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Etiologies and outcome of acute respiratory failure in HIV-infected patients

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Abstract *Objective:* To assess the etiologies and outcome of acute respiratory failure (ARF) in HIV-infected patients over the first decade of combination antiretroviral therapy (ART) use. *Methods:* Retrospective study of all HIV-infected patients ($n = 147$) admitted to a single intensive care unit (ICU) for ARF between 1996 and 2006. *Results:* ARF revealed the diagnosis of HIV infection in 43 (29.2%) patients. Causes of ARF were bacterial pneumonia ($n = 74$), *Pneumocystis jirovecii* pneumonia (PCP, $n = 52$), other opportunistic infections ($n = 19$), and noninfectious pulmonary disease ($n = 33$); the distribution of causes did not change over the 10-year study period. Two or more causes were identified in 33 patients. The 43 patients on ART more frequently had bacterial pneumonia and less frequently had opportunistic infections ($P = 0.02$). Noninvasive ventilation was needed in 49 patients and endotracheal intubation in 42. Hospital mortality was 19.7%. Factors independently associated with mortality were mechanical ventilation [odds ratio (OR) = 8.48, $P < 0.0001$], vasopressor use (OR, 4.48; $P = 0.03$), time from hospital admission to ICU admission (OR, 1.05 per day; $P = 0.01$), and number of causes (OR, 3.19; $P = 0.02$). HIV-related variables (CD4 count, viral load, and ART) were not associated with mortality. *Conclusion:* Bacterial pneumonia and PCP remain the leading causes of ARF in HIV-infected patients in the ART era. Hospital survival has improved, and depends on the extent of organ dysfunction rather than on HIV-related characteristics.

Keywords Outcome · Bacterial pneumonia · *Pneumocystis jirovecii* pneumonia · Bronchoalveolar lavage · Multiple organ failure

Introduction

Acute respiratory failure (ARF) is the leading reason for intensive care unit (ICU) admission in HIV-infected patients, with bacterial pneumonia and *Pneumocystis jirovecii* pneumonia (PCP) accounting for most cases [1–8]. Effects of HIV infection that predispose patients to lung infections include depletion of alveolar CD4 T cells, impairment of humoral immunity, and functional alterations of granulocytes and alveolar macrophages [9, 10]. Changes in the causes of ARF were reported shortly after the introduction of combination antiretroviral therapy (ART) [3, 6, 11]. The drop in HIV RNA levels and increase in CD4 T-cell counts induced by ART were associated with a reduced incidence of opportunistic infections and an increase in life expectancy [12, 13]. As a result of both primary prophylaxis and ART, the percentage of ARF cases due to PCP dropped from 70% to 20–40% [3, 4, 14, 15]. However, most of the available studies of ARF in HIV-infected patients were conducted

before 2000, at a time when ART was not yet widely used, and more recent data are scarce [15–17]. Thus, the possible influence of ART advent on the causes and outcomes of ARF in HIV-infected patients is not fully understood.

The objectives of this study were to determine whether the causes and outcome of ARF in HIV-infected patients have changed in the first decade following the advent of ART, and to assess the effect of ART use on these variables. To this end, we reviewed the medical charts of all HIV-infected patients admitted to our ICU for ARF between 1996 and 2006.[1]

Patients and methods

This retrospective study was conducted in the medical ICU of the Saint-Louis Hospital, a 650-bed university hospital in Paris, France. All HIV-infected patients admitted for ARF between 1 January 1996 and 31 December 2006, were included, unless they were receiving treatment for hematological malignancies or solid tumor. In patients with multiple admissions for ARF during the study period, only the first ICU stay was evaluated. ARF was defined as a respiratory rate of more than 30 breaths/min and respiratory distress symptoms, PaO_2 on room air of less than 60 mm Hg, or need for invasive or noninvasive mechanical ventilation (MV). Of note, admission policies of HIV-infected patients remained identical throughout the study period in our ICU and consisted in broad admission for ARF, regardless of HIV-related history. The ethics committee of the French Society for Critical Medicine approved the study.

Eligible patients were screened by independent query of the entire ICU database by 2 of the investigators. The medical charts of the included subjects were then reviewed by 2 intensivists including a pulmonologist and an infectious disease specialist. Both the ICU charts and the charts from the infectious diseases department supplying HIV follow-up were reviewed. The characteristics of the HIV infection shown in Table 1 were collected. AIDS-defining illnesses before ICU admission were defined according to the latest statement of the Centers for Disease Control and Prevention (CDC) [19]. ART was defined as a combination of 3 or more antiretroviral drugs belonging to at least 2 classes among the following: protease inhibitors, nucleoside reverse transcriptase inhibitors, and nonnucleoside reverse transcriptase inhibitors [20]. We defined patients as receiving ART if the medication was prescribed for more than 30 days. However, patients whose medical charts from the infectious disease department indicated poor compliance with the prescribed ART regimen were classified as not receiving ART. Poor compliance was defined as stationary viral load despite fully active antiretroviral therapy and no evidence of viral resistance according to available genotyping data, or no drug taken for more than 6 months. The demographic data, co-morbidities, and ICU stay characteristics reported in Tables 1 and 2 were collected. Life-sustaining treatments used in the ICU were recorded. The Sepsis-related Organ Failure Assessment (SOFA) score was calculated in each patient and used to define extrarespiratory failures within the first 24 h of the ICU stay [21].

The cause of ARF was determined by consensus among all ICU clinicians. Four nonmutually exclusive diagnostic categories were used: bacterial pneumonia documented clinically and/or microbiologically, PCP, opportunistic lung infections other than PCP and bacterial pneumonia, and noninfectious diseases. Clinically documented bacterial pneumonia was defined as an appropriate history and response to empiric antimicrobial therapy with focal pneumonia on chest X-ray, and either septic shock or predominantly neutrophils on bronchoalveolar lavage (BAL) fluid examination, but no bacterial pathogen isolated. The diagnosis of PCP required documentation of *P. jirovecii* on respiratory samples. The diagnostic strategy, which has been described elsewhere [22], included blood cultures, saline-induced sputum (IS) for *P. jirovecii* testing, expectorated sputum for bacteria and mycobacteria, BAL, distal protected specimen (DPS), pleural fluid culture, *Legionella pneumophila* serogroup I urinary antigen, and *Cryptococcus neoformans* antigenemia.

Statistical analysis

Results are reported as medians and quartiles (25th–75th percentiles) or numbers and percentages. To provide a global overview of survival trends over time, the study period was subdivided into 3 subperiods, i.e., 1996 to 2000, 2000 to 2003, and 2004 to 2006. We sought to assess potential changes over time in term of ICU admissions, frequency of inaugural ARF, respective incidences of the 4 causal groups, and survival. Patient characteristics were compared according to the use of ART and the causes of ARF using the Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and the nonparametric Wilcoxon's rank-sum test or the Kruskal–Wallis test for continuous variables. To investigate association between patient characteristics, use of ART, and hospital death, we first performed univariate analyses to look for a significant influence of each variable on hospital mortality by logistic regression, estimating the odds ratio (OR) with a 95% confidence

[1]This work was presented in part at the American Thoracic Society International Conference, 16–21 May 2008, Toronto, Canada (Abstract no. 2086) [18].

Table 1 Patient characteristics at baseline and throughout the ICU stay

	All patients ($n = 147$)	ART ($n = 43$)	No ART ($n = 104$)	*P*
Demographics				
Age, years	43 [37–51]	46 [39–57]	42 [37–49]	
Male gender	110 (74.8)	35 (81.4)	75 (72.1)	0.33
Caucasians	76 (51.7)	27 (62.8)	49 (47.1)	0.12
Black	42 (28.6)	10 (23.2)	32 (30.8)	0.47
Other ethnicity	29 (19.7)	6 (14.0)	23 (22.1)	0.36
HIV exposure				
MSM	35 (23.8)	14 (32.6)	21 (20.2)	0.16
IDU	25 (17.0)	4 (9.3)	21 (20.2)	0.17
Heterosexual/other/unknown	87 (59.2)	25 (58.1)	62 (59.6)	0.98
HIV-related characteristics				
Newly diagnosed HIV infection	43 (29.2)	NA	43 (41.3)	–
Time (months) since HIV diagnosis[a]	69 [0–149]	97 [39–166]	52 [0–140]	0.22
Previous AIDS-defining illness	60 (40.8)	28 (65.1)	32 (30.8)	0.0002
HIV viral load (copies/mL)[b]	7,000 [100–182,250]	50 [50–17,050]	140,612 [9,625–560,250]	0.002
CD4 lymphocyte count (cells/mm^3)[b]	192 [46–393]	231 [67–485]	83 [26–279]	0.0007
Use of PCP prophylaxis	35 (23.8)	23 (53.5)	12 (11.5)	<0.0001
Co-morbidities unrelated to HIV infection[c]				
Chronic hepatitis C	27 (18.4)	8 (18.6)	19 (18.3)	0.85
Chronic hepatitis B	10 (6.8)	5 (11.6)	5 (4.8)	0.26
Heart failure	13 (8.8)	4 (9.3)	9 (8.6)	0.85
COPD	13 (8.8)	5 (11.6)	8 (7.7)	0.65
Chronic renal failure	7 (4.8)	2 (4.7)	5 (4.8)	0.70
Alcohol abuse	25 (17.0)	8 (18.6)	17 (16.3)	0.93
Current smoking	56 (38.1)	12 (27.9)	44 (42.3)	0.15
Characteristics of the ICU stay				
ICU admission from the emergency room	89 (60.5)	20 (46.5)	69 (66.3)	0.04
Time from hospitalization to ICU transfer, days	0 [0–2]	1 [0–3.5]	0 [0–1]	0.01
Respiratory rate at admission, breaths per min[d]	30 [25–36]	28 [25–30]	32 [25–36]	0.13
PaO_2at admission under 7 [5–10] L/min O_2 flow[d]	70 [54–98]	69 [54–97]	70 [54–99]	0.71
PaO_2/FiO_2 at admission for patients under NIV/MV[d]	178 [164–240]	209 [174–271]	174 [135–220]	0.57
SOFA score at admission	4 [3–7]	4 [2–9]	4 [3–6]	0.76
Life-sustaining therapies used[e]				
Pressure support (NIV)	49 (33.3), 33 success	10 (23.2)	39 (37.5)	0.14
Invasive mechanical ventilation	42 (28.6)	16 (37.2)	26 (25.0)	0.20
Duration of mechanical ventilation, days	6 [3–14]	7 [3–20]	5 [3–13]	0.28
Need for vasoactive agents	39 (26.5)	17 (39.5)	22 (21.1)	0.04
Renal replacement therapy	11 (7.5)	5 (11.6)	6 (5.7)	0.38
Criteria for ARDS[e]	8 (5.4)	2 (4.7)	6 (5.7)	0.90
Pneumothorax[e]	6 (4.1)	1 (2.4)	5 (4.8)	0.81
Ventilator-associated pneumonia[e]	12 (8.2)	4 (9.3)	8 (7.7)	0.99
ICU length of stay, days	5 [3–7]	5 [2–7]	5 [3–7]	0.76
Hospital mortality	29 (19.7)	13 (30.2)	16 (15.4)	0.07

Results are reported as medians and quartiles (25th–75th percentiles) or numbers and percentages, unless otherwise indicated

Each variable was available for all of the 147 patients, except CD4 cell count (available for 67 patients) and HIV viral load (available for 64 patients)

ART combination antiretroviral therapy, *HIV* human immunodeficiency virus, *MSM* men who have sex with men, *IDU* intravenous drug users, *AIDS* acquired immunodeficiency syndrome, *PCP Pneumocystis jirovecii* pneumonia, *COPD* chronic obstructive pulmonary disease, *LDH* serum lactate dehydrogenase, *SOFA* Sepsis-related Organ Failure Assessment, *NIV* noninvasive ventilation, *MV* invasive mechanical ventilation, *ARDS* acute respiratory distress syndrome

[a] Including patients with newly diagnosed HIV infection

[b] Within 6 months before ICU admission (excluding inaugural patients)

[c] COPD, chronic renal failure and chronic heart failure were defined as described elsewhere [38–40]

[d] First value obtained after ICU admission

[e] At any time during the ICU stay

interval (CI). Variables listed in Table 4 were entered into a backward, stepwise multiple logistic regression model in which hospital mortality was the outcome variable of interest.

All tests were 2-sided, and *P* values smaller than 0.05 were considered statistically significant. Analyses were done using the StatView software package version 5.0 (SAS Institute, Cary, NC).

Table 2 Comparison of patient characteristics by cause of acute respiratory failure

Number (%) or median (25th–75th)	Bacterial pneumonia	PCP	Other opportunistic infections	Non-infectious causes	*P*
Patients[a]	74	52	19	33	
Age, years	45 (41–51)	42 (33–47)	33 (30–41)	45 (38–56)	0.008
Time since HIV diagnosis, months	77 [25–166]	0 [0–81]	3 [0–84]	101 [39–171]	<0.0001
Newly diagnosed HIV infection	15 (20.3)	29 (55.8)	10 (47.6)	2 (6.9)	<0.0001
CD4 cell count at ICU admission/mm^3	65 [19–169]	20 [11–42]	34 [14–60]	94 [80–232]	<0.0001
ART	28 (37.8)	3 (5.8)	3 (14.3)	15 (51.7)	0.02
Co-morbidities					
COPD	4 (5.4)	2 (3.8)	0	7 (24.1)	0.003
Heart disease	5 (6.7)	2 (3.8)	1 (4.8)	9 (31.0)	0.0002
Current smoking	29 (39.2)	13 (25.0)	6 (28.6)	14 (48.3)	0.05
LDH at admission, UI/L	520 [365–886]	798 [525–1,089]	900 [473–1,251]	479 [318–683]	NS
Organ failure at admission					
Shock	12 (16.2)	1 (1.9)	0	1 (3.4)	0.001
Acute renal failure	36 (48.6)	2 (3.8)	5 (23.8)	11 (37.9)	<0.0001
Neurologic	25 (33.8)	3 (5.8)	4 (19.0)	5 (17.2)	0.007
SOFA score	6 [3–9]	3 [3–4]	4 [3–5]	4 [3–7]	0.001
PaO_2/FiO_2 ratio at admission, mm Hg	236 [189–273]	243 [200–254]	280 [224–290]	229 [219–290]	NS
Need for vasoactive agents at any time in the ICU	28 (37.8)	5 (9.6)	7 (33.3)	4 (13.8)	0.001
Invasive mechanical ventilation at any time in the ICU	31 (41.9)	7 (13.5)	8 (38.1)	6 (20.7)	0.01
Length of ICU stay, days	4 [2–8]	5 [3–7]	7 [5–13]	4 [2–7]	0.09
Hospital mortality	18 (24.3)	8 (15.3)	7 (33.3)	6 (20.7)	NS

Each variable was available for all of the 147 patients except CD4 cell count and LDH (available for 99 and 128 patients, respectively) *ARF* acute respiratory failure, *HIV* human immunodeficiency virus, *AIDS* acquired immunodeficiency syndrome, *ART* combination antiretroviral therapy, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *SOFA* Sepsis-related Organ Failure Assessment, *LDH* serum lactate dehydrogenase, *NS* non-significant ($P > 0.05$)

[a] The number of causes (176) is larger than the number of patients (147) because some patients had more than one cause

Results

Over the 10-year study period, 269 HIV-infected patients were admitted at least once to our ICU; they accounted for 5% of all admitted patients. We included the 147 (54.6%) patients in whom ARF was the primary reason for ICU admission. Their main characteristics, stratified according to the use of ART, are reported in Table 1. Of these 147 patients, 5 (3.4%) were admitted twice for ARF during the study period. Etiological diagnosis and life-sustaining therapies requirement were similar in both ICU stays for 4 of them, and all were discharged alive from hospital after their second ICU admission, ruling out a potential bias induced by exclusion of this second event on statistical analysis. No patient had 3 or more admissions for ARF during the period. The number of HIV-patients admitted to the ICU for ARF increased throughout the study period ($n = 43$, 41 and 63 for subperiods 1996–2000, 2001–2003 and 2004–2006, respectively, $P < 0.05$), whereas the number of patients with ARF and newly diagnosed HIV infection ($n = 43$) tended to decrease (41.8%, 29.3%, and 20.6% for the same subperiods, respectively, $P = 0.06$) (Fig.1). At ICU admission, 43 patients were on ART overall (29.2%), without significant changes over the study period. No significant differences were found in terms of demographic characteristics, HIV risk factors, and co-morbidities when patients receiving ART were compared with those who did not (Table 1). Admission through the emergency room occurred in 89 (60.5%) patients. Severity of organs failures at ICU admission, assessed by the SOFA score, did not differ significantly

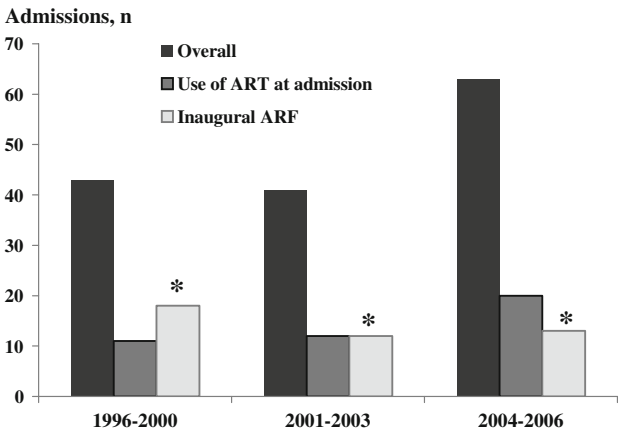

Figure 1 Trends in ICU admissions of HIV-infected patients for acute respiratory failure (overall and inaugural ARF) on the first decade of antiretroviral therapy (ART) use. *asterisks* indicate inaugural ARF which accounted for 41.8% (18/43 patients), 29.3% (12/41), and 20.6% (13/63) of all admissions on the three subperiods 1996 to 2000, 2001 to 2003, and 2004 to 2006, respectively ($P = 0.06$)

between patients with and without ART use before hospitalization (Table 1). Noninvasive pressure support ventilation (NIV) was needed in 49 patients (33.3%), among whom one-third failed NIV and required subsequent tracheal intubation. Overall, 42 (28.6%) patients needed invasive mechanical ventilation (MV), 39 (26.5%) required vasopressors, and 11 (7.5%) required dialysis. Hospital mortality was 19.7% (29 deaths, including 16 in the ICU). Mortality did not change significantly over the study period (20.9%, 19.5%, and 19.0% for 1996–2000, 2001–2003, and 2004–2006, respectively) and was not significantly different across the 4 etiological groups (Table 2).

Table 3 Causes of acute respiratory failure in the 147 HIV-infected patients

	N (%)
Bacterial pneumonia	74 (50.3)
Clinically documented[a]	23 (15.6)
Microbiologically documented	51 (34.7)
Streptococcus pneumoniae[b]	29
Pseudomonas aeruginosa	7
Enterobacteriaceae	6
Haemophilus influenzae[c]	6
Staphylococcus aureus[d]	4
Other bacterial pathogens	2
Pneumocystis jirovecii Pneumonia	52 (35.4)
Opportunistic pneumonia other than PCP	19 (12.2)
Mycobacterium complex *tuberculosis*	8
Including IRIS-induced ARF	1
Non-tuberculosis mycobacteria	2
Cytomegalovirus	5
Others opportunistic pathogens[e]	4
Non-infectious causes	33 (22.4)
Cardiogenic pulmonary edema	8
COPD exacerbation	6
Castelman's disease	5
Kaposi's sarcoma	3
Solid malignancies	2
Newly diagnosed pulmonary nonHodgkin lymphoma	2
Pulmonary hypertension	2
Intra-alveolar hemorrhage	1
Pulmonary embolism	2
Bronchiolitis obliterans with organized pneumonia	1
Status asthmaticus	1
One or more infectious causes	124 (84.4)

HIV human immunodeficiency syndrome, *ICU* intensive care unit, *PCP Pneumocystis jirovecii* pneumonia, *IRIS* immune restoration-induced syndrome, *ARF* acute respiratory failure, *COPD* chronic obstructive pulmonary disease, *AIDS* acquired immunodeficiency syndrome

[a] Clinically documented bacterial pneumonia was defined as an appropriate history and response to empiric antimicrobial therapy with focal pneumonia on chest X-ray, and either septic shock or predominantly neutrophils on BAL fluid examination, without documented bacterial pathogen

[b] Including co-infection with *Haemophilus influenzae* ($n = 1$) and *Staphylococcus aureus* ($n = 1$)

[c] Including co-infection with *Streptococcus pneumonia* ($n = 1$) and *S. aureus* ($n = 1$)

[d] Including the two co-infections with *S. pneumoniae* and *H. influenzae*

[e] Including *Rhodococcus equi* ($n = 1$), *Toxoplasma gondii* ($n = 1$), *Cryptococcus neoformans* ($n = 1$) and *Aspergillus fumigatus* ($n = 1$)

At least 1 cause of ARF was found in 145 patients (98.6%). Infection was far more common than noninfectious pulmonary disease. Table 3 lists the definitive diagnoses. Half the patients had bacterial pneumonia, *Streptococcus pneumoniae* being the most common pathogen. Septic shock occurred in 28 (37.8%) patients with bacterial pneumonia. The second most common cause of ARF was PCP, which was identified in about one-third of patients overall and in two-thirds of patients with newly diagnosed HIV infection. Pneumonia due to other opportunistic pathogens was diagnosed in 19 (12.2%) patients, with *Mycobacterium* complex *tuberculosis* being the most common pathogen ($n = 8$). Table 2 compares patient characteristics across the 4 etiological groups. Patients on ART were more likely to be admitted for bacterial pneumonia or noninfectious pulmonary disease than other patients ($P = 0.02$). AIDS-related causes were significantly more prevalent in the group with newly diagnosed HIV infection ($P < 0.0001$). Neither the distribution of causes nor the prevalence of AIDS-related diagnoses changed significantly over the study period. Two or more causes were found in 33 patients (22.4%). Bacterial pneumonia was present concomitantly with PCP in 9 patients, other opportunistic infections in 8 patients, and noninfectious pulmonary disease in 8 patients. Among the 52 patients with PCP, 8 (15.4%) also had other opportunistic infections, including 5 who had cytomegalovirus (CMV) reactivation with cytological evidence of CMV pneumonia on bronchoalveolar lavage (BAL) fluid. Most of the noninfectious pulmonary diseases were related to co-morbidities; examples were pulmonary edema related to heart failure and hypercapnic ARF related to chronic obstructive pulmonary disease.

Factors independently associated with a diagnosis of PCP were diagnosis of HIV infection at ICU admission (OR, 5.31; CI, 1.31–21.48; $P = 0.02$), time from respiratory symptom onset to ICU admission (OR, 1.06 per day; CI, 1.02–1.1; $P = 0.003$), and PCP prophylaxis (OR, 0.11; CI, 0.020.62, $P = 0.01$). Steroids were given to all patients with PCP and PaO_2 less than 70 mm Hg on room air and/or MV ($n = 46$). NIV was used in 22 (42.3%) of the 52 patients with PCP, of whom only 3 subsequently required tracheal intubation. Invasive MV was used in 7 (13.5%) patients with PCP. Pneumothorax occurred in 4 patients with PCP, including 1 patient who was receiving MV.

Overall in-hospital mortality was 19.7% ($n = 29$, including 16 deaths in the ICU), and remained consistent through the study period. Survival rates were not statistically different between the 4 etiological groups, even if MV was required (Table 2). Significant results

Table 4 Factors associated with in-hospital mortality in 147 HIV-infected patients with acute respiratory failure

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% Confidence interval	*P*	Odds ratio	95% Confidence interval	*P*
Invasive mechanical ventilation[a]	7.85	[3.22–19.13]	<0.0001	8.48	[2.91–24.73]	<0.0001
Vasopressors use[a]	7.48	[3.08–18.15]	<0.0001	4.48	[1.13–17.84]	0.03
Number of ARF causes, per additional cause	2.29	[1.77–8.64]	0.001	3.19	[1.16–8.83]	0.02
Time between hospital admission and ICU transfer, per day	1.05	[1.001–1.10]	0.04	1.05	[1.01–1.09]	0.01
Renal replacement therapy[a]	7.11	[2.24–22.61]	0.0009	NS		–
Pseudomonas aeruginosa pneumonia[b]	6.13	[1.29–29.14]	0.02	NS		–
Cytomegalovirus pneumonia[b]	6.69	[1.06–42.11]	0.04	NS		–
ARDS[a]	4.56	[1.07–19.48]	0.04	NS		–
Time between ICU admission and tracheal intubation, per day	1.48	[1.10–1.99]	0.009	NS		–
Length of NIV, days	1.30	[1.07–1.59]	0.009	NS		–
SOFA[c]	1.32	[1.18–1.48]	<0.0001	NS		–

Multivariate analysis was performed using backward stepwise logistic regression with in-hospital mortality as the outcome variable of interest. The goodness of fit (Hossmer–Lemeshow Chi-square *P* value) was 0.34.

ARF acute respiratory failure, *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome, *NIV* non-invasive ventilation, *SOFA* Sepsis-related Organ Failure Assessment

[a] During the ICU stay

[b] Initial diagnosis (within the first 72 h of ICU stay)

[c] At ICU admission

of univariate analysis are listed in Table 4. Most of variables associated with short-term prognosis reflected severity of organs failures, at admission or during the ICU stay. When etiological parameters were tested, only *Pseudomonas aeruginosa* pneumonia (OR, 6.13; 95% CI, 1.29–29.14; $P = 0.02$) and CMV pneumonia (OR, 6.69; 95% CI, 1.0642.11; $P = 0.04$) were found to be univariately linked to in-hospital mortality. Kaposi's sarcoma was also associated with a poor prognosis (OR, 8.67; 95% CI, 0.76–99.12), but the analysis was underpowered ($n = 3$, $P = 0.08$). By multivariate analysis (Table 4), 4 factors were independently associated with hospital mortality, namely, invasive MV (OR, 8.48; 95% CI, 2.91–24.73; $P < 0.0001$), vasopressor use (OR, 4.48; 95% CI, 1.13–17.84; $P = 0.03$), time from hospital admission to ICU transfer (OR, 1.05 per day; 95% CI, 1.01–1.09; $P = 0.01$), and the number of causes of ARF (OR, 3.19 per additional cause; 95% CI, 1.16–8.83; $P = 0.02$). None of the HIV-related characteristics (ART, CD4 lymphocyte count, and viral load) predicted hospital death.

Discussion

This study reports the causes and short-term outcome of ARF in 147 HIV-infected patients admitted to the ICU during the first 10 years after the advent of ART. The 19.7% hospital mortality rate is consistent with earlier evidence of recent survival gains among critically ill HIV-infected patients [11, 17]. However, in the 2 latest series from the San Francisco General Hospital (1996–1999 and 2000–2004), almost 40% of HIV-infected patients with ARF died before hospital discharge, and ARF was among the critical illnesses associated with the worst outcomes in HIV-infected patients [14, 15]. Comparable findings were obtained in the early ART era [4, 6, 7, 17]. The lower mortality rate in our patients cannot be ascribed to lesser disease severity. Severity of organ dysfunction was comparable to earlier studies, with one-third of patients requiring invasive MV and one-fourth requiring vasopressor support. Differences in terms of HIV-related characteristics, such as CD4 cell count and HIV viral load, should be taken into account for the comparison of short-term outcome between other recent series [4, 15–17] and ours. Nevertheless, and as in these previous studies, we found that these variables were not independent predictors of in-hospital mortality.

The introduction of ART does not explain the improved survival in our study. Fewer than one-third of our patients were on ART at ICU admission, in keeping with other studies [3, 11, 14, 15, 17], and this percentage showed no significant changes over the study period. It has been shown that the use of ART, together with the CD4 T-cell count, influences long-term outcomes of HIV-infected patients after ICU discharge [2, 3]. Our data suggest, however, that ART may have no influence on short-term survival of HIV-infected patients admitted to the ICU for ARF. Similarly, no independent influence of ART on short-term outcome was noted in studies of HIV-infected patients admitted to the ICU for any reason

[17, 23]. In our study, ART use was associated with nonopportunistic causes of ARF and CD4 T-cell counts were significantly lower in patients with opportunistic infections. However, it should be noted that among the 104 patients with newly diagnosed HIV infection, CD4 counts and viral load were available in only 67 and 64 patients, respectively. Nevertheless, the severity of organ failure at admission, as reflected by the SOFA score, was not different between patients receiving ART and those who did not. Moreover, survival was not significantly different across the 4 etiological groups, and HIV-related causes were not independently associated with death before hospital discharge. Thus, improved outcomes in patients with opportunistic pulmonary infections, mainly PCP, may contribute to explaining the lack of a survival advantage in patients on ART.

PCP was an independent predictor of death in most of the previous studies of critically ill HIV-infected patients, particularly when MV was needed or pneumothorax occurred, with hospital mortality rates ranging from 45% to 80% [1, 7, 11, 14–16, 24–26]. Thus, the fact that PCP was slightly more frequent in other recent series [15, 16] could have contributed to the better overall survival in our cohort. However, the mortality rate in our patients with PCP was the lowest reported to date, and this cause was associated with the best short-term outcome. This difference cannot be ascribed to differences in steroids use, as steroids have been extensively prescribed to treat severe PCP since the early 1990s [27]. Recent improvements in the survival of HIV-infected patients with PCP are related to advances in respiratory support modalities, such as the routine use of pressure support ventilation [28] and protective ventilation for intubated patients with PCP [29, 30], who consistently meet criteria for acute lung injury or acute respiratory distress syndrome (ARDS).

By multivariate analysis, independent predictors of hospital mortality included a need for invasive MV, a need for vasopressors, a longer time from hospital admission to ICU admission, and the presence of more than 1 cause of ARF. Transfer of HIV-infected patients from another ward to the ICU has been associated with higher mortality rates than ICU admission from the emergency room [8]. In another study, early intensive management improved the prognosis of patients with severe bacterial sepsis [31]. In our cohort, half the patients had ARF due to bacterial pneumonia, including 37.8% with septic shock. In two-thirds of the patients with bacterial pneumonia, faster ICU admission from the emergency room may have allowed earlier initiation of appropriate sepsis management. Thus, the lower hospital mortality rate compared to earlier studies [6, 32, 33], most notably in patients with bacterial pneumonia, may be partly ascribable to the policy of prompt ICU admission from the emergency department at our hospital. Furthermore, our aggressive diagnostic strategy supplied the etiology of ARF in nearly all our patients. Establishing the etiological diagnosis has been shown to improve survival [34]. Thus, our results suggest that hospital mortality of HIV-infected patients with ARF depends chiefly on the severity of organ failure at admission and during the ICU stay and that improvement in-hospital survival results primarily from advances in intensive care practices, as opposed to improvement in immune status and use of ART.

Our results support earlier evidence that bacterial pneumonia is now a major cause of ARF among HIV-infected patients [4, 6, 8]. ART reduces the risk of bacterial pneumonia during AIDS [35], although HIV-infected patients with mild CD4 T-cell depletion remain at increased risk [36]. This may explain why, despite ART advent, bacterial pneumonia was the most frequent cause of ARF in our study. Two studies found a decrease in the incidence of PCP-related ARF early in the ART era [3, 4]. In our cohort, PCP was diagnosed in one-third of patients overall and was even more common among patients with previously unknown HIV infection. That incidence of PCP remains high is in keeping with recent series from San Francisco and London, where PCP was the most common etiology [15, 17]. The fact that more than half the cases of PCP occurred in patients who were aware of their HIV infection suggests inadequate compliance with PCP prophylaxis. Poor compliance may explain why the frequency of PCP remained unchanged throughout the study period, although the frequency of inaugural ARF tended to decrease. The proportion of noninfectious non-HIV-related causes of ARF was considerably higher than in studies done before the advent of ART [4, 6, 24]. The immune system reconstitution and increased life expectancy obtained with ART expose the patients to exacerbations of co-morbid conditions unrelated to HIV infection, such as chronic obstructive pulmonary disease or chronic heart failure. This observation is the main change in clinical and etiological patterns induced by ART.

Our study has several limitations. First, it has the limitations inherent in its retrospective design. Second, we defined the use of ART and PCP prophylaxis as adherence to these treatments, as opposed to their prescription. We cannot exclude that some patients were misclassified as adherent or nonadherent by the infectious diseases physicians. Difficulties with the evaluation of adherence occur in all studies of HIV-infected patients, even those conducted prospectively. Third, our study was done in a single ICU, which may have led to patient selection bias. The population admitted to an ICU depends on local policies of admission and influences both etiological and outcome patterns [37]. However, HIV infection is not considered a reason for refusing admission at our ICU, and the characteristics of our population are consistent with those of patients in other studies [11, 17].

In conclusion, hospital mortality of HIV-infected patients with ARF depends mainly on the number and severity of organ failure at admission and during the ICU stay and is not influenced by the extent of immune deficiency. Hospital survival has improved when compared with studies from the pre-ART era, which is not ascribable to the advent of highly active antiretroviral therapy. We believe that this evolution results from global progresses in intensive care practices, such as early ICU transfer from the emergency department or other hospital wards, NIV for PCP, and aggressive management of bacterial sepsis, even if our study was not designed to measure the individual effects of these procedures. Finally, we found that bacterial pneumonia was the most common cause of ARF in HIV-infected patients, even if PCP remains a major cause of life-threatening respiratory failure, most notably in patients whose HIV infection was previously unknown.

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