. Pyogenic bacterial pneumonia in human immunodeficiency virus-infected inpatients: a clinical, radiological, microbiological, and epidemiological study. Clin Infect Dis. 1998; 26:964–971. [PubMed: 9564484]
36. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. AIDS. 2002; 16:85–95. [PubMed: 11741166]
37. Wallace JM, Rao AV, Glassroth J, et al. Respiratory illness in persons with human immunodeficiency virus infection. Am Rev Respir Dis. 1993; 148:1523–1529. [PubMed: 8256894]
38. Viale P, Scudeller L, Signorini L, et al. HIV- associated community-acquired pneumonia in the highly active antiretroviral therapy era. AIDS. 2002; 16:2361–2362. [PubMed: 12441819]
39. Hull MW, Phillips P, Montaner JSG. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. Chest. 2008; 134:1287–1298. [PubMed: 19059959]
40. Rodriguez-Barradas MC, Goulet J, Brown S, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the veterans aging cohort 5-site study. Clin Infect Dis. 2008; 46:1093–1100. [PubMed: 18444830]

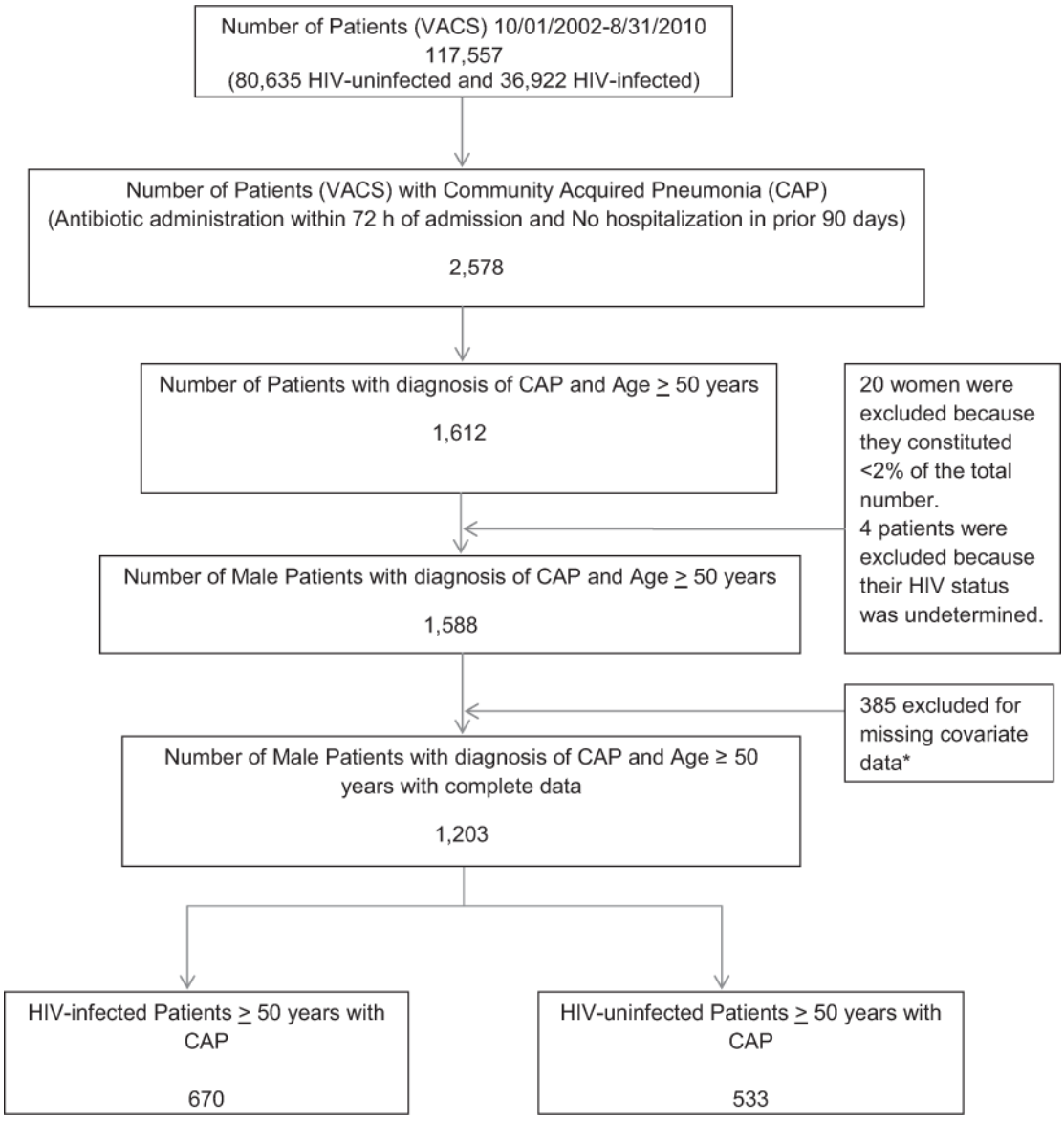


**Fig. 1.**

The Veterans Aging Cohort Study (VACS) community-acquired pneumonia (CAP) cohort. *Race, smoking status, pulmonary comorbidity, alcohol-related and drug-related diagnoses within the year prior to admission and VACS Index score.

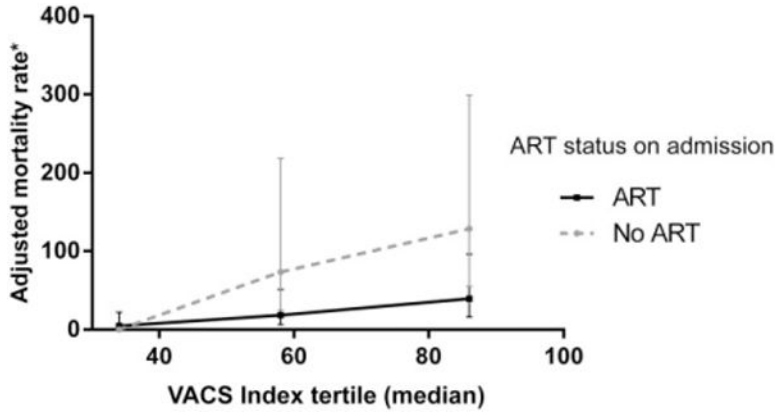


**Fig. 2.**

Adjusted 30-day mortality rate by Veterans Aging Cohort Study (VACS) Index and antiretroviral therapy (ART). *Deaths/1000 person-months and 95% confidence interval, adjusted for race, smoking status, pulmonary comorbidity, and alcohol-related and drug-related diagnoses within the year prior to admission.

**Table 1**

Veterans Aging Cohort Study (VACS) Index score

| Component Variable | Value | Point Scored |
|---|---|---|
| Age (years) | < 50 | 0 |
| | 50 to 64 | 12 |
| | ≥ 65 | 27 |
| HIV components | | |
| CD4 count (cells/μL) | ≥ 500 | 0 |
| | 350 to 499 | 6 |
| | 200 to 349 | 6 |
| | 100 to 199 | 10 |
| | 50 to 99 | 28 |
| | < 50 | 29 |
| HIV-1 RNA (copies/ml) | < 500 | 0 |
| | 500 to 99,999 | 7 |
| | ≥ $1 \times 10^5$ | 14 |
| Organ system components | | |
| Haemoglobin (g/dL) | ≥ 14 | 0 |
| | 12 to 13.9 | 10 |
| | 10 to 11.9 | 22 |
| | < 10 | 38 |
| FIB-4 | < 1.45 | 0 |
| | 1.45 to 3.25 | 6 |
| | >3.25 | 25 |
| eGFR (mL/min) | ≥ 60 | 0 |
| | 45 to 59.9 | 6 |
| | 30 to 44.9 | 8 |
| | < 30 | 26 |
| Hepatitis C virus coInfection | | 5 |

ALT, alanine transaminase; AST, aspartate transaminase; FIB-4, fibrosis index: (years of age × AST)/(platelets × square root ALT); eGFR, estimated glomerular filtration rate. Contents of this table are derived from www.vacohort.org.

**Table 2**

Characteristics of 1203 male veterans (HIV-infected and uninfected) hospitalized with community-acquired pneumonia (CAP)

| | Total | | HIV-infected | | HIV-uninfected | | |
|---|---|---|---|---|---|---|---|
| **Characteristic** | ***n*** | **%** | ***n*** | **%** | ***n*** | **%** | ***P**** |
| Number of patients | | | 670 | 55.7 | 533 | 44.3 | |
| Age category (years at admission) | | | | | | | < 0.001 |
| 50–64 years | 1021 | 84.9 | 600 | 89.6 | 421 | 79.0 | |
| ≥ 65 years | 182 | 15.1 | 70 | 10.4 | 112 | 21.0 | |
| Race | | | | | | | 0.049 |
| Non-white | 679 | 56.4 | 395 | 59.0 | 284 | 53.3 | |
| White | 524 | 43.6 | 275 | 41.0 | 249 | 46.7 | |
| Smoking status | | | | | | | 0.162 |
| Current | 780 | 64.8 | 448 | 66.9 | 332 | 62.3 | |
| Past | 196 | 16.3 | 98 | 14.6 | 98 | 18.4 | |
| Never | 227 | 18.9 | 124 | 18.5 | 103 | 19.3 | |
| Pulmonary comorbidity | | | | | | | 0.040 |
| Yes | 135 | 11.2 | 64 | 9.6 | 71 | 13.3 | |
| Alcohol-related diagnosis within the year prior to admission | | | | | | | 0.075 |
| Yes | 215 | 17.9 | 108 | 16.1 | 107 | 20.1 | |
| Drug-related diagnosis within the year prior to admission | | | | | | | 0.021 |
| Yes | 210 | 17.5 | 132 | 19.7 | 78 | 14.6 | |
| Type of pneumonia (principal diagnostic code) | | | | | | | 0.811 |
| Viral | 23 | 1.9 | 14 | 2.1 | 9 | 1.7 | |
| Bacterial | 163 | 13.6 | 93 | 13.9 | 70 | 13.1 | |
| Unspecified | 1017 | 84.5 | 563 | 84.0 | 454 | 85.2 | |
| 30-day mortality (died) | 64 | 5.3 | 37 | 5.5 | 27 | 5.1 | 0.726 |
| Readmission within 30 days of discharge (readmitted)[†] | 151 | 13.2 | 91 | 14.3 | 60 | 11.8 | 0.218 |
| | ***n*** | **Mean (SD)** | ***n*** | **Mean (SD)** | ***n*** | **Mean (SD)** | ***P**** |
| Length of stay (days) | 1203 | 7.3 (9.9) | 670 | 7.1 (10.1) | 533 | 7.5 (9.7) | 0.435 |
| VACS Index score[‡] | 1203 | 52.2 (24.4) | 670 | 60.1 (25.1) | 533 | 42.3 (19.6) | < 0.001 |

| Characteristic | Total | | HIV-infected | | HIV-uninfected | | |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *P*[*] |
| Organ system components | | | 670 | 32.7 (19.4) | 553 | 27.2 (17.5) | < 0.001 |
| HIV components | | | 670 | 13.8 (12.6) | NA | NA | |
| | | | **VACS Index score** | | | | |
| | | | *n* | **Mean (SD)** | | | |
| CD4 count | | | | | | | |
| ≥ 500 cells/μL | | | 152 | 42.3 (18.9) | NA | NA | |
| 350–499 cells/μL | | | 117 | 54.2 (21.3) | NA | NA | |
| 200–349 cells/μL | | | 161 | 59.1 (19.9) | NA | NA | |
| 100–199 cells/μL | | | 109 | 62.1 (22.5) | NA | NA | |
| 50–99 cells/μL | | | 62 | 82.5 (21.4) | NA | NA | |
| < 50 cells/μL | | | 69 | 88.1 (20.8) | NA | NA | |
| HIV viral load | | | | | | | |
| < 500 copies/mL | | | 358 | 51.4 (22.5) | NA | NA | |
| 500–99,999 copies/mL | | | 231 | 64.7 (22.6) | NA | NA | |
| ≥ $10^5$ copies/mL | | | 81 | 85.0 (22.2) | NA | NA | |
| Antiretroviral therapy (on admission) | | | | | | | |
| Yes | | | 548 | 57.8 (24.4) | NA | NA | |
| No | | | 122 | 70.2 (25.5) | NA | NA | |

NA, not applicable; VACS, Veterans Aging Cohort Study.

[*] *t*-test for VACS Index; $\chi^2$ test for all proportions.

[†] Excluding those who died during hospitalization or were lost to follow-up.

[‡] Component scores do not sum to the VACS Index score because there is an additional age component (see Table 1).

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**Table 3**

Multivariable association between Veterans Aging Cohort Study (VACS) Index score and outcomes in 1203 HIV-infected and uninfected male veterans hospitalized with community-acquired pneumonia

| | Time to death within 30 days of admission† *n* = 1203 (64 deaths) | | Readmission within 30 days of discharge‡ *n* = 1147 (151 readmissions) | | Length of stay (days)§ *n* = 1203 | |
|---|---|---|---|---|---|---|
| **Variable** | **HR (95% CI)** | ***P*** | **OR (95% CI)** | ***P*** | **Slope (95% CI)** | ***P*** |
| VACS Index score | 1.17 (1.12,1.23) | < 0.001 | 1.08 (1.05, 1.12) | < 0.001 | 0.24 (0.12, 0.36) | < 0.001 |
| **Model 2: HIV-uninfected participants only** * | | | | | | |
| | ***n* = 533** | | ***n* = 509** | | ***n* = 533** | |
| VACS Index score | 1.20 (1.10, 1.32) | < 0.001 | 1.13 (1.05, 1.21) | < 0.001 | 0.30 (0.08, 0.52) | 0.006 |
| **Model 3: HIV-infected participants only** * | | | | | | |
| | ***n* = 670** | | ***n* = 638** | | ***n* = 670** | |
| VACS Index score | 1.20 (1.13,1.28) | < 0.001 | 1.07 (1.02, 1.12) | 0.003 | 0.29 (0.13, 0.45) | < 0.001 |
| **Model 4: HIV-infected participants only (VACS index and ART analysis)** * | | | | | | |
| | ***n* = 670** | | ***n* = 638** | | ***n* = 670** | |
| VACS Index score | 1.19 (1.12,1.26) | < 0.001 | 1.07 (1.02, 1.12) | 0.003 | 0.25 (0.09, 0.85) | 0.001 |
| No ART versus ART | 2.94 (1.51, 5.72) | 0.002 | 1.12 (0.62, 2.00) | 0.714 | 2.69 (0.65, 4.73) | 0.008 |
| **Model 5: HIV-infected participants only (VACS Index components and ART analysis)** ¶ | | | | | | |
| | ***n* = 670** | | ***n* = 638** | | ***n* = 670** | |
| VACS Index score (HIV components)# | 1.10 (0.97,1.24) | 0.138 | 1.02 (0.93, 1.12) | 0.625 | 0.22 (0.1, 0.54) | 0.161 |
| VACS Index score (Organ System Components)# | 1.23 (1.14, 1.33) | < 0.001 | 1.10 (1.04, 1.17) | 0.001 | 0.25 (0.05, 0.45) | 0.014 |
| No ART versus ART | 3.22 (1.63, 6.36) | < 0.001 | 1.16 (0.64, 2.09) | 0.627 | 2.73 (0.69, 4.77) | 0.008 |

All models include VACS Index and component scores in five-point increments.

ART, antiretroviral therapy; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

[*] Models adjusted for race, smoking status, pulmonary comorbidity, and alcohol-related and drug-related diagnoses within the year prior to admission.

[†] Time-to-event Cox regression model.

[‡] Logistic regression model.

[§] General linear regression model.

[¶] Models additionally adjusted for race, smoking status, pulmonary comorbidity, alcohol-related and drug-related diagnoses within the year prior to admission and age 50–64/≥ 65 years.

[#] See Table 1 for definitions.