

Causes of Death in Hospitalised Human Immunodeficiency Virus (HIV)-infected Patients at a National Referral Centre in Singapore: A Retrospective Review from 2008 to 2010

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Abstract

Introduction: Highly active antiretroviral therapy (HAART) has improved outcomes for individuals infected with human immunodeficiency virus (HIV). This study describes the causes of death in hospitalised HIV-positive patients from 2008 to 2010 in Tan Tock Seng Hospital, the national referral centre for HIV management in Singapore. **Materials and Methods:** Data were retrospectively collected from HIV-positive patients who died in Tan Tock Seng Hospital from January 2008 to December 2010. **Results:** Sixty-seven deaths occurred in the study period. A majority of patients died of non-acquired immune deficiency syndrome (AIDS)-defining illnesses (54.7%). The median CD4 count was 39.5 (range, 20.0 to 97.0), and 7 patients had HIV viral loads of <200 copies/mL. There were 27 deaths due to opportunistic infections, 27 due to non-AIDS-defining infections, 4 due to non-AIDS-associated malignancies. This study also describes 3 deaths due to cardiovascular events, and 1 due to hepatic failure. Patients who had virologic suppression were more likely to die from non-AIDS-defining causes. **Conclusion:** Causes of death in HIV-positive patients have changed in the HAART era. More research is required to further understand and address barriers to testing and treatment to further improve outcomes in HIV/AIDS.

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Key words: AIDS, Causes of death, HIV, Mortality, Singapore

Introduction

The advent of the highly active antiretroviral therapy (HAART) era has greatly reduced the mortality and incidence of new diagnoses of acquired immune deficiency syndrome (AIDS)-defining illnesses (ADIs) in individuals infected with human immunodeficiency virus (HIV) in many countries.¹⁻⁵ This has led to a paradigm shift in the management of HIV, from that of a highly lethal infection to a chronic condition. Consequently, mortality due to comorbid conditions is becoming more common. In spite of widespread access to HAART, the incidence of death due to ADIs is still high in some countries, especially when the infection is diagnosed late.⁶⁻⁸ It is important to have accurate data on the causes of mortality in the HIV-infected in both these settings, so as to develop better strategies aimed at early diagnosis and treatment, and management of non-AIDS conditions which might otherwise compromise prognosis. This study was undertaken to describe the distribution of the

causes of death in hospitalised patients in our institution in Singapore. Tan Tock Seng Hospital (TTSH) is a 1481-bed teaching hospital in Singapore, which is also the national referral centre for HIV management.

Materials and Methods

We conducted a retrospective review of all HIV patients who were admitted at the Communicable Disease Centre (CDC) and Tan Tock Seng Hospital (TTSH) between January 2008 and December 2010.

Data were obtained through the Management Information Department of the Office of Clinical Governance of TTSH. We obtained demographic data on sex, age, ethnicity on all HIV patients who were admitted during the study period. In addition, clinical case records of all deaths were reviewed, and epidemiological, clinical and laboratory data at the time of death were collected. The data collected

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were: age, gender, ethnicity, mode of transmission, date of diagnosis, CD4 T-lymphocyte count, plasma HIV-RNA, viral hepatitis serological status and details on antiretroviral (ARV) regimen.

Cause of death was obtained from the case records, which was coded according to the International Classification of Diseases, 10th Revision (ICD-10). Death was considered to be AIDS-defining if the cause of death was an ADI as classified by the US Centers for Disease Control.⁹ All other causes of death were considered to be due to non AIDS-defining illnesses.

SPSS for Windows Version 18.0 was used for all statistical analyses. We compared proportions using Pearson Chi-square, means using ANOVA tests and medians using Kruskal Wallis test. This study was reviewed and approved by the Singapore National Healthcare Group (NHG) Domain Specific Ethics Review Board Committee.

Results

From 2008 to 2010, there were a total of 1662 admissions to CDC and TTSH. The median length of stay for all patients excluding those who died was 5 days [Interquartile range (IQR), 3 to 9, minimum (min): 1 day, maximum (max): 269 days]. The median age was 47 years old (IQR 40 to 54, min: 18 days, max: 89 days). Among these, 91% were male.

There were a total of 67 deaths during the study period. The case records for all 67 deaths were available for review. Among these deaths, 59 were male (88.1%), and the mean age at death was 51.8 years (range, 18 to 77). The ethnic composition of the cohort was as follows: 59 Chinese (88.1%), 7 Malay (10.4%), and 1 Eurasian (1.5%). The mode of transmission of HIV infection was heterosexual in 82.1%, homosexual in 6.0%, bisexual in 4.5%, and via injecting drug use in 4.5%. Mode of transmission was unknown in 2 cases (3.0%). Eleven patients (16.4%) were uninfected with hepatitis B, and 3 (4.5%) had concurrent hepatitis C infection.

Fourteen deaths (20.9%) occurred in patients who were being admitted to hospital for the first time. Of the 53 patients who had been admitted more than once, the mean number of repeat admissions was 3.3 (range, 1 to 5). The mean length of stay during the terminal hospitalisation was 24.2 days (range, 1 to 145 days). Twenty-one patients (31.3%) were admitted to the intensive care unit (ICU) during their hospitalisation.

The CD4 T-lymphocyte count at the time of admission for the terminal event was known for 58 patients, and the median value was 39.5. Nine patients had never had a previous CD4 count measurement, indicating that HIV infection was first diagnosed during their terminal admission to hospital. HIV-RNA viral load was available for 29 of

the patients. Seven patients (24.1%) had suppression of viraemia with a viral load of less than 200 copies/mL. The median HIV-RNA viral load was 4.8 log copies/mL (range, 0 to 6.7 log copies/mL).

At the time of death, 18 patients (26.9%) were antiretroviral naïve, and a further 4 (6.0%) were not on treatment due to non-compliance. Of the patients who had ever been started on HAART, 37 (55.5%) were receiving triple agent HAART, 4 (6.0%) were on dual nucleoside reverse transcriptase inhibitor (NRTI) therapy, one was on NRTI and protease inhibitor (PI) combination therapy. The median duration of ARV therapy receipt was 1.8 years (range, 0.1 to 6.5 years), and 16 patients (33.3%) had ever had an interruption to their treatment.

The diagnoses at time of death are outlined in Table 1. Thirty-one deaths (45.3%) were classified as ADIs, comprising opportunistic infections (OIs), AIDS-associated malignancies (primary central nervous system lymphoma), or other AIDS-associated systemic disease (HIV-associated dilated cardiomyopathy). Ten of the 14 patients (71.4%) died during their first ever admission to hospital succumbed

Table 1. Diagnosis at Time of Death in 67 HIV-Infected Patients Admitted to Tan Tock Seng Hospital, Singapore (2008 to 2010)

Diagnosis	Number	%
AIDS-associated	31	43.5
<i>Pneumocystis jirovecii</i> pneumonia	14	20.9
Cerebral toxoplasmosis	4	6.0
Disseminated <i>Mycobacterium tuberculosis</i> infection	3	4.5
Disseminated MAC infection	3	4.5
Primary central nervous system lymphoma	2	3.0
Lymphoma (AIDS-associated)	1	1.5
Progressive multifocal leukoencephalopathy	1	1.5
CMV encephalitis	1	1.5
Disseminated CMV infection	1	1.5
HIV-associated dilated cardiomyopathy	1	1.5
Non AIDS-associated	36	54.7
Pneumonia (non- <i>Pneumocystis</i>)	22	32.8
Bacteraemia	4	6.0
Non AIDS-defining malignancies	4	6.0
Cardiovascular disease	3	4.5
Septic encephalopathy of unknown origin	1	1.5
Hepatic failure	1	1.5
Immune thrombotic thrombocytopenic purpura	1	1.5

AIDS: acquired immune deficiency virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus; MAC: mycobacterium avium-intracellulare complex

to an ADI.

The other deaths (54.7%) were classified as non AIDS-defining events. There were 27 cases (40.3%) of non AIDS-related infections: 22 cases (32.8%) of pneumonia and 4 cases (6.0%) of bacteraemia, comprising 2 instances of *Pseudomonas aeruginosa*, and once each of *Escherichia coli* and *Aeromonas* bloodstream infection. There was also a case of death attributed to septic encephalopathy of unknown origin. The 4 cases of non AIDS-associated malignancies in this series included lung, gastric and breast cancer, as well as a case of metastatic cancer with unknown primary source. There were 3 deaths (4.5%) attributed to cardiovascular disease, due to acute myocardial infarction, cor pulmonale and sudden cardiac death respectively.

Table 2 shows a comparison between patients who died from AIDS-defining and non AIDS-defining illnesses. There were no statistically significant differences between the 2 groups in terms of age, sex, CD4 counts, or previous receipt of ARV therapy. However, amongst the 7 patients who had a suppressed viral load of <200 copies/mL, 6 (85.7%) died of non AIDS-defining illness, which was

statistically significant.

Discussion

Our retrospective study showed that during 2008 to 2010, non AIDS-defining illnesses (54.7%) as a cause of death have outnumbered AIDS ADIs. This is in contrast to an earlier study by Bellamy et al,¹⁰ which found that 63.1% of HIV mortality in Singapore from the pre-HAART to early HAART years was due to ADIs.

We also found a disproportionate mortality (82.1%) in individuals infected via heterosexual transmission, despite comprising only a slim majority (52%) of new infections in Singapore in 2010.¹¹ A probable reason is that this group sought testing and treatment later in the course of disease, and hence had worse outcomes. This trend is reflected in an earlier study in Singapore which showed a disproportionate representation of men who have sex with men (MSM) amongst those with acute HIV infection,¹² reflecting healthcare access earlier in the course of disease, with possible mortality benefit.

The increase in non AIDS-associated deaths reflects a trend seen in many resource-rich settings, where broad access to healthcare and ARV drugs have reduced the prevalence of AIDS.^{1-5,13-15} We also found that virologic suppression was a predictor for death due to non-ADIs, corroborating other published data.¹⁵ This heterogeneous group of diagnoses is dominated by non-pneumocystis pneumonia (PCP) and bacterial sepsis, underscoring the HIV-infected person's increased susceptibility to infection, which is seen in other series.^{8,16,17} HIV patients with unsuppressed viral loads and whose cell-mediated immunity remains profoundly suppressed are especially vulnerable to sepsis and the poor prognosis it portends. Bellamy et al¹⁰ also found that pneumonia, whether bacterial or of unknown aetiology, as well as bacterial septicaemia, were the commonest non AIDS-defining diagnoses at time of death in Singapore in an earlier survey.¹⁰

We describe 4 cases of non AIDS-associated cancers, not seen in any of the earlier Singapore study. This is likely due to effective treatment and hence improved survival, leading to the increased pick-up of cancers not linked to profound immunosuppression. Lung cancer, and its link to smoking, has been described as the commonest non AIDS-defining malignancy elsewhere,^{15,18,19} and this warrants further study locally.

However, OIs remain significant causes of death in our study. PCP, cerebral toxoplasmosis and disseminated mycobacterial disease were all observed, indicating the persistence of severely impaired immunity characterising the pre-HAART era. This is consistent with Singapore data showing that older, heterosexual patients tend to

Table 2. Comparison Between AIDS and Non AIDS-Associated Deaths in Hospitalised HIV-Infected Patients (Tan Tock Seng Hospital, Singapore, 2008 to 2010)

	AIDS-Defining Illnesses (N = 31)	Non AIDS-Defining Illnesses (N = 36)	Total	P Value
Age				
Median [IQR]	50 [38 to 58]	52.5 [43.5 to 67.8]		0.09
Gender				
Male: N (%)	27 (87.1)	32 (88.9)	59	0.82
Female: N (%)	4 (12.9)	4 (11.5)	8	
Latest CD4 at death*				
Median [IQR]	49 [26 to 114.5]	110 [20 to 235]		0.23
Min-max	10-403	2-472		
Latest VL (Log10)†				
<200 copies/mL: N (%)	1 (14.3)	6 (85.7)	7	0.002
>200 copies/mL: N (%)	18 (81.8)	4 (18.2)	22	
ARV regimen				
None (naïve): N (%)	8 (25.8)	10 (27.8)		0.86
Ever on: N (%)	23 (74.2)	26 (72.2)		

AIDS: acquired immune deficiency virus; ARV: antiretroviral; IQR: interquartile range; VL: viral load

*Missing value 21 for previous CD4

†Missing value 42 for latest VL

present with low CD4 counts and with multiple OIs. This is a phenomenon observed in resource-limited developing countries,²¹⁻²⁵ highlighting the presence of gaps in HIV care provision in Singapore despite being a developed economy. A worrying phenomenon is that more than a quarter of those in our study had never been on treatment. Ever having been on treatment is used in the literature as a surrogate metric of the success of strategies aimed at reducing HIV infection, including “test and treat”, and efforts at retaining patients in treatment programmes by increasing compliance. Never having been treatment thus reflects either a failure to diagnose infection prior to hospitalisation, or a failure to retain those who did initiate ARV therapy. More research is needed to guide future healthcare policy to reduce these potentially preventable causes of death.

We report 3 deaths due to cardiovascular disease, 2 of whom were on HAART. This mirrors the increasing survival of HIV-infected patients previously described.^{1,4,18,25,26} We did not extract data on traditional cardiovascular risk factors in our study population, but it is likely due to the development of metabolic derangements common with greater age and prolonged exposure to ARVs with adverse mitochondrial side effects.

Deaths attributable to hepatic disease are becoming more prominent in both developed^{1,4,15} and developing countries.²⁰ We report one fatality due to hepatic failure. This lower incidence could be due to the low rate of co-infection with hepatitis C virus (HCV), which has been described by Hernando et al as conferring increased all-cause and liver-related mortality.²⁷ Screening for, and treating HCV infection is important in HIV-positive individuals as cleared and treated infection has been shown to reduce the risk of death.²⁸

The persistence of considerable mortality despite the availability of ARVs seen in our study is consistent with other series. Sabin et al² described poor outcomes in patients maintained on suboptimal ARV regimens which were initiated prior to the availability of HAART. This may have been an important contributory factor for those of our patients on dual agent therapy, or on regimens containing older, less efficacious NRTIs.

Delayed diagnosis and the lack of treatment due to poor access to healthcare or poor compliance all lead to more severe immune compromise and hence greater risk of death.²⁹ Nine cases in our series were diagnosed with HIV infection only after admission. This is in keeping with data from the Singapore Ministry of Health which showed that 54% of new diagnoses were made in the course of healthcare, with voluntary screening being the source of only 12% of new HIV diagnoses.¹¹ Moreover, the introduction of voluntary opt-out inpatient HIV testing in Singapore hospitals has seen low levels of acceptance, with an opt-in rate of 21% in our

hospital from 2009 to 2010.³⁰ Undiagnosed HIV infection remains a major public health problem,³¹ and increasing the take-up of testing is key to reducing mortality, through earlier diagnosis and treatment.

Rubin et al³² found that differences in socioeconomic status led to unequal reduction in mortality due to inequities in access to healthcare and ARVs. Further study should be undertaken to better understand the role of cost and access to treatment in the mortality of HIV-infected patients in Singapore.

Limitations in our study include its design as a retrospective survey, which made it difficult to assess the longitudinal effect of various risk factors on mortality in HIV-infected individuals.

In addition, classifying cause of death from a review of clinical records means not every patient was fully investigated to satisfy diagnostic criteria for each terminal condition. However, every attempt was made to ensure the accuracy of diagnosis. A further limitation is that our study could not ascertain that the diagnosis at death was consistent with the diagnosis at admission, that is, some patients could in fact have died from conditions that manifested after hospitalisation, e.g. nosocomial pneumonia. This is primarily due to the inconsistency in documentation in the case records, that is, symptoms at admission rather than a unifying diagnosis was recorded. It was also a single centre review—however, as the national referral centre for HIV/AIDS medicine in the country managing the vast majority of HIV-positive patients, the trends observed in our study are likely to reflect greater national trends in HIV mortality. Moreover, there is a paucity of extant data on AIDS-related deaths emanating from the other healthcare institutions in Singapore, likely due to the aforementioned reason. These limitations are, however, attenuated by the fact that the previous survey on HIV mortality by Bellamy et al¹⁰ was also based on single centre data, namely the CDC, and hence a comparative analysis of HIV-related deaths in the 2 different periods is possible. Lastly, while we observed a predominance of non-ADIs in those who were virologically suppressed, we were unable to derive statistically significant differences between those who died of AIDS-defining and non AIDS-defining illnesses. This was likely due to the small sample size in the period of study.

There is evidence that overall mortality of HIV-infected patients is on the decline in Singapore. Unpublished data from Chua et al³⁰ show that the mortality rate of HIV patients at the CDC from 1991 to 2001 was between 45% and 51%, compared to 8% in 2008, 7% in 2009, and 2% in 2010 during the period of this review (unpublished data). This change in the risk of death is concurrent with a change in cause of death, and requires a change in efforts to further improve the health of survival of those living with HIV.

Conclusion

Understanding the causes of death in HIV-infected patients is essential to the management of this condition, and will allow policymakers and stakeholders to make informed decisions in a timely fashion such as expanding access to effective treatment through increasing awareness and reducing the cost of seeking care.

Further study is needed to elucidate and remove barriers to testing and treatment of HIV infection and important comorbid conditions. Healthcare policy aimed at reducing mortality should be directed towards (i) early diagnosis, (ii) universal access to treatment, (iii) screening for concurrent hepatitis B and C infection, (iv) presence of cardiovascular disease and malignancy, and (v) addressing socioeconomic and cultural impediments to the management of HIV.

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