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CLINICAL AND EPIDEMIOLOGICAL STUDY

All-cause mortality in hospitalized HIV-infected patients at an acute tertiary care hospital with a comprehensive outpatient HIV care program in New York City in the era of highly active antiretroviral therapy (HAART)

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Abstract
Purpose The overall mortality rate among human immunodeficiency virus (HIV)-infected patients has significantly declined in the era of highly active antiretroviral therapy (HAART). However, little is known about the causes of death for HIV-infected patients who are hospitalized in acute care hospitals.
Methods A retrospective chart review of hospitalized HIV-infected patients from 2004 to 2008 was undertaken.
Results Among 9,101 hospitalized HIV-infected patients, 237 deaths were identified, with an overall mortality rate of 237/9,101 (2.6 %). The mortality rate did not differ from year to year (2–3 %). Charts for 208 patients were available for review and were analyzed. The following medians were noted: age 49 years, CD4+ T cell count 137 cells/μL, HIV viral load (VL) $\log_{10}$ 3.93, length of stay 16 days. The proportion of men were 71.6 %, African Americans (AAs) were 62.5 %, and HAART use was 52.4 %, with an overall good adherence rate of only 17.3 %. The major causes of death were non-acquired immunodeficiency syndrome (AIDS)-related illness (81.7 %, 170/208): sepsis (34.6 %, 72/208), non-recurrent bacterial pneumonia (19.7 %, 41/208), cardiac disease (5.8 %, 12/208), liver disease (4.3 %, 9/208), and non-AIDS-related malignancy (4.3 %, 9/208). The major causes of death due to AIDS-related illness (18.3 %, 38/208) were: *Pneumocystis jirovecii* pneumonia (4.8 %, 10/208) and AIDS-related encephalopathy, including progressive multifocal leukoencephalopathy/cryptococcal meningitis/cerebral toxoplasmosis (3.4 %, 7/208). Mortality due to AIDS-related illnesses was associated with younger age (median age 44 vs. 50 years, $p = 0.001$), female sex (44.7 vs. 24.7 %, $p = 0.013$), and lower CD4+ T cell counts (median 10 vs. 66, $p = 0.001$).
Conclusion The mortality rate in our hospitalized HIV-infected patients remained low. Non-AIDS-related illnesses were the major causes of death, with sepsis being the most common. Low CD4+ T cell count and female sex were associated with deaths due to AIDS-related illness. Poor adherence to HAART was also noted in those patients to whom treatment was offered in the outpatient setting. Further prospective studies are needed in order to better define the epidemiology and outcomes for hospitalized HIV-infected patients in the era of HAART.

Keywords HIV · Hospitalization · Mortality · Highly active retroviral therapy (HAART)

Introduction

Life expectancy for human immunodeficiency virus (HIV)-infected patients has been significantly improved in the era of highly active antiretroviral therapy (HAART), largely due to the reduction in mortality attributable to acquired immunodeficiency syndrome (AIDS)-related illnesses [1]. However, non-AIDS mortality has been increasing. A

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recent study from New York City that analyzed 12,715 deaths in HIV-infected patients reported to the New York City HIV/AIDS Reporting System and Vital Statistics Registry between 1999 and 2004 identified that non-HIV-related causes of death have increased by 32.8 %. This increase was attributed to substance abuse, cardiovascular disease, and non-AIDS-defining malignancies [2]. Also, other recent analyses of HIV cohort studies from Europe and North America showed that more than half of the mortality in HIV-infected patients was due to non-AIDS-related illnesses, including non-AIDS malignancies, non-AIDS infections, violence/drug-related causes, liver disease, and cardiovascular disease [3]. Although these large cohort studies showed the trend of increased non-AIDS mortality in HIV-infected patients, little is known about the causes of death for HIV-infected patients who are hospitalized in acute care hospitals. Therefore, we investigated the outcomes of hospitalized HIV-infected patients in order to describe and evaluate the specific causes of death of hospitalized HIV-infected patients in large tertiary acute care hospital in New York City.

Methods

St. Luke's-Roosevelt Hospital Center (SLRHc) is a 1,076-bed, full-service, tertiary acute care hospital, serving the Upper West Side of Manhattan, New York City, with an active comprehensive HIV program [the Center for Comprehensive Care (CCC)]. Annually, the CCC offers both outpatient and inpatient medical care to over 5,000 HIV-infected patients by HIV-trained doctors. We performed an Institutional Review Board-approved retrospective medical chart review of all adult HIV-infected inpatients who died from 2004 to 2008 at SLRHc.

Clinical variables for data collection included demographic characteristics (age, sex, ethnicity), medical comorbidities other than HIV (cardiac disease defined by congestive heart failure or myocardial infarction; pulmonary disease defined by chronic obstructive pulmonary disease or asthma; liver disease defined by hepatitis or end-stage liver disease, including liver cirrhosis and liver failure; kidney disease defined by serum creatinine >1.5 mg/dl; presence of diabetes mellitus), history of HAART, CD4+ T cell count and HIV viral load at the time of hospital admission, and the cause of death determined on the basis of clinical, laboratory, and microbiologic data by medical chart review.

Death due to an AIDS-defining illness was defined as death attributable to one of the Centers for Disease Control and Prevention (CDC) category C diseases. Death due to sepsis was defined as the death of a patient with a blood culture positive for a bacterial pathogen but without bacterial pneumonia and/or with evident refractory hypotension that required vasopressor therapy in the absence of another cause of refractory hypotension. The death of a patient due to non-recurrent bacterial pneumonia was defined as having either compatible chest radiograph findings (patchy alveolar infiltrates or consolidation) and a blood culture result positive for a bacterial pathogen, or compatible chest radiograph findings and two of the three following conditions: a sputum culture result revealing a pathogen known to cause bacterial pneumonia, fever (temperature of >38 °C), or an elevated level of polymorphonuclear leukocytes, as determined by a differential of white blood cells (WBCs) in peripheral blood with less than two episodes within a 1-year period (recurrent bacterial pneumonia as an AIDS-defining condition was defined as two or more episodes within a 1-year period). Death due to liver disease was defined as the death of a patient with underlying liver disease and one of the following conditions: coagulopathy, bleeding esophageal varices, hepatic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis. Death due to definite *Pneumocystis jirovecii* pneumonia (PCP) was defined as the death of a patient with respiratory failure and a positive result of silver stain on a bronchoalveolar lavage specimen. Death due to probable PCP was defined as the death of a patient with respiratory failure and two or more of the following conditions: hypoxia, compatible chest radiograph findings demonstrating an interstitial infiltrate, or an elevated lactate dehydrogenase level without microbiologic confirmation of another infectious process. Death due to malignancy was defined as the death of a patient with a biopsy-proven malignancy and without another probable cause of death. Death due to cytomegalovirus (CMV) infection was defined as the death of a patient with biopsy-proven or culture-proven end-stage organ disease due to CMV. A patient was considered to have died of *Mycobacterium avium-intracellulare* (MAI) infection if this infection was proven by culture from sterile sites. Finally, death due to *Mycobacterium tuberculosis* (MTB) infection was defined as the death of a patient with positive culture from respiratory specimen or lymph node without other identifiable causes of death.

Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS). Dichotomous variables were compared using Fisher's exact test or Pearson's χ^2 test. For continuous variables, the Mann–Whitney *U*-test was used. A p-value <0.05 was considered to be statistically significant.

Results

Among 9,101 hospitalized HIV-infected patients from 2004 to 2008 at SLRHc, 237 deaths were identified, with

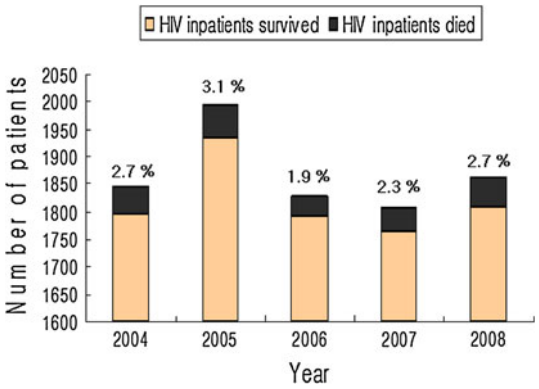

Fig. 1 Hospital admissions and mortality rates of human immunodeficiency virus (HIV)-infected inpatients per year, in the period 2004–2008. Yearly mortality rates of HIV-infected inpatients are known

an overall inpatient mortality rate of 2.6 % (237/9101). The yearly inpatient mortality rates were 2.7, 3.1, 1.9, 2.3, and 2.7 %, respectively, in the years 2004 to 2008 (Fig. 1). Mortality rate data for hospitalized HIV-negative patients were available from 2005 to 2008 at SLRHc. The overall inpatient mortality rate for HIV-negative patients was 1.6 % (2,690/169,421), with yearly inpatient mortality rates of 1.5, 1.6, 1.6, and 1.7 %, respectively. Of the 237 patients who died at SLRHc from 2004 to 2008, medical charts were available for 208 patients for review and analysis. Our study cohort of 208 patients consisted of mostly men (71.6 %) and African Americans (62.5 %). The proportion of patients on HAART was 52.4 %. The median age, CD4+ T cell count (cells/μL), and HIV viral load (copies/ml) $\log_{10}$ at the time of hospital admission were 49 years, 137 cells/μL, and 3.93, respectively. The median length of hospital stay was 16 days. Major causes of death were non-AIDS-related illness (81.7 %, 170/208): sepsis (34.6 %, 72/208), non-recurrent bacterial pneumonia (19.7 %, 41/208), cardiac disease (5.8 %, 12/208), liver disease (4.3 %, 9/208), non-AIDS-related malignancy (4.3 %, 9/208), violence/substance abuse (4.3 %, 9/208), gastrointestinal hemorrhage (3.4 %, 7/208), *Clostridium difficile* infection (2.9 %, 6/208), and non-infectious and non-specific encephalopathy (2.4 %, 5/208). Causes of death due to AIDS-related illness (18.3 %, 38/208) were PCP (4.8 %, 10/208), AIDS-related encephalopathy, including progressive multifocal leukoencephalopathy/cryptococcal meningitis/cerebral toxoplasmosis (3.4 %, 7/208), MAI/MTB infection (1.9 %, 4/208), wasting syndrome due to AIDS (1.9 %, 4/208), AIDS-related malignancy (1.4 %, 3/208), CMV disease (1.4 %, 3/208), and recurrent bacterial pneumonia (3.4 %, 7/208). These are shown in Table 1.

We categorized the patients into two groups for further analysis: patients who died of non-AIDS-related illness (non-AIDS mortality group) (81.7 %, 170/208) and patients who died of AIDS-related illness (AIDS mortality group) (18.3 %, 38/208). Younger age was noted in the AIDS mortality group. The median age was 44 years, with interquartile range (IQR) 38–49 years and 50 years with IQR 43–55 years, respectively, for the AIDS mortality group and the non-AIDS mortality group, $p = 0.001$. There were more females in the AIDS mortality group (44.7 %, 17/38) than in the non-AIDS mortality group (24.7 %, 42/170), $p = 0.013$. Among the medical co-morbidities, the presence of liver disease was more prevalent in the non-AIDS mortality group (39.0 %, 69/177) than in the AIDS mortality group (19.4 %, 6/31), $p = 0.036$. There was a trend towards more patients with other co-morbidities, including cardiac/pulmonary disease, liver disease, and diabetes mellitus in the non-AIDS mortality group; however, this trend was not statistically significant. There were no significant differences in the proportion of patients on HAART (50.0 % for the AIDS mortality group vs. 52.9 % for the non-AIDS mortality group, $p = 0.743$), duration of HAART (median duration of HAART was 57 and 66 months for the AIDS mortality group and the non-AIDS

Table 1 Causes of death in hospitalized human immunodeficiency virus (HIV)-infected patients from 2004 to 2008

Cause of death	Number of patients (%) ($N = 208$)
Non-AIDS-related illness	170 (81.7)
Sepsis	72 (34.6)
Non-recurrent bacterial pneumonia	41 (19.7)
Cardiac disease	12 (5.8)
Liver disease	9 (4.3)
Non-AIDS malignancy	9 (4.3)
Violence/substance abuse	9 (4.3)
Gastrointestinal hemorrhage	7 (3.4)
Clostridium difficile infection	6 (2.9)
Non-infectious and non-specific encephalopathy	5 (24)
AIDS-related illness	38 (18.3)
Pneumocystis jirovecii pneumonia	10 (4.8)
AIDS-related encephalopathy[a]	7 (3.4)
MAI/MTB infection[b]	4 (1.9)
Wasting syndrome due to AIDS	4 (1.9)
AIDS-related malignancy	3 (1.4)
CMV[c] disease	3 (1.4)
Recurrent bacterial pneumonia	7 (3.4)

[a] Including progressive multifocal leukoencephalopathy/cryptococcal meningitis/cerebral toxoplasmosis

[b] *Mycobacterium avium-intracellulare*/*Mycobacterium tuberculosis* infection

[c] Cytomegalovirus

Table 2 Characteristics of HIV-infected inpatients who died stratified by the causes of death (non-AIDS mortality vs. AIDS mortality)

	Non-AIDS mortality, $N = 170$	AIDS mortality, $N = 38$	p Value
Age median (IQR[a])	50 (43–55)	44 (38–49)	0.001
Sex			
Female (%)	42 (24.7)	17 (44.7)	0.013
Male (%)	128 (75.3)	21 (55.3)	
Ethnicity			
White (%)	22 (12.9)	1 (2.6)	0.085
Hispanic (%)	31 (18.2)	8 (21.1)	0.687
African American (%)	103 (60.6)	27 (71.1)	0.228
Asian (%)	0 (0.0)	1 (2.6)	0.183
Unknown (%)	14 (8.2)	1 (2.6)	0.315
Presence of co-morbidities[b]			
Cardiac disease (%)	38 (22.4)	4 (10.5)	0.101
Pulmonary disease (%)	24 (14.1)	3 (7.9)	0.426
Liver disease (%)	66 (38.8)	9 (23.7)	0.079
Diabetes mellitus (%)	20 (11.8)	3 (7.9)	0.774
Kidney disease (%)	21 (12.4)	5 (13.2)	1.000
Use of HAART[c] (%)	90 (52.9)	19 (50.0)	0.743
Duration of HAART[d] (IQR)	66 (42–89)	57 (13–95)	0.568
Adherence to HAART (%)	33 (19.4)	3 (7.9)	0.090
CD4+ T cell[e] median (IQR)	66 (14–213)	10 (3–105)	0.001
HIV VL[f] $\log_{10}$ median (IQR)	4.33 (1.88–5.02)	4.68 (3.91–5.11)	0.158
Hospital stay[g] median (IQR)	10 (4–22)	14 (6–23)	0.366

[a] Interquartile range

[b] Cardiac disease defined by congestive heart failure or myocardial infarction, pulmonary disease defined by chronic obstructive pulmonary disease or asthma, liver disease defined by hepatitis or end-stage liver disease, including liver cirrhosis and liver failure, kidney disease defined by serum creatinine >1.5 mg/dl

[c] Use of highly active antiretroviral therapy (HAART) at the time of hospital admission

[d] Duration of HAART in months

[e] CD4+ T cell count (cells/μL) at the time of hospital admission

[f] HIV viral load (copies/ml) at the time of hospital admission

[g] Hospital stay in days until death

mortality group, respectively, $p = 0.568$), and adherence to HAART (7.9 % for the AIDS mortality group vs. 19.4 % for the non-AIDS mortality group, $p = 0.090$) between the two groups, although there was a tendency of lower adherence rates of HAART in the AIDS mortality group. Of note, there were significantly lower CD4+ T cell counts at the time of hospital admission in the AIDS mortality group compared to the non-AIDS mortality group; the median CD4+ T cell count (cells/μL) with IQR was 10 (3–105) and 66 (14–213) for the AIDS mortality group and the non-AIDS mortality group, respectively, $p = 0.001$. These are shown in Table 2.

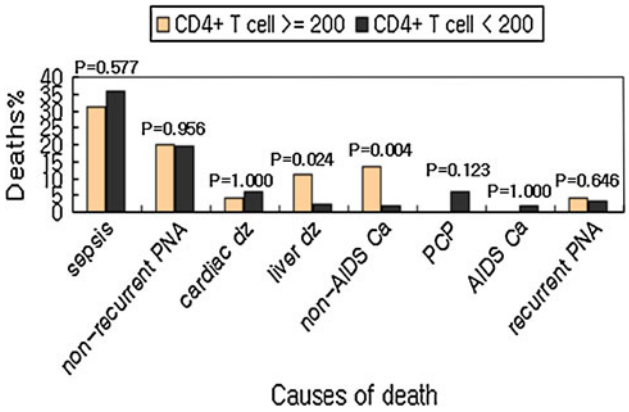

Fig. 2 Causes of death for HIV-infected inpatients stratified by CD4+ T cell count (cells/μL). Causes of death: *non-recurrent PNA*, non-recurrent bacterial pneumonia; *cardiac dz*, cardiac disease; *liver dz*, liver disease; *non-AIDS Ca*, non-AIDS-related malignancy; *PCP*, *Pneumocystis jirovecii* pneumonia; *AIDS Ca*, AIDS-related malignancy; *recurrent PNA*, recurrent bacterial pneumonia

Stratified analysis for patients by CD4+ T cell count of ≥200 cells/μL or <200 cells/μL was then conducted in order to evaluate the causes of death in regard to the CD4+ T cell count at the time of hospital admission. Among 208 HIV-infected inpatients who died, there were 45 patients (21.6 %, 45/208) with a CD4+ T cell count ≥200 cells/μL and 163 patients (78.4 %, 163/208) with a CD4+ T cell count <200 cells/μL. There was significantly greater use of HAART and adherence to HAART in patients with a CD4+ T cell count ≥200 cells/μL [use of HAART 73.3 % (33/45) and adherence to HAART 42.2 % (19/45)] than in patients with a CD4+ T cell count <200 cells/μL [use of HAART 46.6 % (76/163) and adherence to HAART 10.4 % (17/163)], $p = 0.001$ and $p < 0.001$, respectively. As shown in Fig. 2, 11.1 % of patients (five patients, 5/45) with a CD4+ T cell count ≥200 cells/μL died of liver disease, compared with 2.5 % of patients (four patients, 4/163) with a CD4+ T cell count <200 cells/μL, $p = 0.024$. There were also more deaths from non-AIDS-related malignancy in patients (13.3 %, 6/45) with a CD4+ T cell count ≥200 cells/μL than in patients (1.8 %, 3/163) with a CD4+ T cell count <200 cells/μL, $p = 0.004$. Although there were no deaths from PCP and AIDS-related malignancy in patients with a CD4+ T cell count ≥200 cells/μL, these findings were not statistically significant.

Discussion

Our study demonstrated an overall mortality rate of 2.6 % for hospitalized HIV-infected patients from 2004 to 2008 at

an acute care facility hospital with an active comprehensive HIV program providing both inpatient and outpatient medical care, including access to HAART, in New York City. This inpatient mortality rate for HIV-infected patients was higher than that of HIV-negative patients at the same institution during the study period; however, it was significantly lower than the inpatient mortality rates for HIV-infected patients observed in the United States pre-HAART era (6–12 %) [4, 5]. There are several potential explanations for the decreased mortality rate for HIV-infected inpatients in our patient populations. First, the introduction of HAART has affected the overall mortality of HIV-infected patients by marked reductions in AIDS-related deaths, including deaths from opportunistic infection-related deaths in the United States [6]. In addition, the use of HAART has also led to a decreased number of hospital admissions among HIV-infected patients, from 149,000 in 1995 to 70,000 in 2003 in the United States [7]. As the number of hospital admissions among HIV-infected patients decreases in the era of HAART, the number of physicians with experience in managing the hospital care of HIV-infected patients is likely to decrease as well. However, attending physicians providing inpatient medical care for HIV-infected patients at our institution (SLRHc) are staff members of the CCC and all have specialized training in managing HIV-related medical issues and have experience in both outpatient and inpatient settings. Previous studies suggested that greater physician experience in the care of persons with AIDS improves survival [8, 9]. Therefore, our results of an overall low mortality rate for HIV-infected inpatients may indicate the importance of inpatient medical care being provided by physicians with experience in HIV/AIDS in the HAART era.

We found that the majority of HIV-infected inpatients died from non-AIDS-related illness. However, the proportions of specific causes of death from non-AIDS-related illness were significantly different from recent studies [6, 10, 11] conducted at outpatient settings, in which chronic non-AIDS-related illness, including cardiovascular disease, liver disease, and non-AIDS-related malignancy, were the major causes of deaths. In contrast, more than half of the deaths in our study were attributable to acute non-AIDS-related illness, including sepsis and non-recurrent bacterial pneumonia. This difference in the proportion of specific causes of non-AIDS-related deaths might be explained by the severity of medical illness of HIV-infected patients, which require inpatient care versus outpatient care. Recent studies conducted among critically ill HIV-infected patients admitted to the intensive care unit (ICU) in the era of HAART revealed that major causes for ICU admission were respiratory failure, including bacterial pneumonia and PCP, followed by sepsis [12–15] with the changing epidemiology of decreased numbers of PCP diagnoses [13, 14]. Of note, low CD4+ T cell count [15–17] and diagnosis of sepsis [12, 15, 17] were independently associated with increased hospital mortality in critically ill HIV-infected patients. Furthermore, bacterial infections [18, 19] and bacterial pneumonia [20] were increasingly found in HIV-infected patients with low CD4+ T cell count. Given the low CD4+ T cell count (median 137 cells/μL) at the time of hospital admission in our cohort of HIV-infected patients who died in the hospital, the results of our study may indicate that patterns of mortality in hospitalized HIV-infected patients closely resemble those of critically ill HIV-infected patients admitted to the ICU in the era of HAART.

Several variables, including female sex and lower CD4+ T cell count, were associated with mortality in HIV-infected inpatients due to AIDS-related illness in our study. Also, there was the tendency of a lower adherence rate of HAART in the AIDS mortality group. These results are similarly related to findings from previous studies, which may explain the possible association with mortality due to AIDS-related illness; women were also less likely to receive HAART [21] and were associated with increased AIDS disease progression, as well as decreased survival in the HAART era [22], not only from inequalities in the access to HAART, but also possibly from psychosocial factors, such as active substance abuse, lack of social support, and depression [21]. Lower CD4+ T cell count and higher HIV viral load have been associated with advanced AIDS disease [23], and our finding that lower CD4+ T cell count was associated with AIDS-related illness mortality is consistent with the findings from another study [10].

Our data demonstrated that significantly more HIV-infected inpatients who died at the hospital due to either liver disease or non-AIDS-related malignancy had admission CD4+ T cell count $\geq$200 cells/μL. There was significantly more use of HAART with better adherence to HAART in HIV-infected inpatients who died at the hospital with admission CD4+ T cell count $\geq$200 cells/μL. There was also an increased tendency for better adherence to HAART in HIV-infected inpatients who died due to non-AIDS-related illness. These findings are closely related to recent studies [6, 10, 11] conducted at the outpatient setting among HIV-infected patients with median CD4+ T cell count ranging from 287 to 528 cells/μL, in which chronic non-AIDS-related illness, including liver disease, and non-AIDS-related malignancy were the major causes of deaths, suggesting that the proportion of deaths due to non-AIDS-related illness will likely increase among hospitalized HIV-infected patients with good adherence to HAART.

This study has several limitations. First, as our study is retrospective and observational in study design, we cannot

exclude bias completely because the causes of death in our study were based on the review of medical charts. However, we used consistent definitions to minimize the potential bias. Second, our data is from a single acute care hospital in New York City, which may not be generalized to other clinical settings, especially those serving different ethnic groups of HIV-infected patients with different adherence rates to HAART in the United States or HIV-infected patients in resource-limited countries. Third, our study period was from 2004 to 2008 and did not include more recent years from 2009 to 2011, when there were more newly available options of HAART, such as raltegravir and maraviroc, as well as changes in HIV care towards the earlier initiation of HAART at the higher CD4+ T cell count, which might have affected the inpatient mortality for HIV-infected patients.

Despite these limitations, we have demonstrated a low mortality rate for hospitalized HIV-infected patients in the era of HAART. However, there was an overall low rate of adherence to HAART among hospitalized HIV-infected patients who died. The majority of deaths were due to non-AIDS-related illness, especially those caused by sepsis and non-recurrent bacterial pneumonia. Low CD4+ T cell count and female sex were associated with deaths due to AIDS-related illness, indicating the need for better HIV management strategies for these underrepresented minority groups of HIV-infected patients. Further prospective studies involving larger numbers of hospitalized HIV-infected patients are needed in order to better define the epidemiology and outcomes for hospitalized HIV-infected patients in the era of HAART.

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Conflict of interest All authors declared that they have no conflicts.

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