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Survival for Patients with Human Immunodeficiency Virus Admitted to the Intensive Care Unit Continues to Improve in the Current Era of Highly Active Antiretroviral Therapy

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Abstract

Background—The highly active antiretroviral therapy (ART) era (1996-present) has been associated with improved survival among HIV-infected outpatients, but ICU data from 2000-present are limited.

Methods—We conducted a retrospective study of HIV-infected adults admitted to the ICU at San Francisco General Hospital (2000-2004). The primary outcome was survival to hospital discharge.

Results—During the 5-year study period, there were 311 admissions for 281 patients. Respiratory failure remained the most common indication for ICU admission (42% overall), but the proportion of patients with respiratory failure decreased each year from 52% to 34% (p = 0.02). Hospital survival rates significantly increased during the 5-year period (p = 0.001). ART use at admission was not associated with survival, but it was associated with higher CD4 cell counts, lower plasma HIV RNA levels, higher serum albumin, and lower proportions of AIDS-associated admission diagnoses and PCP. In multivariate analysis, a higher serum albumin level (Adjusted Odds Ratio, AOR = 2.08, 95% Confidence Interval, CI = 1.41-3.06, p = 0.002) and absence of mechanical ventilation (AOR = 6.11, 95% CI = 2.73-13.72, p < 0.001) were associated with survival.

Conclusions—In this sixth in a series of consecutive studies started in 1981, we found that the epidemiology of ICU admission diagnoses continues to change. Our study also found that survival for critically ill HIV-infected patients continues to improve in the current era of ART. Although ART

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use was not associated with survival, it was associated with predictors that were associated with survival in multivariate analysis.

Keywords

acquired immune deficiency syndrome; highly active antiretroviral therapy; human immunodeficiency virus; intensive care; mechanical ventilation; outcomes; respiratory failure

Introduction

The introduction of human immunodeficiency virus (HIV) protease inhibitors in 1996 heralded the highly active antiretroviral therapy (ART) era and was associated with improved survival among HIV-infected outpatients.[1] Studies from San Francisco during this early period (1996-1999) found that use of ART was also associated with improved survival among HIV-infected patients admitted to the intensive care unit (ICU).[2, 3] However, more recent studies from New York and London found that survival of these patients is independent of ART,[4-7] raising the question of whether ART use is associated with survival in the current period. In the absence of prospective randomized clinical trials to guide intensive care of HIV-infected patients, outcome-focused observational studies can provide important information.[8]

ICU admission diagnoses and survival among HIV-infected patients have changed throughout the HIV epidemic. In the 1980s and early-to-mid 1990s, *Pneumocystis* pneumonia (PCP) was responsible for a high burden of disease, and survival was low;[9-15] later studies demonstrated improved survival, even among PCP patients.[2, 3, 16, 17] Although respiratory failure has remained the most common indication for ICU admission,[2, 5, 7] PCP incidence has decreased.[4, 17] In the early HAART era (1996-1999), ICU admissions due to HIV-associated conditions decreased.[18] However, few studies have reported on the current ART era (2000-present),[6, 7, 19] and it is unknown whether ICU admission diagnoses and survival continue to change.

Therefore, we conducted a retrospective cohort study of HIV-infected patients admitted to the ICU at San Francisco General Hospital in the current ART era. Our goals were to identify trends in ICU admission diagnoses and survival, to compare clinical characteristics and outcome in patients according to ART use, and to determine the predictors of survival in the current ART era. Earlier results of this study were presented in abstract form.[20]

Methods

Study Design and Subjects

We conducted a retrospective cohort study of all HIV-infected adults admitted to the ICU at San Francisco General Hospital (SFGH) from 2000 through 2004. SFGH is an urban public hospital, with 375 beds and 30 intensive care beds. A computerized search of SFGH ICU admissions using the Ninth International Classification of Diseases (ICD-9) diagnostic code for HIV (042) identified patients with HIV admitted to the ICU. The University of California, San Francisco Committee on Human Research approved the study protocol.

Data collection

Investigators (KP, LD, AC) reviewed medical records of patients using standardized chart abstraction forms.[2, 17] If patients were re-admitted to the ICU during the same hospitalization, only the data from the first admission were recorded. ICU admission diagnoses and AIDS (acquired immune deficiency syndrome)-associated illnesses were classified using a predetermined list identical to prior studies.[2, 17] ART was defined as the use of at least two classes of antiretroviral drugs [21] at the time of hospital admission. Clinical information included

demographics, CD4 count and plasma HIV RNA if available within six months of admission (usually available within one month), and serum albumin within one week of hospital admission, and need for mechanical ventilation. We calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II scores.[22] The primary outcome was survival to hospital discharge. Data were entered into a customized database (Microsoft Access 2003, Redmond, WA) and subjected to electronic validation rules.

Statistical analysis

SAS version 9.0 (SAS Institute, Cary, NC) was used for statistical analysis. Statistical significance was predetermined in reference to a p-value of <0.05. Continuous data were compared using the Student's t-test or the Wilcoxon rank sum test, and comparisons of frequencies were made with the chi-squared test or Fisher's exact test. We used linear regression to assess trends in the yearly proportions of patients with each characteristic of interest (ICU admission diagnosis, diagnosis of an AIDS-associated illness or PCP, use of ART at admission, and survival). To describe the epidemiology of patients in the current era, we compared patient characteristics according to use of ART at hospital admission. To identify predictors of survival, we compared survivors with non-survivors. Unadjusted odds ratios for survival were computed for each candidate variable. Variables with p-values <0.20 for the appropriate test were included in model-building procedures in logistic regression.[23] Subset selection and backwards elimination multivariate logistic regression were used to determine the most parsimonious variables, using all available data. Final model fit was assessed using the Hosmer-Lemeshow and specification tests.[24]

Results

There were 311 ICU admissions for 281 patients. Twenty-five patients (9%) had more than one ICU admission during the 5-year study period. Because few patients had repeat ICU admissions, each ICU admission that occurred during a subsequent hospitalization was treated as a separate event. The predictors of survival identified from the multivariate analysis were unchanged if these repeat patient admissions were excluded.

Trends in ICU admission diagnoses and survival

The annual number of ICU admissions ranged from 50 in 2000 to a peak of 75 in 2002 (Table 1). Respiratory failure remained the most common indication for ICU admission (42% overall), but the proportion of patients with respiratory failure decreased each year from 52% in 2000 to 34% in 2004 (p = 0.02). Although the proportion of patients with an AIDS-associated diagnosis plateaued during the study period (p = 0.17), the proportion with PCP significantly decreased from 24% to 9% (p = 0.03). In contrast, hospital survival rates increased over the study period, peaking at 77% in 2003 (p = 0.001) while the proportion of patients on ART remained stable (p = 0.11).

Patient characteristics and use of HAART at the time of admission

Overall, 101 of 306 patients (33%) with available data were using ART at the time of hospital admission (Table 2). This number included six patients admitted to the ICU for complications arising from ART. No patient was started on ART in the ICU.

Patients on ART were similar to those not on ART with respect to age, gender, race/ethnicity, and HIV risk factor. Patients on ART were more likely than non-ART patients to have a history of prior HIV-associated opportunistic infection, PCP, and malignancy (p-value for all comparisons < 0.05). ART-users had a significantly higher median CD4 count (141 cells/ul versus 95 cells/ul, p = 0.021) and a significantly lower mean log viral load (3.71 log copies/ml versus 4.81 log copies/ml, p < 0.001) than non-ART-users. ART patients had significantly

higher mean serum albumin levels but similar median serum lactate dehydrogenase levels and median APACHE II scores compared to non-ART patients.

Overall, 21% of patients presented to the ICU with an AIDS-associated diagnosis, two-thirds of whom presented with PCP. A significantly lower proportion of patients on ART presented with an AIDS-associated admission diagnosis compared to patients not on ART (12% versus 25%, $p = 0.008$). Similarly, a significantly lower proportion of ART-users presented with PCP compared to non ART-users (3% versus 19%, $p < 0.001$). Only three patients who were on ART had PCP (7% of 42 PCP cases).

Respiratory failure was the most common ICU admission diagnosis for all patients (42%), and was equally frequent among patients on ART (40%) and those not on ART (44%). PCP was the most common etiology of respiratory failure (28%) but was significantly less frequent among patients on ART (8% of respiratory failure admissions) than among those not on ART (38% of respiratory failure admissions, $p = 0.002$). Among non-ART-users, PCP was the most common cause of respiratory failure. In contrast, among ART-users, obstructive airways disease was the most common cause of respiratory failure.

Other indications (GI bleeding, cardiac indications, metabolic disorders, traumatic injuries, and post-operative care) were aggregately the second most common indication for ICU admission for patients who were on ART (28%).

In contrast, sepsis was the second most common indication for ICU admission among patients not on ART (22%). Among patients with a diagnosis of sepsis, the etiologic agent was unknown for 40% of patients. Few patients had pneumococcal or staphylococcal infections; these infections accounted for 8% and 13% of sepsis admissions, respectively. The most common etiologic agents identified were gram negative rods (18% of sepsis admissions).

Overall survival was high (69%) and was comparable between patients on ART and those not on ART. Respiratory failure, PCP, and GI bleeding were associated with the lowest rates of survival compared to all other diagnoses (Figure 1). However, survival was greater than fifty percent in every diagnosis category.

Predictors of survival to hospital discharge

In univariate analyses, there were no differences between survivors and non-survivors with respect to age, gender, race/ethnicity, medical history, ART use, PCP prophylaxis use, CD4 count, log viral load, or AIDS-associated admission diagnosis (all p-values > 0.05). Injection drug users and patients with other/unknown HIV risk factors (e.g., heterosexual sex) had increased survival compared to men who have sex with men (Table 3). A higher serum albumin level or lower APACHE II score was associated with survival. In contrast, the need for mechanical ventilation, respiratory failure as an admission diagnosis (compared to all other diagnoses), and PCP (compared to no PCP) were all associated with decreased survival.

In multivariate analysis, higher serum albumin level and absence of mechanical ventilation were associated with survival (Table 3). No interaction was identified between covariates. Because of collinearity between APACHE II scores and albumin, and APACHE II scores and mechanical ventilation, we first excluded APACHE II scores from logistic regression modeling. When APACHE II scores were included in logistic regression, and albumin and mechanical ventilation were excluded due to collinearity, only APACHE II scores remained significantly associated with survival in backwards selection.

Discussion

This study is notable in that it is the sixth in a series of consecutive studies started in 1981 to examine the critical care provided to HIV-infected patients at SFGH.[9, 12, 13, 17, 2] In addition, our study is among the few studies to examine HIV patients admitted to the ICU since the year 2000, and we have noted several important trends. Our study shows that in the current era of ART, respiratory failure remains the most common indication for ICU admission but the proportion with respiratory failure has decreased. In addition, the proportion with PCP has decreased. Compared to our previous study, AIDS-associated illnesses are less common (from 37% to 21%).[2] While the use of ART has increased since the previous study (from 25% to 33%),[2] the yearly proportions of patients on ART in our present study remains stable. Although ART use at admission was not associated with survival, it was associated with lower proportions of AIDS-associated admission diagnoses and PCP and a higher serum albumin, which was associated with survival in multivariate analysis. Finally, our study shows that survival for critically ill HIV-infected patients continues to improve in the current era of ART.

The improved survival in our ICU-based study mirrors the trends in other ICU cohorts. For example, a study from London (1999-2005) reported an overall hospital survival rate of 68% in their HIV-infected ICU patients, which was comparable to the overall survival rate of 65% in their non-HIV general medical ICU patients,[7] and nearly identical to that in our study (69%). Regrettably, no data were presented in the London study to examine whether the hospital survival rate improved during their study period as it did in our present study. We believe that the improved survival during our study period relates at least in part to the decreased proportions with respiratory failure requiring mechanical ventilation and with PCP. The need for mechanical ventilation and PCP are well-recognized predictors associated with a decreased survival,[2, 5, 6] and in our study, these diagnoses were associated with among the lowest survival. However, it is also possible that general improvements in ICU care may have contributed to the improved survival. Our study period coincided with the adoption of low tidal volumes for acute lung injury,[25] early-goal directed therapy for sepsis,[26] and intensive insulin therapy.[27] However, we did not record systematically which patients received these interventions, so their potential effects on survival in critically ill HIV-infected patients remain unknown.

The improved survival in our study appears to be independent of the use of ART. In our study, patients receiving ART had a survival of 67% compared to 70% in those patients not receiving ART. This finding is similar to those from recent studies in New York and London.[4, 6] In the New York study, these proportions were 51% compared to 49%, while in the London study, the proportions were 67% compared to 66%. While the long-term benefits of ART on survival among HIV-infected outpatients are indisputable, there may be no short-term benefits in ICU patients with critical illness. Since we did not collect information on adherence to ART prior to ICU admission, and our observational study did not measure antiretroviral drug resistance, the impact of non-adherence or drug resistance as explanations cannot be excluded. However, it is also possible that the effects of ART are mediated by its impact on CD4 cell count, plasma HIV RNA level, serum albumin and, most importantly, by its impact on ICU admission diagnosis (AIDS-associated, PCP), all of which were associated with ART use in our study.

We acknowledge that our study has several limitations. First, we conducted our study at a single institution, in an urban public hospital; since clinical practice and demographics may differ across institutions, the external validity of our study may be limited. However, since we used the same protocol and data collection instrument in this study as in our prior study,[2] our comparisons between the early ART era and the current era at SFGH are internally valid. Second, we did not follow patients after hospital discharge; therefore, the predictors of long-term survival and any impact of ART on long-term survival remain unknown. Given the

retrospective nature of our study design, we chose to focus on survival to hospital discharge, where we had information on all patients, rather than on longer term survival, where we would have had missing data due to losses to follow-up. Third, patients were admitted with a broad spectrum of critical illnesses and received heterogeneous treatments, limiting our conclusions regarding the independent effects of any specific treatment or intervention. Studies that examine specific patient subsets (e.g., those with respiratory failure and acute lung injury) are better suited to examine the impact of a specific intervention (e.g., low tidal volume ventilation). Next, measurement error inherent to our study design may have limited our ability to identify an association between CD4 cell count or plasma HIV RNA level and survival, since these potential predictors were obtained at different time points prior to ICU admission. Finally, the observational nature of our study limits any firm conclusions regarding ART use and survival. Patients on ART at the time of ICU admission were potentially different than patients not on ART with respect to unmeasured characteristics.

Despite these limitations, this study of HIV-infected patients admitted to the SFGH ICU represents the latest in a consecutive series of studies that started in 1981 and is, to our knowledge, the only institutional series spanning the entire HIV/AIDS epidemic. We found that survival for critically ill HIV-infected patients continues to improve in the current era of ART. We also found that the improved survival appeared to be independent of the use of ART. In multivariate analysis, the absence of the need for mechanical ventilation and higher serum albumin levels were both independent predictors associated with improved survival. Further study of critically ill HIV patients may help confirm these trends.

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Abbreviations

HIV, Human immunodeficiency virus; ART, Highly active antiretroviral therapy; ICU, Intensive care unit; PCP, *Pneumocystis* pneumonia; SFGH, San Francisco General Hospital; ICD-9, Ninth International Classification of Diseases; AIDS, acquired immune deficiency syndrome; APACHE, Acute Physiology and Chronic Health Evaluation.

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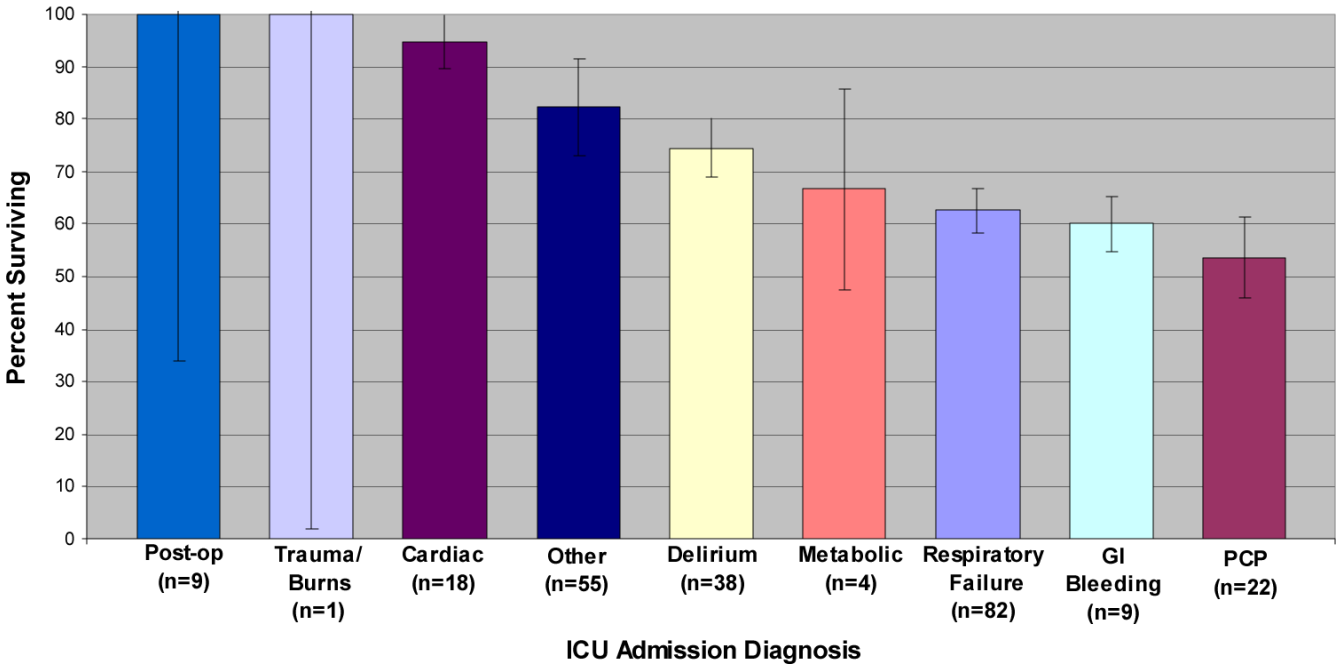

Figure 1.

Proportions* of HIV-infected Patients Surviving 311 Hospitalizations in the ICU, By Admission Diagnosis

Legend:*Per 100 ICU admissions, with bars displaying standard errors. n = number of patients who survived

Table 1

Admissions, ICU diagnoses, ART use, and survival among 311 ICU admissions of HIV-infected patients, according to study year*

		Year of Enrollment					
	Total	**2000**	**2001**	**2002**	**2003**	**2004**	**P-value†**
Admissions	311	50	52	75	66	68	
ICU Diagnosis (%)							0.02
Respiratory Failure	131 (42)	26 (52)	24 (46)	32 (43)	26 (39)	23 (34)	
Sepsis	62 (20)	11 (22)	9 (17)	14 (19)	11 (17)	17 (25)	
Neurologic	51 (16)	7 (14)	8 (15)	13 (17)	16 (24)	7 (10)	
Other	67 (22)	6 (12)	11 (21)	16 (21)	13 (20)	21 (31)	
AIDS-associated (%)	65 (21)	17 (34)	9 (17)	12 (16)	14 (21)	13 (19)	0.17
PCP diagnosis (%)	43 (14)	12 (24)	8 (15)	8 (11)	9 (14)	6 (9)	0.03
ART use (%)	101 (33)	18 (37)	16 (31)	26 (35)	16 (24)	25 (37)	0.11
Survival (%)	215 (69)	29 (58)	31 (60)	53 (71)	51 (77)	51 (75)	0.001

Definitions of abbreviations: AIDS = acquired immunodeficiency disease syndrome; ART = highly active antiretroviral therapy; ICU = intensive care unit; PCP = *Pneumocystis* pneumonia.

**Legend:* Data are presented as numbers unless otherwise indicated.

†P-values correspond to the F-statistic for linear regression. Linear trend was concluded if $p < 0.05$.

Table 2

Characteristics of HIV-infected patients during 306 admissions to the ICU at San Francisco General Hospital, 2000 - 2004, according to use of ART at the time of hospital admission

Characteristic	All patients (n = 306)	No ART (n = 205)	ART (n = 101)	P-value
Age, years, mean (range)	44 (24-72)	43 (24-71)	46 (25-72)	0.65
Gender*, n (%)				0.078
Male	235 (79.7)	152 (76.8)	83 (85.6)	
Female	60 (20.3)	46 (23.2)	14 (14.4)	
Race/ethnicity, n (%)				0.30
White	125 (40.9)	79 (38.5)	46 (45.5)	
African American	115 (37.6)	77 (37.6)	38 (37.6)	
Other/unknown	66 (21.6)	49 (23.9)	17 (16.8)	
HIV risk factor, n (%)				0.14
Men who have sex with men	54 (17.7)	30 (14.6)	24 (23.8)	
Users of injection drugs	170 (55.6)	118 (57.6)	52 (51.5)	
Other/unknown	82 (26.8)	57 (27.8)	25 (24.8)	
Medical history, n (%)				
History of prior opportunistic infection	172 (57.7)	104 (52.3)	68 (68.7)	0.007
History of PCP	63 (21.1)	35 (17.6)	28 (28.3)	0.033
History of malignancy	39 (13.0)	17 (8.5)	22 (22.0)	0.001
PCP prophylaxis at time of admission	141 (46.5)	69 (33.8)	71 (72.7)	<0.001
Clinical data				
CD4 count†, cells/ul, median (IQR)	109 (211)	95 (213)	141 (198)	0.021
HIV viral load‡, copies/ml, mean log (SD)	4.47 (1.72)	4.81 (0.97)	3.71 (1.37)	<0.001
Albumin§, g/dl, mean (SD)	2.7 (0.8)	2.6 (0.8)	2.9 (0.9)	0.006
LDH//, U/L, median (IQR)	320 (288)	352 (304)	449 (223)	0.087
APACHE II score**, median (IQR)	22 (14)	22 (12)	22 (16)	0.34
Mechanical ventilation, n (%)	205 (67.7)	143 (70.1)	62 (62.6)	0.19
AIDS-associated admission diagnosis, n (%)	63 (20.6)	51 (24.9)	12 (11.9)	0.008
PCP diagnosis, n (%)	42 (13.8)	39 (19.0)	3 (3.0)	<0.001
Admission diagnosis, n (%)				
Respiratory failure	130 (42.3)	90 (43.9)	40 (39.6)	
Sepsis	62 (20.3)	45 (22.0)	17 (16.8)	
Neurologic	50 (16.3)	34 (16.6)	16 (15.8)	
Other	64 (21.1)	36 (17.6)	28 (27.7)	
Survival, n (%)	212 (69.3)	144 (70.2)	68 (67.3)	0.70

Definition of abbreviations: AIDS = acquired immunodeficiency virus; APACHE = Acute Physiology and Chronic Health Evaluation; ART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; ICU = intensive care unit; IQR = interquartile range; LDH = lactate dehydrogenase; n = number; PCP = *Pneumocystis* pneumonia.

* *Legend:* Five transgender patients were excluded from gender-stratified analysis.

† Data were available for 265 admissions.

[‡] Data were available for 211 admissions.

[§] Data were available for 273 admissions.

[//] Data were available for 184 admissions.

[**] Data were available for 261 admissions.

Table 3

Univariate and multivariate predictors of survival-to-hospital discharge in 306 ICU admissions of HIV-infected patients

Characteristic	Unadjusted OR (95% CI)	P-Value*	Adjusted OR (95% CI)	P-Value†
No intubation versus mechanical ventilation	6.34 (3.02-13.1)	<0.001	6.11 (2.73-13.7)	<0.001
Albumin, per 1 g/dl increase	2.09 (1.47-2.98)	<0.001	2.08 (1.41-3.06)	0.002
HIV risk factor				
IDU versus MSM	2.16 (1.13-4.11)	0.020	*NA*	*NA*
Other/unknown versus MSM	2.00 (0.97-4.13)	0.061	*NA*	*NA*
No PCP diagnosis versus diagnosis of PCP in ICU	1.99 (1.02-3.90)	0.044	*NA*	*NA*
APACHE II score, per 1 point increase	0.88 (0.85-0.92)	<0.001	*NA*	*NA*
Admission diagnosis				
Sepsis versus respiratory failure	1.15 (0.60-2.22)	0.68	*NA*	*NA*
Neurologic versus respiratory failure	1.77 (0.84-3.74)	0.13	*NA*	*NA*
Other diagnoses‡ versus respiratory failure	3.05 (1.42-6.56)	0.004	*NA*	*NA*

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; g/dl = grams per deciliter; HIV = human immunodeficiency virus; ICU = intensive care unit; IDU = injection drug use; MSM = men who have sex with men; NA = not applicable (data for statistically insignificant predictors were not included); PCP = *Pneumocystis* pneumonia.

*Legend: Wald p-values correspond to univariate analyses.

†Wald p-values correspond to multivariate model, which excludes APACHE II scores due to collinearity.

‡Other diagnoses include gastrointestinal bleeding, cardiac conditions, metabolic disorders, trauma, and post-operative care.