Low tidal volume ventilation is associated with reduced mortality in HIV-infected patients with acute lung injury

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ABSTRACT

Background: Respiratory failure remains the leading indication for admission to the intensive care unit (ICU) and a leading cause of death for HIV-infected patients in spite of overall improvements in ICU mortality. It is unclear if these improvements are due to combination antiretroviral therapy, low tidal volume ventilation for acute lung injury, or both. A study was undertaken to identify therapies and clinical factors associated with mortality in acute lung injury among HIV-infected patients with respiratory failure in the period 1996–2004. A secondary aim was to compare mortality before and after introduction of a low tidal volume ventilation protocol in 2000.

Methods: A retrospective cohort study was performed of 148 consecutive HIV-infected adults admitted to the ICU at San Francisco General Hospital with acute lung injury requiring mechanical ventilation. Demographic and clinical information including data on mechanical ventilation was abstracted from medical records and analysed by multivariate analysis using logistic regression.

Results: In-hospital mortality was similar before and after introduction of a low tidal volume ventilation protocol, although the study was not powered to exclude a clinically significant difference (risk difference −5.4%, 95% CI −21% to 11%, p = 0.51). Combination antiretroviral therapy was not clearly associated with mortality, except in patients with *Pneumocystis* pneumonia. Among all those with acute lung injury, lower tidal volume was associated with decreased mortality (adjusted odds ratio 0.76 per 1 ml/kg decrease, 95% CI 0.58 to 0.99, p = 0.043), after controlling for *Pneumocystis* pneumonia, serum albumin, illness severity, gas exchange impairment and plateau pressure.

Conclusions: Lower tidal volume ventilation is independently associated with reduced mortality in HIV-infected patients with acute lung injury and respiratory failure.

Outcome-focused observational studies in critically ill HIV-infected patients admitted to the intensive care unit (ICU) have helped determine effective care practices since the beginning of the HIV epidemic. In particular, several reports from San Francisco General Hospital (SFGH) have documented how intensive care in this population has evolved since 1981.[1–5] Because respiratory failure has been the leading cause of ICU admission and death throughout, several studies from our institution and from others have examined factors associated with mortality in patients with this presentation. Important factors have included greater severity of illness, lower serum albumin, the presence of *Pneumocystis carinii* pneumonia (PCP) and, among those with respiratory failure due to PCP, pneumothorax.[2 3 5–8]

Following the introduction of combination antiretroviral therapy (CART) in 1996,[9] studies at SFGH linked decreased ICU mortality to use of CART and to increases in non-AIDS admission diagnoses.[5 8] At other institutions, the use of CART was also associated with a greater likelihood of a non-AIDS admission diagnosis, but not with decreases in ICU utilisation, respiratory failure, or in-hospital mortality.[10 11] Finding no mortality benefit for CART, some authors have speculated that changing practices of ICU care rather than CART may explain decreased mortality over time.[12] Unfortunately, none of these studies has evaluated specific ICU therapies.[13]

One therapy associated with decreased ICU mortality in patients with respiratory failure is the use of low tidal volumes (V_T) for mechanical ventilation in patients with acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS), as described in the ARDS Network (ARDSNet) study in 2000.[14] Because low V_T ventilation is theoretically protective against barotrauma,[15] it may be an important therapy for HIV-infected patients with severe respiratory failure due to PCP. Although no association between V_T and barotrauma was observed in the ARDSNet study, pressure-volume relationships differ in HIV-infected patients with PCP and ALI compared with HIV-uninfected patients with ALI of different aetiologies,[16] and the ARDSNet study included few HIV-infected patients.[14] We therefore wished to examine whether low V_T ventilation might be beneficial to HIV-infected patients with ALI.

To assess whether CART, low V_T ventilation or other factors have an impact on mortality in this population, we assembled a retrospective cohort of all HIV-infected patients admitted to the ICU at SFGH between 1996 and 2004 with respiratory failure and ALI or ARDS (henceforth referred to aggregately as ALI). Our primary aim was to identify which therapies and clinical factors were associated with mortality in this population. A secondary aim was to compare mortality among these patients before and after introduction of a low V_T ventilation protocol at SFGH in September 2000. Some patients, including all 74 enrolled in the pre-ARDSNet period, were included in previous publications, and some of the results have been previously reported in abstract form.[5 8 17 18] However, this is the first study to evaluate

comprehensively the impact of low VT ventilation on mortality in HIV-infected patients admitted to the ICU with ALI.

METHODS

Clinical investigators (AM, AC, MB, LH) identified all HIV-infected patients with ALI admitted to the ICU at SFGH between 1996 and 2004 by searching the hospital's administrative database for patients with a discharge diagnosis of HIV disease (Ninth International Classification of Disease (ICD-9) code 042) and by merging this list with a registry of all patients with ALI. Investigators (AM, AC, LD, RK) reviewed medical records using standardised chart abstraction forms and identified study subjects from the subset of patients who required mechanical ventilation and met the American-European Consensus Criteria for ALI at any time during the ICU stay.[19] For patients with multiple ICU visits within one hospitalisation, only the first ICU admission was considered. For one patient who developed ALI during two different hospitalisations (378 days apart), each episode was considered separately.

Predictor variables consisted of demographic characteristics including age, sex, race/ethnicity and HIV risk factor, clinical characteristics including HIV disease history (eg, PCP prophylaxis; CART, defined as use of ⩾3 antiretroviral agents from at least two drug classes on or after admission), aetiology of ALI (eg, microscopically confirmed PCP, clinically defined non-PCP pneumonia, clinically defined non-pulmonary cause of ALI) and height. Predictor variables also included laboratory data such as CD4+ T cell count (within 6 months), HIV RNA (within 6 months), haematocrit, serum albumin and lactate dehydrogenase (LDH), arterial pH, and arterial oxygen and carbon dioxide tensions. Ventilator parameters included mode of ventilation, expired tidal volume (VT), respiratory rate (RR), minute ventilation (VE), peak inspiratory pressure (PIP), end-inspiratory plateau pressure (Pplat), mean airway pressure (Paw) and positive end-expiratory pressure (PEEP). Mechanical ventilation variables were recorded at the first ventilator check (which included arterial blood gas measurement and recording of static lung mechanics) after intubation on day 1 and on subsequent days at the time of the ventilator check closest to midday. Because ventilator settings on initiation of mechanical ventilation may not reflect the subsequent treatment strategy or mechanics, and because individual ventilator checks may record outlying values, we averaged all ventilator measurements over the first 3 days after the onset of ALI to increase accuracy and precision. Measures of illness severity at onset of ALI, including the Acute Physiology and Chronic Health Evaluation (APACHE-II) score,[20] the Severe Acute Physiology (SAPS-II) score[21] and the Lung Injury Score (LIS),[22] were calculated from abstracted variables. In addition, we calculated the following variables: compression-corrected VT (VT − 2.5 ml/cm H_2O × [PIP − PEEP]), quasi-static respiratory system compliance (Crs = VT/[Pplat − PEEP]), ratio of arterial oxygen tension to inspired oxygen concentration (Pa_{O_2}/Fi_{O_2}), oxygenation index (O_2 index = [Fi_{O_2} × Paw]/Pa_{O_2}) and ideal body weight.[23] The principal outcome variable was in-hospital mortality within 3 months.

Data analysis

Data were single-entered but subjected to internal logic and formatting checks. All analyses were performed using STATA 9.0 (Stata Corporation, College Station, TX, USA) with significance specified in reference to a two-tailed type I error (p value) <0.05. Bivariate analyses were performed using the χ^2 test or Fisher exact test for dichotomous variables and the *t* test or Mann-Whitney test for continuous variables.

For the secondary aim of the study—comparing mortality before and after the ARDS Network protocol was introduced at SFGH on 1 September 2000—we divided the dataset into two time periods. (Henceforth, we explicitly use the term "period" to avoid confusion with the "eras" described in the previous articles from this institution. We refer to the block of time from January 1996 to August 2000 as "the pre-ARDSNet period" or "the earlier period" and the block of time from September 2000 to December 2004 as "the post-ARDSNet period" or "the later period".) The sample size resulted from our a priori decision to limit the analysis to these 9 years.

Unlike the ARDSNet studies but similar to other studies of low VT ventilation,[24] the ARDSNet Protocol at SFGH allows use of pressure-limited, volume-targeted ventilator modes to permit patient control over inspiratory flow. Otherwise, the ARDS Network protocol in use at SFGH follows exactly that outlined in the original ARDSNet study,[14] targeting tidal volumes of 4–6 ml/kg ideal body weight to maintain plateau pressures <30 cm H_2O.

Multivariate logistic regression analysis using backward selection was performed to assess whether demographic, clinical, laboratory and ventilator predictors or measures of illness severity and gas exchange impairment were associated with in-hospital mortality, and to control for potential confounders of the relationship between the predictors of primary interest (VT and CART) and in-hospital mortality. Because of the small sample size, we chose an inclusive cut-off ($p<0.2$) for the empirical level of significance at which we would retain variables. We also included predictor variables if they altered by 10% or more the logit of any predictor variable that was also associated with the outcome at $p<0.2$.[25] Because PIP, Pplat, PEEP and LIS were highly correlated, we selected Pplat to represent these variables since it has the greatest face validity for measuring lung distension in ALI. Similarly, Pa_{O_2}/Fi_{O_2} was chosen to represent worst Pa_{O_2}/Fi_{O_2} and O_2 index because it is clinically familiar. The SAPS-II score was chosen in preference to the APACHE-II score because it better fit the assumptions of the logistic model. In addition, the variables serum albumin, PCP, CART use and VT (adjusted for ideal body weight) were included in the model because of high face validity

Table 1 Demographic and clinical characteristics of 148 HIV-infected patients with ALI in the ICU

Characteristic*	Pre-ARDSNet period 1996–2000 (n = 74)	Post-ARDSNet period 2000–2004 (n = 74)	p Value
Mean (SD) age (years)	41.8 (7.8)	42.4 (8.6)	0.68
Male sex (%)	60 (81)	51 (74)	0.30
Caucasian ethnicity (%)	37 (52)	36 (49)	0.68
MSM HIV risk factor (%)	25 (34)	24 (32)	0.86
CART on admission or while in ICU (%)	20 (27)	28 (38)	0.16
PCP prophylaxis on admission (%)	31 (46)	26 (36)	0.23
Previous PCP (%)	18 (25)	14 (19)	0.42
Pulmonary cause of ALI (%)	57 (77)	63 (85)	0.21
PCP (%)	24 (32)	27 (36)	0.60
Pneumothorax (%)	10 (14)	16 (22)	0.20

*Up to 24 observations missing per era, as for HIV risk factor.
ALI, acute lung injury; ARDSNet, Acute Respiratory Distress Syndrome Network study; CART, combination antiretroviral therapy; ICU, intensive care unit; PCP, *Pneumocystis* pneumonia; MSM, men having sex with men; SD, standard deviation.

and prespecified importance to the research question. To control for confounding due to changes in ICU outcomes over time, we included a dichotomous variable for care in the period after introduction of the ARDSNet ventilation protocol compared with care in the prior period. Interaction terms to test the hypotheses that having PCP or a low CD4 count might enhance any mortality benefit of CART, or that lower V_T might be effective in patients with PCP or in patients cared for in the post-ARDSNet period, were also evaluated. The final model was assessed for goodness of fit using the Hosmer-Lemeshow test and for omitted covariates and model misspecification using the link test.[24]

RESULTS

Of the 685 consecutive HIV-infected adults admitted to the ICU at SFGH between 1996 and 2004, 148 (22%) had ALI. Half were admitted before the introduction of the ARDSNet protocol and half after. Of the 148 patients with ALI, 132 (89%) had ARDS, the most severe form of ALI. The principal causes of ALI were PCP (34%), non-PCP pneumonia (38%), sepsis (15%) and aspiration pneumonitis (7%). As a proportion of all ICU admissions for HIV-infected persons, ALI was more common in the post-ARDSNet period (25%) than in the pre-ARDSNet period (19%) ($p = 0.045$).

In-hospital mortality in the post-ARDSNet period (54%) was similar to that in the pre-ARDSNet period (59%), but the wide confidence intervals surrounding the point estimate of the risk difference prevented exclusion of a clinically important increase or decrease in mortality (risk difference −5.4%, 95% confidence interval (CI) −21% to 11%, $p = 0.51$). ICU mortality was slightly lower, 51% in the earlier period and 46% in the later period, with the same risk difference (risk difference −5.4%, 95% CI −21% to 11%, $p = 0.51$). From the earlier to the later period there were no significant differences in median days of mechanical ventilation (8 vs 8, $p = 0.39$), days in ICU (9 vs 8.5, $p = 0.93$) or days in hospital (20 vs 19, $p = 0.78$).

The demographic, clinical and laboratory characteristics of persons with ALI were similar between the two periods (tables 1 and 2). The proportions with PCP did not differ between the two periods, nor did the proportion suffering pneumothorax change significantly after introduction of the ARDSNet protocol. A similar proportion of patients received CART in the later period (38%) as in the earlier period (27%) ($p = 0.16$), and CD4 counts and HIV RNA levels were comparable in the two periods. Although the median CD4 count did not differ between those taking and not taking CART (78.5 vs 60, $p = 0.78$), log HIV RNA was lower in those taking CART than in those not taking CART (4.7 vs 5.2, $p = 0.005$).

Table 2 Laboratory parameters and illness severity of 148 HIV-infected patients with ALI in the ICU

Characteristic*	Pre-ARDSNet period 1996–2000 (n = 74)	Post-ARDSNet period 2000–2004 (n = 74)	p Value
Median (IQR) CD4+ T cell count (cells/μl)	65 (17–230)	67 (18–188)	0.91
Median (IQR) $\log_{10}$ HIV RNA (copies/ml)	4.9 (4.2–5.3)	5.2 (4.1–5.5)	0.20
Mean (SD) albumin (g/dl)	2.28 (0.54)	2.40 (0.72)	0.28
Median (IQR) LDH (IU)	365 (255–517)	366 (239–576)	0.96
Mean pH† <7.25 (%)	23 (31)	24 (32)	0.86
Mean (SD) $Paco_2$† (mm Hg)	39 (10)	40 (8.9)	0.43
Mean (SD) Pao_2† (mm Hg)	93 (24)	93 (23)	0.88
Mean (SD) APACHE-II score	24 (6.6)	23 (5.9)	0.19
Mean (SD) SAPS-II score	55 (18)	53 (14)	0.53
LIS ⩾2.75 (%)	29 (42)	51 (69)	0.001

*Up to 35 observations missing, as for HIV RNA.
†Physiological variables averaged over days 1–3.
ALI, acute lung injury; ARDSNet, Acute Respiratory Distress Syndrome Network study; APACHE-II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; LIS, Lung Injury Score; $Paco_2$, carbon dioxide tension; Pao_2, arterial oxygen tension; SAPS-II, Severe Acute Physiology Score II; SD standard deviation.

The use of pressure-regulated modes of ventilation at any time during the first 3 days in the ICU was more common in the post-ARDSNet period (39%) than in the pre-ARDSNet period (22%) ($p = 0.020$), a difference reflecting the increased use of dual modes of ventilation in the later period (table 3). Mean V_T, corrected for ideal body weight and averaged over days 1–3, was lower in the later period than in the earlier period (6.6 ml/kg vs 9.1 ml/kg, $p<0.001$). Although the respiratory rate was higher ($p<0.001$) and V_E lower ($p = 0.002$) in the later period than in the earlier period, the number of patients with moderate or severe acidaemia (pH <7.25) was similar (31% in the pre-ARDSNet period vs 32% in the post-ARDSNet period, $p = 0.86$) and mean $Paco_2$ was stable between periods (39 vs 40, $p = 0.43$). Assuming CO_2 production remained stable from the earlier period to the later period, this finding suggests that wasted ventilation (dead-space fraction) declined in the post-ARDSNet period.

Median Pplat tended to be lower ($p = 0.082$) and median PEEP was higher ($p = 0.037$) after introduction of the ARDSNet protocol at SFGH. Overall severity of lung injury, as measured by LIS, was substantially worse in the later period than in the earlier period, primarily because respiratory system compliance was lower in the later period (28 ml/cm H_2O post-ARDSNet protocol vs 36 ml/cm H_2O pre-ARDSNet protocol, $p<0.001$). Mean plateau pressure was higher in those who developed pneumothoraces than in those who did not (29 vs 26 cm H_2O, $p = 0.054$), although compliance and other static pressures did not differ ($p \geqslant 0.19$ for all comparisons). Mean V_T was lower among those with PCP than among those with other causes of ALI (7.0 vs 8.2 ml/kg, $p = 0.002$).

In unadjusted analyses, most HIV-related variables—including CD4 count, HIV RNA, use of CART, use of PCP prophylaxis and presence of PCP—were not clearly associated with death (table 4). In contrast, higher levels of non-HIV-related variables—PIP and Pplat—were clearly associated with mortality. Other ALI-related variables, including higher V_T, higher PEEP and higher LIS, showed trends towards increased mortality. Markers of severity of illness, including lower serum albumin; higher APACHE-II and higher SAPS-II scores; lower Pao_2/Fio_2 and lower worst Pao_2/Fio_2; and higher O_2 index were also significantly associated with death.

To construct a causal multivariate model we included variables for severity of illness, static lung mechanics, V_T and oxygenation on the grounds of their empirical associations with both period and mortality at $p<0.2$. We also included the prespecified variables CART, PCP, albumin and period on the grounds of face validity. The final model showed ALI-related variables to be more strongly associated with mortality than HIV-related factors (table 4). After controlling for period of ICU care, Pao_2/Fio_2 and use of CART, the presence of PCP, lower serum albumin, higher SAPS-II score and higher Pplat were all independently associated with increased mortality. Lower V_T was independently associated with decreased mortality (adjusted odds ratio 0.76 per 1 ml/kg decrease, 95% CI 0.58 to 0.99, $p = 0.043$). During stepwise removal of predictors from the

Table 3 Ventilation parameters for 148 HIV-infected patients with ALI in ICU

Characteristic*	Pre-ARDSNet period 1996–2000 (n = 74)	Post-ARDSNet period 2000–2004 (n = 74)	p Value
Pressure-regulated ventilation (%)	16 (22)	29 (39)	0.020
Mean (SD) V_T† (ml/kg)	9.1 (2.0)	6.6 (1.5)	<0.001
Mean (SD) RR† (breaths/min)	22 (5.8)	25 (6.2)	<0.001
Median (IQR) V_E† (l/min)	14 (11–17)	11 (10–14)	0.002
Mean (SD) PIP† (cm H_2O)	36 (8.2)	35 (7.5)	0.37
Median (IQR) Pplat† (cm H_2O)	29 (23–31)	26 (23–29)	0.082
Median (IQR) Paw† (cm H_2O)	15 (12–18)	17 (13–19)	0.098
Median (IQR) PEEP† (cm H_2O)	7.0 (5.0–9.3)	8.3 (5.0–10)	0.037
Mean (SD) Crs† (ml/cm H_2O)	36 (11)	28 (11)	<0.001
Median (IQR) Pao_2/Fio_2† (mm Hg)	144 (111–193)	137 (103–179)	0.49
Median (IQR) worst Pao_2/Fio_2† (mm Hg)	125 (84–174)	120 (90–159)	0.88
Median (IQR) O_2 index† (mm Hg/cm H_2O)	10 (6.5–16)	12 (8.8–16)	0.20

*Up to 11 observations missing, as for V_T and PIP. †Physiological variables averaged over days 1–3.
ALI, acute lung injury; ARDSNet, Acute Respiratory Distress Syndrome Network study; Crs, respiratory system compliance; Fio_2, fractional inspired oxygen concentration; ICU, intensive care unit; IQR, interquartile range; O_2, oxygenation; Pao_2, arterial oxygen tension; PIP, peak inspiratory pressure; Pplat, end-inspiratory plateau pressure; Paw, mean airway pressure; PEEP, positive end-expiratory pressure; RR, respiratory rate; SD, standard deviation; V_E, minute ventilation; V_T, tidal volume.

final model, PCP was the principal confounder suppressing the association between lower V_T and mortality. CART was not independently associated with mortality (p = 0.82), and excluding it from the model had no effect on the other variables. The same associations were observed with alternative model building approaches, including stepwise forward selection and automated regression techniques.

After including interaction terms in the model, there was a strong association between CART and decreased mortality among those with PCP (adjusted odds ratio 0.14, 95% CI 0.024 to 0.83, p = 0.031). There was no interaction between CART and CD4 count, between lower V_T and PCP, or between lower V_T and period of enrolment (p>0.10 for each interaction).

Excluding influential data points did not significantly alter the overall model. There was no evidence that quadratic terms or additional covariates would improve the model (p = 0.15 by the Wald link specification test), which appeared robust across all strata (p = 0.64 by the Hosmer-Lemeshow statistic).

DISCUSSION

Our study is the first to show that survival among HIV-infected patients with respiratory failure and ALI is associated with a specific non-HIV-related ICU therapy, lower V_T ventilation. CART was associated with greatly reduced odds of death only in patients with PCP, but this diagnosis was a rare cause of respiratory failure in the ICU. The decrease in mortality that we observed after introduction of the ARDSNet protocol did not reach statistical significance, probably because of insufficient sample size. Measuring V_T as a continuous variable, however, gave the study adequate power to show that lower V_T was associated with significantly reduced odds of mortality.

This study updates previous studies of critically ill HIV-infected patients by showing that CART may benefit some HIV-infected patients with respiratory failure (eg, those with PCP) but not necessarily all. While one study reported a long-term survival benefit from use of CART in critically ill HIV-infected patients,[10] most studies have reported no increase in survival to discharge.[10 11 26] A study at a university hospital in the UK also demonstrated no survival benefit to CART in patients with PCP.[12] Only studies from SFGH, including those with and without PCP, have shown a CART-associated decrease in hospital deaths.[5 8] Patient selection is one possible reason for these discrepancies. Almost a quarter of those on CART in our study had it initiated after hospital admission, a practice which is uncommon among other studies reporting this information.[11 12] In addition, all patients on CART in this study were using a regimen that included a protease inhibitor, an antiretroviral class which may have anti-*Pneumocystis* activity.[27] Determining which of these factors accounts for the CART-associated decrease in PCP mortality will require studies that either randomise patients or adjust for the propensity of clinicians to treat with CART.

This study confirms the previously reported independent associations with mortality of several clinical variables including illness severity, serum albumin and the presence of PCP.[2 4] To previous data showing that non-HIV admission diagnoses are an important predictor of survival in HIV-infected patients in the ICU,[5] this study adds the observation that one such diagnosis—ALI—is becoming more severe. Although the reasons for this finding are unclear, the greater frequency of severe LIS in the post-ARDSNet protocol period probably reflects lower Crs which has been associated with low V_T ventilation, possibly through increased atelectasis, elastic recoil and patient-ventilator dyssynchrony.[28 29]

As the largest study of HIV-associated respiratory failure to date, this study provides specific physiological data associating the use of lower V_T in ALI with decreased odds of in-hospital death. These results support previous findings that lower V_T in ALI is associated with decreased mortality in clinical trial and practice settings,[14 17] and reinforce the recommendation that HIV-infected persons with ALI requiring mechanical ventilation receive low V_T ventilation, ideally by protocol.[30]

Unlike previous PCP-focused studies of HIV-associated respiratory failure,[7 8] pneumothorax was not associated with mortality in this study. Furthermore, as in other studies of ALI,[31 32] barotrauma did not explain the mortality benefit of lower V_T ventilation in this population. We observed a probable decrease in dead-space fraction from the early period to the later period, possibly due to a low V_T-associated reduction in alveolar distension (as indicated by reduced Pplat). Given the known association between dead-space fraction and mortality in ARDS,[33] this observation bears further investigation as a potential mechanism for decreased mortality in ALI.

This study shows that Pplat is independently associated with death in HIV-infected patients with ALI, as previously reported in HIV-negative patients.[34] The association between lung mechanics and outcome in ALI probably depends on more than V_T, however, since the association between Pplat and death persisted even after adjusting for its principal determinants—Crs, V_T and PEEP. Although these adjustments do not account for the contribution of chest wall compliance to total elastic recoil, chest wall compliance is minimally disturbed in direct causes of ALI.[16 35] Since 80% of our patients with ALI had direct lung injury, primarily from pneumonia, Pplat is probably an accurate reflection of lung stress in this cohort. It has recently been shown that lung overdistension commonly occurs in ARDS despite the use of the ARDSNet protocol, and that a relatively higher mortality is associated with even modestly

Table 4 Variables associated with mortality in 148 HIV-infected patients with ALI in the ICU

	Unadjusted analysis		Adjusted‡ analysis	
Characteristic*	**Odds ratio (95% CI)**	**p Value**	**Odds ratio (95% CI)**	**p Value**
Age per 10-year increase	1.19 (0.80 to 1.79)	0.39	–	–
Male vs female sex	1.36 (0.62 to 3.00)	0.44	–	–
Caucasian vs non-Caucasian ethnicity	1.21 (0.63 to 2.34)	0.57	–	–
MSM vs other HIV risk factor	2.22 (1.08 to 4.58)	0.031	–	–
CART use vs non-use	0.67 (0.33 to 1.33)	0.25	0.89 (0.34 to 2.35)	0.82
PCP prophylaxis use vs non-use	1.68 (0.84 to 3.36)	0.14	–	–
Previous PCP vs no previous PCP	1.60 (0.70 to 3.62)	0.26	–	–
Extrapulmonary vs pulmonary cause of ALI	2.19 (0.89 to 5.35)	0.086	–	–
PCP vs non-PCP cause of ALI	1.46 (0.73 to 2.92)	0.29	3.19 (1.15 to 8.89)	0.029
Pneumothorax vs absence of pneumothorax	1.27 (0.53 to 3.02)	0.59	–	–
CD4+ T cell count (per 100 cells/μl decrease)	1.14 (0.95 to 1.38)	0.16	–	–
HIV RNA (per 1 $\log_{10}$ copies/ml increase)	1.03 (0.78 to 1.37)	0.82	–	–
Albumin (per 1 g/dl decrease)	2.48 (1.41 to 4.37)	0.002	2.51 (1.23 to 5.13)	0.012
LDH (per 100 IU increase)	1.02 (0.93 to 1.12)	0.65	–	–
pH† $<$7.25 vs $\geq$7.25	3.10 (1.44 to 6.64)	0.004	–	–
$Paco_2$† $<$30 or $>$50 mm Hg vs 30–50 mm Hg	3.05 (1.21 to 7.71)	0.018	–	–
Pao_2† (per 10 mm Hg decrease)	1.23 (1.05 to 1.43)	0.010	–	–
APACHE-II score (per 5 point increase)	1.50 (1.12 to 2.00)	0.007	–	–
SAPS-II score (per 20 point increase)	1.92 (1.18 to 3.12)	0.008	2.41 (1.24 to 4.70)	0.010
LIS $\geq$2.75 vs $<$2.75	1.93 (0.99 to 3.79)	0.054	–	–
Pressure-regulated vs volume-regulated ventilation	0.82 (0.40 to 1.66)	0.58	–	–
V_T† (per 1 ml/kg decrease)	0.87 (0.74 to 1.03)	0.11	0.76 (0.58 to 0.99)	0.043
RR† (per 5 breath/min increase)	1.03 (0.78 to 1.34)	0.86	–	–
V_E†$>$12 l/min vs $\leq$12 l/min	1.53 (0.80 to 2.95)	0.20	–	–
PIP† (per 5 cm H_2O increase)	1.40 (1.11 to 1.77)	0.005	–	–
Pplat† (per 5 cm H_2O increase)	2.05 (1.44 to 2.93)	$<$0.001	2.13 (1.36 to 3.33)	0.001
Paw† (per 5 cm H_2O increase)	1.50 (1.03 to 2.20)	0.037	–	–
PEEP† (per 5 cm H_2O increase)	1.91 (0.97 to 3.77)	0.061	–	–
Crs† (per 20 ml/cm H_2O decrease)	0.94 (0.53 to 1.68)	0.84	–	–
Pao_2/Fio_2† (per 50 mm Hg decrease)	2.07 (1.47 to 2.92)	$<$0.001	1.37 (0.88 to 2.12)	0.17
Worst Pao_2/Fio_2† (per 50 mm Hg decrease)	2.48 (1.68 to 3.68)	$<$0.001	–	–
O_2 index† (per 5 mm Hg/cm H_2O increase)	1.95 (1.40 to 2.73)	$<$0.001	–	–
Post-ARDSNet vs pre-ARDSNet protocol period	0.80 (0.42 to 1.54)	0.51	2.17 (0.73 to 6.47)	0.16

*Up to 35 observations may be missing (as for HIV RNA), but odds ratios are calculated using only actual observations.
†Physiological variables averaged over days 1–3.
‡Adjusted for all characteristics with odds ratios listed in the adjusted analysis column of the table. The adjusted model included 130 subjects.
ALI, acute lung injury; APACHE-II, Acute Physiology and Chronic Health Evaluation II; ARDSNet, Acute Respiratory Distress Syndrome Network study; CART, combination antiretroviral therapy; CI, confidence interval; Crs, respiratory system compliance; Fio_2, fractional inspired oxygen concentration; ICU, intensive care unit; LDH, lactate dehydrogenase; LIS, Lung Injury Score; MSM, men having sex with men; O_2, oxygenation; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; PCP, *Pneumocystis* pneumonia; PIP, peak inspiratory pressure; Pplat, end-inspiratory plateau pressure; Paw, mean airway pressure; PEEP, positive end-expiratory pressure; RR, respiratory rate; SAPS-II, Severe Acute Physiology Score II; V_E, minute ventilation; V_T, tidal volume.

higher Pplat (mean of 28 cm H_2O).[36] The strong association of Pplat with mortality is consistent with the previously proposed mechanism of systemic release of inflammatory mediators.[37]

A previous study of lung mechanics in HIV-infected patients with severe PCP found that these patients lack characteristic inflection points on the pressure-volume curve.[16] The absence of inflection points implies that increasing static pressures cannot increase alveolar recruitment or improve gas exchange. If increasing Pplat also increases mortality, as our study suggests, strategies that aim to optimise PEEP may be contraindicated in this population.

There are several limitations to this study. The observational design limits its ability to infer causality because uncontrolled patient factors may have influenced the decision to prescribe CART or lower V_T, especially in the early part of this study when CART was new and when the use of low V_T for ALI had not yet been established as a standard protocol. Although multivariate analysis suggests that lower V_T is associated with decreased mortality, we did not observe any substantial decline in mortality during the period of our study. This may be because the study was inadequately powered or because lower tidal volumes were more frequently used in patients at greatest risk of death, such as those with PCP.

Unmeasured factors may have confounded the reported associations with mortality. For example, overall improvements in ICU care during this period may have been associated with changes in practitioner or patient/family attitudes towards palliative care which could have impacted on in-hospital mortality. Other therapies associated with improved ICU survival such as intensive insulin therapy and early goal-directed therapy for sepsis were popularised during the post-ARDSNet period and thereby could have accounted for some of the mortality benefit. While we did not gather data to assess these possibilities, we did attempt to control for such temporal differences in ICU care using a variable for period of care (pre- versus post-ARDSNet) as a surrogate for such changes. Since this variable was not associated with mortality and did not alter our causal model, temporal differences are unlikely to have

acted as significant confounders. Furthermore, no other ICU protocols were in systematic use at SFGH during the study period.

In summary, survival of critically ill HIV-infected patients with ALI and respiratory failure was associated with ventilation with lower VT. Among the subset of patients with PCP and ALI, use of CART on or after admission was strongly correlated with lower mortality. Even after adjustment for VT, lower Pplat was independently associated with a decrease in the odds of death in all patients studied. Future studies of outcomes in HIV-infected patients in the ICU should consider the interaction between HIV- and non-HIV-associated admission diagnoses and specific therapies in the ICU.

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