Original Article

DOI: 10.5582/bst.2016.01195

Trends and characteristics of all-cause mortality among HIV-infected inpatients during the HAART era (2006-2015) in Shanghai, China

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Summary **Globally, the overall mortality rate among HIV-infected patients has significantly declined during the HAART era. Deaths among HIV-infected inpatients need to be characterized in order to formulate intervention strategies to further improve medical care for this population and their prognosis. In the current study, deaths among HIV-infected inpatients from 2006 to 2015 at a medical center for HIV infection and AIDS patient care in Shanghai, China were retrospectively analyzed. Trends in mortality rates and the proportion of deaths caused by AIDS or non-AIDS-related illnesses were evaluated. A bivariate analysis was performed to identify the demographic and clinical factors associated with AIDS or non-AIDS-related deaths among HIV-infected inpatients. Among 6,473 HIV-infected patients who were discharged from 2006 to 2015, 326 deaths (5.04%) were identified. The yearly mortality rate declined significantly over time ($\chi^2 = 34.41$, $p < 0.001$). Results revealed that most deaths were attributed to AIDS-related illnesses (76.9 %, 233/303), and the proportion of causes of death did not change significantly over time ($\chi^2 = 13.847$, $p = 0.127$). Bivariate analysis identified characteristic factors associated with AIDS-related mortality. Compared to patients who died of non-AIDS illnesses, patients who died of AIDS-related illnesses had a CD4+ T cell count lower than 50 cells/μL (OR 4.587, 2.377-8.850) and fewer liver (OR 0.391, 0.177-0.866) or renal comorbidities (OR 0.188, 0.067-0.523) on admission. Results indicated that the overall in-hospital mortality rate among HIV-infected patients has declined over the past decade. However, AIDS-related illnesses were still the major causes of deaths among HIV-infected inpatients, suggesting that further efforts are needed to improve AIDS care in China.**

Keywords: Hospital mortality, HIV infection, AIDS, antiretroviral therapy

1. Introduction

Highly active antiretroviral therapy (HAART) has led to a dramatic decline in mortality among people living with human immunodeficiency virus (HIV) infection (PLWH) or acquired immune deficiency syndrome (AIDS) (*1*), with improved life expectancy approaching that of the general population (*2*). As a large multinational study from prior to 1995 to 2006 indicated, the excess mortality rate among HIV-infected individuals decreased from 40.8 to 6.1 per 1000 person-years (*3*).

In the current HAART era, AIDS is more like a chronic manageable disease rather than a rapidly progressing and fatal one (*2*). Therefore, the focus of HIV/AIDS care has been shifting from inpatient medical treatment to outpatient-based chronic disease management. However, the hospitalization rate and inpatient mortality rate remained higher in PLWH despite increasing accessibility to HAART in comparison to

Released online in J-STAGE as advance publication January 30, 2017.

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either the general population or HIV-negative individuals (*4-6*).

Deaths among HIV-infected inpatients during the HAART era need to be characterized in order to formulate intervention strategies to improve medical care and further reduce mortality in this population. Recent studies examining deaths of HIV-infected inpatients in the United States revealed that the in-hospital mortality rate declined significantly and that major causes of deaths had shifted to non-AIDS-related diseases (*4,7*). In settings with limited medical resources such as sub-Saharan Africa, the in-hospital mortality rate among HIV-infected adults remained high and AIDS-related illnesses still caused most deaths (*8*). To the extent known, the mortality trends or the causes of death among Chinese HIV-infected inpatients have seldom been reported during the HAART era. The current study retrospectively reviewed the outcomes, calculated the mortality, and analyzed the causes of death in HIV-infected inpatients at a medical center for HIV infection and AIDS in Shanghai over the past decade (2006-2015).

2. Materials and Methods

2.1. *Subjects*

This study was conducted at the Shanghai Clinical Center for Public Health (SCCPH), a tertiary care hospital affiliated with Fudan University. The SCCPH is the only designated medical institution that has provided outpatient and inpatient care for PLWH in Shanghai since the 1990s. Currently, about 6,000 HIV-infected patients in Shanghai are being regularly followed by the SCCPH. In 2015, more than 1,300 HIV-infected patients were admitted for AIDS or non-AIDS-related illnesses. All deaths of HIV-infected inpatients at the SCCPH from January 1, 2006 to December 31, 2015 were retrospectively reviewed. This study was approved by ethics committee of the SCCPH.

2.2. *Data collection*

A standardized data collection tool was used to abstract demographic characteristics (*i.e*. age, gender, duration of hospital stay), medical comorbidities besides AIDS-related diseases (cardio-cerebrovascular disease including hypertension, congestive heart failure, myocardial infarction, and stroke; diabetes mellitus; pulmonary disease including chronic obstructive pulmonary disease and asthma; liver disease including chronic hepatitis B or C and liver cirrhosis; kidney dysfunction defined by serum creatinine > 1.5 mg/dL; and anemia defined as hemoglobin < 100 g/L; thrombocytopenia defined as a blood platelet count < 100×10^9/L), a history of HAART administration, and the CD4+ T cell count on admission.

Two HIV-trained clinicians independently identified the causes of deaths based on clinical, laboratory, radiological, and microbiologic data through a comprehensive review of medical records. If there was disagreement over the cause of death, the final determination was made by consensus between the two clinicians. The causes of deaths were classified as AIDS-related or non-AIDS-related illnesses based on published definitions. Death caused by one of the Centers for Disease Control and Prevention (CDC) category C diseases was defined as AIDS-related death (*9,10*). Non-AIDS illnesses included non-AIDS infections, cardiovascular disease, liver disease, non-AIDS malignancy, renal disease, gastrointestinal hemorrhage, and trauma. Infectious etiologies not on the list of AIDS-defining conditions were classified as non-AIDS infection, e.g. sepsis and non-recurrent bacterial pneumonia (*4*). Cardiovascular disease was deemed to cause death if patients had one of the following clinical manifestations: cardiac arrest, ischemic or hemorrhagic stroke, congestive heart failure, myocardial infarction, or cardiac arrhythmia. Death from liver disease was deemed to occur when one of the following manifestations occurred with underlying liver disease: coagulopathy, bleeding esophageal varices, hepatic encephalopathy, hepatorenal syndrome, or spontaneous bacterial peritonitis. Death from renal disease was defined as death from primary renal failure. Deaths caused by gastrointestinal bleeding without underlying liver disease were attributed to gastrointestinal hemorrhage.

2.3. *Statistical analysis*

Statistical analysis was performed using SPSS version 19.0 for Windows. Overall or yearly mortality rates were calculated as the percentage of deaths overall or yearly among patients who were diagnosed with an HIV infection or AIDS and discharged (*4,7*). The chi-squared test was used to compare categorical variables, and group comparisons of quantitative variables were performed using a parametric (analysis of variance) or nonparametric technique (Wilcoxon test) in accordance with the distribution of the variable. Bivariate analysis was used to determine factors associated with AIDS versus non-AIDS-related deaths in the cohort.

3. Results

3.1. *Mortality among HIV-infected inpatients*

In total, there were 326 in-hospital deaths among 6,473 HIV-infected patients discharged from the SCCPH from 2006 to 2015 (Figure 1), with an overall mortality rate of 5.04% (326/6,473). Notably, the mortality rate among HIV-infected inpatients ($\chi^2 = 34.41$, $p < 0.001$) tended to decline during this period, in which the yearly inpatient mortality rates were 12.33% (9/73), 8.84% (16/181), 8.2% (25/305), 5.74% (24/418), 6.67% (37/555), 4.42% (31/701), 5.44% (46/845), 4.49%

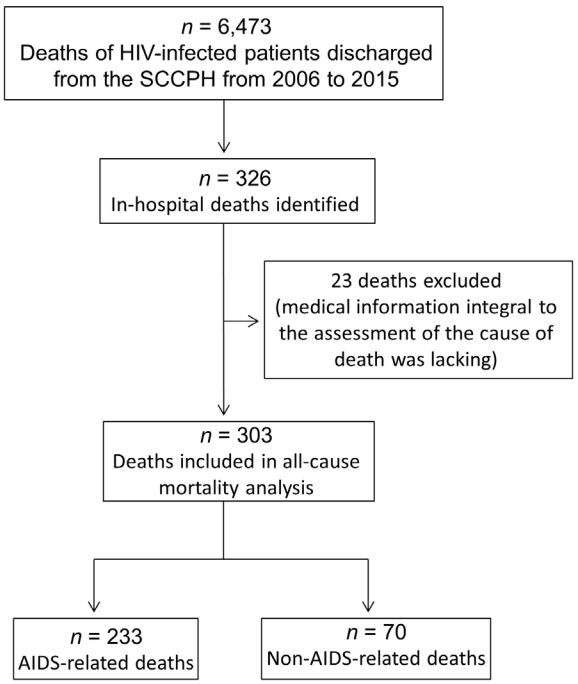

Figure 1. Flow for identifying the study population. Among 6,473 HIV-infected patients who were discharged from the SCCPH from 2006 to 2015, there were 326 deaths. In 23 deaths, medical information integral to the assessment of the cause of death was lacking, so those deaths were excluded. The remaining 303 deaths were included in an all-cause mortality analysis. Of those deaths, 233 were caused by AIDS-related illnesses (76.9%) while the remaining 70 were non-AIDS-related.

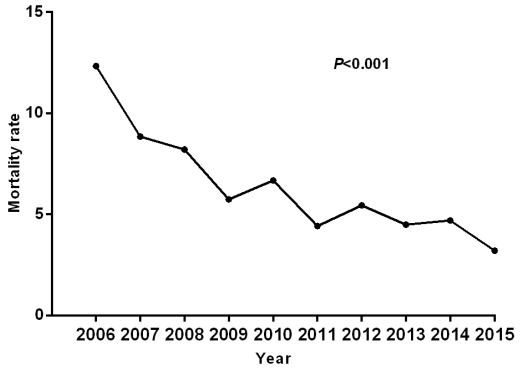

Figure 2. Yearly mortality rates among HIV-infected inpatients from 2006-2015. The yearly inpatient mortality rate declined from 12.33% in 2006 to 3.20% in 2015.

(42/935), 4.70% (54/1,148), and 3.20% (42/1,312), respectively (Figure 2).

3.2. *Analysis of causes of death*

Out of 326 deaths of HIV-infected patients, 23 lacked medical information integral to the assessment of the cause of death, so those deaths were excluded from further analysis (Figure 1). The remaining 303 deaths were included in the all-cause mortality analysis, and the demographic and clinical characteristics of these deaths are summarized in Table 1. The vast majority

Table 1. Demographics and clinical characteristics of HIV-infected inpatients who died from 2006 to 2015

Items	Total $n = 303$	2006 $n = 9$	2007 $n = 15$	2008 $n = 22$	2009 $n = 23$	2010 $n = 33$	2011 $n = 29$	2012 $n = 42$	2013 $n = 40$	2014 $n = 49$	2015 $n = 41$	p value
Age, Years, median (interquartile range)	48 (37-56)	44 (28-57)	45 (40-56)	49 (39-52)	50 (37-57)	47 (41-54)	49 (37-55)	51 (36-56)	52 (39-60)	50 (33-60)	44 (34-53)	0.372
Male gender N (%)	274 (90.4)	7 (77.8)	14 (93.3)	19 (86.4)	21 (91.3)	31 (93.9)	26 (89.7)	38 (90.5)	36 (90.0)	44 (89.8)	38 (92.7)	0.964
CD4+ T cell count/mm^3, median (interquartile range)	20 (7-66)	34 (16-91)	73 (16-298)	6 (3-63)	10 (5-24)	27 (3-52)	19 (10-43)	21 (9-59)	14 (7-106)	28 (9-67)	18 (7-56)	0.166
Hospital stay, Days, median (interquartile range)	15 (7-30)	21 (5-27)	23 (12-53)	12 (7-31)	17 (9-35)	22 (11-52)	16 (8-28)	14 (6-29)	21 (11-35)	13 (6-27)	9 (5-22)	0.257
On ART N (%)	62 (20.5)	0 (0)	5 (33.3)	2 (9.1)	4 (17.4)	9 (27.3)	6 (20.7)	11 (26.2)	8 (20.0)	9 (18.4)	8 (19.5)	0.724
Duration of ART, Months, median (interquartile range)	12 (4-18)	--	5 (5-17)	48 (12-84)	5 (3-9)	6 (2-18)	8 (1-15)	6 (2-12)	20 (12-42)	18 (12-60)	5 (4-11)	0.230
Comorbidities												
Cardia-cerebrovascular disease N (%)[a]	31 (10.2)	0 (0)	2 (13.3)	5 (22.7)	4 (17.4)	4 (12.1)	1 (3.4)	1 (2.4)	7 (17.5)	6 (12.2)	1 (2.4)	0.070
Pulmonary disease N (%)[b]	4 (1.3%)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	1 (3.4)	0 (0)	0 (0)	2 (4.1)	0 (0)	0.514
Liver disease N (%)[c]	50 (16.5%)	5 (55.6)	5 (33.3)	3 (13.6)	6 (26.1)	7 (21.2)	2 (6.9)	7 (16.7)	5 (12.5)	3 (6.1)	7 (17.1)	0.011
Kidney dysfunction N (%)[d]	28 (9.2)	1 (11.1)	1 (6.67)	1 (4.5)	1 (4.3)	3 (9.1)	1 (3.4)	2 (4.8)	2 (5.0)	6 (12.2)	10 (24.4)	0.064
Diabetes mellitus N (%)	23 (7.6)	0 (0)	0 (0)	3 (13.6)	1 (4.3)	2 (6.1)	3 (10.3)	2 (4.8)	6 (15.0)	3 (6.1)	3 (7.3)	0.570
Anemia N (%)[e]	101 (33.3)	2 (22.2)	9 (60.0)	4 (18.2)	9 (39.1)	9 (27.3)	9 (31.0)	17 (40.5)	12 (30.0)	13 (26.5)	17 (41.5)	0.217
Thrombocytopenia N (%)[f]	72 (23.8)	4 (44.4)	4 (26.7)	3 (13.6)	8 (34.8)	6 (18.2)	5 (17.2)	10 (23.8)	8 (20.0)	11 (22.4)	13 (31.7)	0.532

[a]Cardia-cerebrovascular disease including hypertension, congestive heart failure, myocardial infarction, and stroke. [b]Pulmonary disease including chronic obstructive pulmonary disease and asthma. [c]Liver disease including chronic hepatitis B or C and liver cirrhosis. [d]Kidney dysfunction defined as serum creatinine > 1.5 mg/dL. [e]Anemia defined as hemoglobin < 100g/L. [f]Thrombocytopenia defined as thrombocytes < 100×10^9/L.

Table 2. Causes of death among HIV-infected inpatients from 2006 to 2015

Cause of death	Number of patients $n = 303$ (%)
AIDS-related death	233 (76.9)
Pneumocystis jirovecii pneumonia	80 (26.4)
NTM/MTB infection[a]	56 (18.5)
AIDS-related encephalopathy[b]	47 (15.5)
Recurrent bacterial pneumonia	31 (10.2)
AIDS-related malignancy[c]	18 (5.9)
Wasting syndrome	1 (0.4)
Non-AIDS-related death	70 (23.1)
Sepsis	18 (5.9)
Liver disease	11 (3.6)
Non-recurrent bacterial pneumonia	9 (3.0)
Gastrointestinal hemorrhage	8 (2.6)
Non-AIDS-related malignancy	7 (2.3)
Cardiovascular disease	6 (2.0)
Renal disease	5 (1.7)
Trauma	2 (0.7)
Other[d]	4 (1.3)

[a]Nontuberculous mycobacteria or mycobacterium tuberculosis infection. [b]AIDS-related encephalopathy including progressive multifocal leukoencephalopathy, cryptococcal meningitis, cerebral toxoplasmosis, and CMV encephalitis. [c]AIDS-related malignancy including Kaposi sarcoma and non-Hodgkin's lymphoma. [d]Included bacterial meningitis, acute myelitis, neurological disorders, and malaria.

of these patients were male (90.4%, 274/303), with a median age of 48 years (IQR 37-56 years). Of those patients, 62 (62/303, 20.5%) were taking HAART when admitted. The median CD4+ T cell count on admission was 20 cells/μL (IQR 7-66 cells/μL) and the duration of hospitalization was 15 days (IQR 7-30 days). Variables other than liver comorbidities on admission did not change significantly over the 10-year period.

All causes of the 303 deaths that were analyzed are summarized in Table 2. Major causes of death were AIDS-related illnesses (76.9%, 233/303), with Pneumocystis pneumonia (PCP) (26.4 %, 80/303) and recurrent bacterial pneumonia (10.2%, 31/303) as the two most common causes followed by nontuberculous mycobacteria (NTM) or Mycobacterium tuberculosis (MTB) infection (18.5%, 56/303), and AIDS-related encephalopathy (15.5%, 47/303) including progressive multifocal leukoencephalopathy, cryptococcal meningitis, cerebral toxoplasmosis, and CMV encephalitis. Other less frequent AIDS-related causes of death were AIDS-related malignancy (5.9%, 18/303) (*i.e.* Kaposi sarcoma and non-Hodgkin's lymphoma) and wasting syndrome due to AIDS (0.4%, 1/303). A point worth noting is that non-AIDS-related illnesses caused roughly 1/4 (23.1%, 70/303) of the inpatient deaths at the SCCPH. Sepsis (5.9%, 18/303) and liver diseases (3.6%, 11/303) were the two major non-AIDS-related causes of death. Other common causes were non-recurrent bacterial pneumonia (3%, 9/303), gastrointestinal hemorrhage (2.6%, 8/303), non-AIDS-related malignancy (2.3%, 7/303), cardiovascular disease (2%, 6/303), renal disease (1.7%, 5/303), and trauma (0.7%, 2/303). The remaining non-AIDS-related deaths was caused by other comorbidities

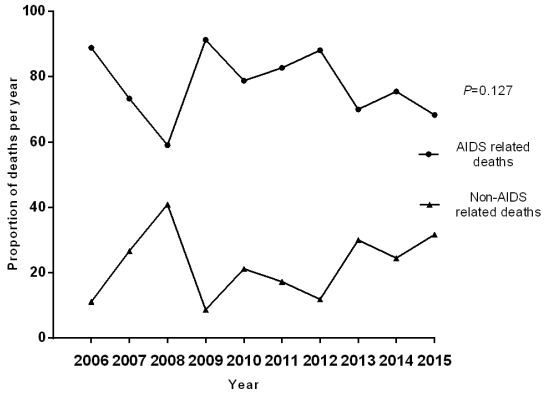

Figure 3. Trends in deaths caused by AIDS versus non–AIDS illnesses from 2006-2015. The proportion of AIDS-related and non-AIDS-related deaths did not differ significantly over time.

(1.3%, 4/303) such as bacterial meningitis, acute myelitis, a neurological disorder, and malaria. As shown in Figure 3, the proportion of AIDS-related or non-AIDS-related deaths did not change significantly over time ($\chi^2 = 13.847$, $p = 0.127$).

3.3. *Characteristic factors associated with AIDS-related or non-AIDS-related deaths*

Compared to patients who died from non-AIDS-related illness, patients who died from AIDS were younger (median age: 47 *vs*. 51 years, $p = 0.017$), they had a lower CD4+ T cell count (median 17 *vs*. 69 cells/μL, $p < 0.001$), and they were less likely to be receiving HAART (16.3% *vs*. 34.3%, $p = 0.001$) on admission. In contrast, comorbidities on admission including kidney dysfunction (27.1% *vs*. 3.9%, $p < 0.001$), cardia-cerebrovascular disease (21.4% *vs*. 6.9%, $p < 0.001$), diabetes mellitus (15.7% *vs*. 5.2%, $p = 0.003$), anemia (51.4% *vs*. 27.9%, $p < 0.001$), thrombocytopenia (35.7% *vs*. 20.2%, $p = 0.007$), and liver disease (24.3% *vs*. 14.2%, $p = 0.045$) were more common among non-AIDS-related deaths (Table 3).

The factors associated with the cause of death were further analyzed using multivariate logistic regression (Table 3). Factors including a CD4+ T cell count < 50 cells/μL (OR: 4.587; 95% CI: 2.387-8.815) and fewer comorbidities such as liver (OR: 0.402; 95% CI: 0.182-0.886) and kidney comorbidities (OR: 0.192; 95% CI: 0.069-0.535) on admission were independently associated with AIDS-related deaths.

4. Discussion

A comprehensive awareness of the deaths among HIV-infected inpatients is believed to be essential to improving the outcomes and quality of medical care provided by medical personnel. However, a nationwide study of the details of deaths among HIV-infected inpatients in China still needs to be conducted.

Table 3. Univariate and multivariate analysis of clinical characteristics and comorbidities associated with AIDS-related deaths

Items	AIDS-related deaths, *n* = 233	Non-AIDS-related deaths, *n* = 70	Univariate analysis[a]		Multivariate analysis[b]	
			p value	OR (95% CI)	*p* value	OR (95% CI)
Clinical characteristics						
Male gender	211 (90.6)	63 (90.0)	0.889	1.006 (0.921-1.099)	0.777	0.853 (0.284-2.5621)
Age > 60 y	36 (15.5)	19 (27.1)	0.026	0.491 (0.260-0.926)	0.385	1.407 (0.652-3.036)
CD4+ T cell < 50 cells/mm^3	183 (78.5)	26 (37.1)	< 0.001	2.115 (1.548-2.829)	< 0.001	4.587 (2.377-8.850)
On HAART	38 (16.3)	24 (34.3)	0.001	0.476 (0.308-0.735)	0.475	0.766 (0.370-1.589)
Comorbidities						
Cardia-cerebrovascular disease	16 (6.9)	15 (21.4)	< 0.001	0.320 (0.167-0.615)	0.310	0.600 (0.224-1.606)
Pulmonary disease	2 (0.9)	2 (2.9)	0.199	0.300 (0.043-2.094)	0.280	0.280 (0.028-2.820)
Liver disease	33 (14.2)	17 (24.3)	0.045	0.583 (0.347-0.982)	0.021	0.391 (0.177-0.866)
Kidney dysfunction	9 (3.9)	19 (27.1)	< 0.001	0.142 (0.067-0.300)	0.001	0.188 (0.067-0.523)
Diabetes mellitus	12 (5.2)	11 (15.7)	0.003	0.328 (0.151-0.710)	0.158	0.445 (0.145-1.368)
Anemia	65 (27.9)	36 (51.4)	< 0.001	0.542 (0.399-1.147)	0.119	0.579 (0.291-1.151)
Thrombocytopenia	47 (20.2)	25 (35.7)	0.007	0.565 (0.377-0.847)	0.389	0.720 (0.341-1.520)

[a] χ^2 test. [b]Multivariate logistic regression.

The current study investigated the mortality rate, the underlying causes, and the possible factors correlated with different causes of death among HIV-infected inpatients at the SCCPH. Since the SCCPH is the most influential medical center for HIV/AIDS patient care in Eastern China, the findings of this study may partially depict the outcomes for HIV-infected patients admitted for inpatient care during the HAART era in China, and especially those with access to vast medical resources.

Results revealed an overall mortality rate of 5.04% for HIV-infected inpatients at the SCCPH from 2006 to 2015. This rate was higher than that reported in Western countries during the HAART era (2-3%) (*4,5*), but it was significantly lower than that reported in sub-Saharan Africa (*8*). Therefore, this difference presumably reflects an association between socio-economic status and the outcomes of HIV infection to some extent.

Importantly, a marked decline in the yearly mortality rate (from 12.33% in 2006 to 3.2% in 2015) among HIV-infected inpatients was noted in the current study, and a similar trend has been noted in the West. There are several potential explanations for this trend. First and foremost, increased accessibility to HAART due to promotion of the National Free Antiretroviral Therapy Program (NFATP) since 2004 has been crucial to improving outcomes for HIV-infected inpatients (*11,12*). Second, the efforts of both government and social groups have raised public awareness of HIV infection over the last decade (*13*) and the coverage of HIV screening and surveillance has expanded, especially among high-risk populations. One recent study found that testing for HIV increased more than two-fold among men who have sex with men (MSM) from 2008 to 2012 in Nanjing, the capital of Jiangsu Province in Eastern China, while testing programs for MSM were promoted (*14*). Moreover, the SCCPH is the designated medical facility providing inpatient care for HIV-infected patients in Shanghai and Eastern China, so medical personnel at the SCCPH have gained experience managing HIV infection and AIDS-related illnesses. This may explain why the survival of HIV-infected inpatients has improved during the HAART era, as a study previously reported (*15*).

The current results revealed that the deaths of HIV-infected patients admitted to the SCCPH were mainly caused by AIDS-related illnesses. Results also revealed no significant change in the proportion of causes of death due to AIDS or non-AIDS-related illnesses over the last decade. Similar results were reported in another study investigating outcomes for HIV-infected patients after discharge from a hospital in Beijing, the capital of China (*16*). However, the major causes of death among HIV-infected inpatients in Western countries have shifted to non-AIDS-related illnesses during the HAART era, and the proportion of non-AIDS-related deaths has increased over time (*4,7*). These differences might be correlated with the current status of the HIV epidemic in China. A cross-sectional study conducted in 10 provinces of mainland China from 2009 to 2010 revealed that more than 70% of newly diagnosed cases of HIV infection were categorized as late presentation (defined as a CD4 count ≤ 200 cells/μL at HIV diagnosis), and the study found that late presentation was associated with increased AIDS-related morbidity and mortality (*17*). Similarly, another recent study also reported that most Chinese HIV-infected patients (72.6%) had a concurrent AIDS diagnosis at the time of HIV diagnosis or developed AIDS within 1 year after HIV diagnosis (*18*). In contrast, studies conducted in the West reported that no more than 30% of HIV-infected individuals presented with CD4+ T cells < 200/μL (*19*). The current study also found that most deceased HIV-infected inpatients, and especially those who died of AIDS-related illnesses, had a low CD4+ T cell count (< 50 cell/μL) and were not receiving HAART when admitted. These factors are the two biggest risk factors for developing AIDS-related illnesses such as opportunistic infections and malignancies (*20,21*). Despite the increasing

accessibility to HAART and increased public awareness of HIV infection, further efforts are needed to improve AIDS care and management in China.

Similar to findings from recent studies (*4,7*), the current results revealed that a lower CD4+ T cell count (< 50/μL) was a characteristic of mortality due to AIDS-related illness, and liver or kidney comorbidities on admission were more common in patients who died of non-AIDS-related illnesses. Consequently, the current study has highlighted the need for physicians to pay closer attention to these clinical features and the need to optimize decision-making accordingly.

Admittedly, this study had several limitations. First, it was an observational and retrospective study, so the possibility of bias in assigning causes of death by reviewing medical records cannot be ruled out. Second, this study did not include a proper control group such as HIV-infected inpatients who survived or HIV-negative inpatients who died in hospital, which would otherwise substantiate the current conclusions. The findings of this study may not fully depict the overall outcomes for HIV-infected inpatients in China, and especially those in regions with different socioeconomic levels and medical resources. Further prospective studies involving HIV-infected inpatients at multiple centers need to be conducted in order to better ascertain the outcomes for and characteristics of these patients in China during the HAART era.

5. Conclusion

Although the yearly overall mortality rate among HIV-infected inpatients tended to decline, this study found that the major causes of deaths were attributed to AIDS-related illnesses over the past decade. In light of those circumstances, further efforts are needed to improve HIV surveillance and AIDS care in China.

Acknowledgements

The authors wish to thank the staff of the Infectious Diseases Department at the SCCPH for their dedication and hard work. This study was supported by the National Natural Science Foundation of China (NSFC No. 81571977 and No. 31500697), the Shanghai Pujiang Program (No. 15PJ1407300), and the Program to Support Medical Science of the Shanghai Science and Technology Committee (No. 16411960400). The authors have no conflicts of interest to disclose.

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(Received October 26, 2016; Revised December 20, 2016; Accepted January 11, 2017)